Introduction

WHAT’S DIFFERENT ABOUT A USP DRUG INFORMATION MONOGRAPH

The Veterinary Medicine Expert Committee on Drug Information gratefully acknowledges the financial support of its parent organization, the United States Pharmacopeia, to publish these monographs. It also is appreciative to the Food Animal Residue Avoidance Databank (FARAD) for supplying slaughter and milk withdrawal information where extra-label drug use in food animals is noted. This information is provided in cooperation with MICROMEDEX, a Thomson Healthcare Company.

USP history, organizational structure, and publications

In pursuit of its mission to promote public health, the United States Pharmacopeia (USP) develops authoritative information about the appropriate use of medicines, including those used in animals. This non-government, not-for-profit organization draws on a long-standing dedication to public involvement in the establishment of scientific standards. USP achieves its goals through the contributions of volunteers representing health care professions, as well as science, academia, the U.S. government, the pharmaceutical industry, and consumer organizations.

USP was established in 1820 with the primary goal of setting standards for the identity, strength, and quality of medicinal compounds and this remains at the core of the organization. Currently, USP provides standards for more than 3,800 prescription and non-prescription drugs, nutritional and dietary supplements, veterinary drugs, and health care products. These standards are published in the United States Pharmacopeia (USP) and the National Formulary (NF), which are officially recognized in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 321 et seq.). USP also produces Reference Standards, which are an integral part of USP’s standards program.

The development of USP information on the best use of medications was begun in 1970, growing out of the public process of developing quality standards. USP information advisory panels were created to assure that the information under development is evidence-based, consensus-established, practical, and clinically relevant. This work was expanded into a separate public health program and in 1980, the first USP DI® was published. Today, in association with MICROMEDEX, USP continues to provide oversight and approval of drug information content in the USP DI® database, which covers nearly all medicines in the U.S. and Canada.

The veterinary drug information monograph creation process

Very soon after the USP DI® was first published, an advisory panel on veterinary medicine was created. Since 1982, veterinary pharmacologists, veterinary pharmacists, and other specialists have contributed their time and expertise in creating and revising drug information through USP’s unique process. This drug information is developed by exhaustive compilation of approved product label information and also collection and analysis of publicly available data on each drug from research studies and clinical reports. Careful attention is paid to differentiating species-specific information. With the agreement of MICROMEDEX, information from the human USP DI® database is included where it may be helpful. Each draft chapter or monograph is then put through a review process that includes USP Veterinary Medicine Committee members, regulatory representatives, pharmaceutical manufacturers, ad hoc specialists, and public review. At present, USP monographs are the only drug information source in veterinary medicine undergoing such extensive expert review, a process through which the credibility of the information is maintained.

USP drug information is a work-in-progress. The information is in constant revision and is a continuous collection of the current judgments of experts in the use of medications. The following chapters have been developed over 7 years, with information added and revised, as necessary.

Unique features

This special issue of the Journal of Veterinary Pharmacology and Therapeutics contains a series of drug information monographs on antimicrobials used in veterinary medicine. What makes this information different from other sources of veterinary drug information? A succinct listing would include:

- The incorporation of extra-label and label indications and dosages for all domestic species. See the section below, “Finding the specific drug information you need; Label and extra-label uses,” for details on how this information is differentiated.
- The inclusion of slaughter and milk withdrawals when extra-label drug use in food animals is considered an acceptable option for therapy. Withdrawal times have been provided by FARAD for the specified conditions noted.
- The inclusion of information about both U.S. and Canadian veterinary drug products.
- The grouping of indications into three categories. The “Accepted” category indicates that clear evidence exists to support use of the drug for a particular purpose. “Acceptance not established” (potentially useful) indicates that use of the drug for an indication may be worthy of consideration if superior therapies do not exist, but the evidence is either scant or subject to concern based on experimental design. If a use is viewed as ineffective or has been replaced by clearly superior therapies, the indication is deemed “Unaccepted.” These categorizations are applied to label and extra-label uses.
- The use of tables of scientific evidence to address controversial issues during the review process, particularly relative to extra-label drug use.
- Review of the information by a Food and Drug Administration (FDA) liaison to the committee. Although comments made by the FDA are taken quite seriously, those opinions are nonbinding on the USP. The information contained in these monographs should not be considered an endorsement or “acceptance” by the FDA as to a given use or dosage.
- The review of each monograph by the USP Veterinary Medicine Committee. This committee consists of 10 to 15 volunteers recognized as experts in pharmacology, internal medicine, or species discipline(s).
Introduction

Finding the specific drug information you need

Label and extra-label uses

The *Indications* section of each drug monograph is designed to provide information about indications in drug product labeling in the U.S. and Canada. Extra-label indications for which clinical and research data have been evaluated are also included. Indications found in product labeling are listed first. Brackets around an indication signify that it is not found in any product labeling in the U.S. at the time of last major revision. Some indications are followed by a superscript 1, meaning they are not included in Canadian product labeling.

Examples of bracket and superscript 1 placement in the monographs:

[Pneumonia, bacterial (treatment)] An extra-label use in the U.S.
An indication is included in Canadian product labeling.

Pneumonia, bacterial (treatment)¹ An indication found in U.S.
product labeling but not in Canadian product labeling.

[Pneumonia, bacterial (treatment)]¹ An extra-label use in both the
U.S. and Canada.

Species and dosage forms

Within each category of the *Indications* section the information is arranged in a hierarchy as follows: indication, followed by the species to which that indication applies, and finally the dosage forms used in that species for that indication. You will see that some species and dosage forms are also given bracket and superscript 1 designations: these have the same meaning for species and dosage forms as described above for indications. To decrease clutter and confusion, only the highest level of the hierarchy is given a bracket or superscript 1 (indication > species > dosage form). That is, if the indication is not found on any label in the U.S. (a bracketed, extra-label use) then the species under it will not be bracketed because it is obvious that no species are on the label of any product in the United States for this indication.

Dosing

In the USP veterinary drug information monographs, dosage forms are always listed separately to provide an opportunity to list specific information for each type of product. In the *Dosage Forms* section, indications and species are bracketed or given a superscript 1 following the same rules applied in the *Indications* section, except that they reflect the labeling of the specific dosage form. Dosages listed are not always label dosages even if the species is in the product labeling.

Label and extra-label withdrawal times

Established withdrawal times from product labeling are listed in the *Withdrawal times* tables for each dosage form labeled for use in food-producing animals. But be sure to consult the approved labeling on the product you are using for the specific government established dose and withdrawal time. Extra-label withdrawal times are listed in the *Withdrawal times* section for each extra-label use and/or dose recommended for food-producing animals. As always, veterinarians will use their own clinical judgment, following the guidelines of the Animal Medicinal Drug Use Clarification Act, to determine a safe extra-label withdrawal time.

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Some commonly used brand names are:

- **Amifuse E** (Amikacin)
- **Rokaphlme-V** (Amikacin)
- **Amifuside Injection** (Amikacin)
- **Amifuside Intravenous Solution** (Amikacin)
- **Amiject D** (Amikacin)
- **Amikacin C Injection** (Amikacin)
- **Amikacin E Solution** (Amikacin)
- **Amiject C** (Amikacin)
- **Amiject D** (Amikacin)
- **Amiject E Solution** (Amikacin)
- **Amiject C** (Amikacin)
- **Amifuse E Solution** (Amikacin)
- **Amifusidok A** (Amikacin)
- **Amifuside B** (Amikacin)
- **Amifuside C** (Amikacin)
- **Amifuside D** (Amikacin)
- **Amifuside E Solution** (Amikacin)
- **Amifuside F** (Amikacin)
- **Amiject C** (Amikacin)
- **Amiject D** (Amikacin)
- **Amiject E Solution** (Amikacin)
- **Amiject F** (Amikacin)
- **Amifuside G** (Amikacin)
- **Amifuside H** (Amikacin)
- **Amifuside I** (Amikacin)
- **Amifuside J** (Amikacin)
- **Amifuside K** (Amikacin)
- **Amifuside L** (Amikacin)
- **Amifuside M** (Amikacin)
- **Amifuside N** (Amikacin)
- **Amifuside O** (Amikacin)
- **Amifuside P** (Amikacin)
- **Amifuside Q** (Amikacin)
- **Amifuside R** (Amikacin)
- **Amifuside S** (Amikacin)
- **Amifuside T** (Amikacin)
- **Amifuside U** (Amikacin)
- **Amifuside V** (Amikacin)
- **Amifuside W** (Amikacin)
- **Amifuside X** (Amikacin)
- **Amifuside Y** (Amikacin)
- **Amifuside Z** (Amikacin)

**Antibacterial (systemic).**

**INDICATIONS:**

- **Amikacin**
- **Gentamicin**
- **Neomycin**
- **Dihydrostreptomycin**
- **Apramycin**

**CATEGORY:**

Antibacterial (systemic).

**INDICATIONS:**

Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**GENERAL CONSIDERATIONS:**

- Aminoglycosides are utilized primarily in the treatment of infections caused by aerobic gram-negative organisms. They are not active against anaerobic organisms. In addition to their strength in the treatment of gram-negative pathogens, aminoglycosides can be effective against some Gram-positive organisms, such as *Staphylococcus aureus*.
- Some mycobacteria, some mycoplasma strains, and some spirochetes. They are sometimes administered concurrently with other antibacterials for a possible synergistic effect. However, the use of aminoglycosides in the treatment of infection in animals has been tempered by toxicity considerations in the animal treated. Often, systemic use is limited to the treatment of serious gram-negative infections resistant to less toxic medications. Also, local environment at the therapeutic site can affect the efficacy of these drugs, acidic or purulent conditions can hamper their effect, and the presence of cations (calcium or magnesium ions, for example) can decrease antibacterial effect.

Streptomycin was the earliest aminoglycoside introduced. It is active against mycobacteria, *Leptospira*, *Francisella tularensis*, and *Yersinia pestis*, but only some mycoplasma, gram-negative organisms, and *Staphylococcus* species. Dihydrostreptomycin is chemically very similar to streptomycin. The introduction of newer aminoglycosides has eclipsed the significance of dihydrostreptomycin and streptomycin in the face of increasing bacterial resistance, although some dosage forms of these medications are still available.

Neomycin became available for use a few years after streptomycin. Neomycin has been effective against many gram-negative organisms and *Staphylococcus aureus*. However, the use of neomycin is limited by a relatively high risk of toxicity with systemic use, it is not available for parenteral administration.

Kanamycin was introduced as a less toxic alternative to older aminoglycosides and was soon followed by gentamicin and later by amikacin. The spectrum of activity of kanamycin primarily focuses on gram-negative organisms and a few gram-positive organisms. The prevalence of resistance of some pathogens, including *Escherichia coli* and *Salmonella* species, to kanamycin is higher than to gentamicin, and this has limited the use of kanamycin. The use of kanamycin has also been eclipsed by the derivation of amikacin, a drug with a very similar pharmacokinetic profile but superior activity against pathogens such as *Pseudomonas* species and kanamycin-resistant *Enterobacteriaceae*.

Gentamicin has been widely used in the treatment of gram-negative organisms and some gram-positive organisms. As with other aminoglycosides, use is limited by risk of toxicity. In vitro tests have shown gentamicin to be active against *Salmonella arizonae* (*Arizona hinshawi*) and *Enterobacter aerogenes*. E. coli and *Klebsiella* species are still resistant to gentamicin, with many isolates showing minimal inhibitory concentrations above the limits set for resistance.

Gentamicin has been shown to be active against *Salmonella arizonae* (*Arizona hinshawi*) and *Enterobacter aerogenes*. E. coli and *Klebsiella* species are still resistant to gentamicin, with many isolates showing minimal inhibitory concentrations above the limits set for resistance.

In addition to the new M3000, which is resistant to gentamicin, in *vitro* tests have shown amikacin to be effective against E. coli, *Klebsiella* and *Pseudomonas* species resistant to gentamicin. Citrobacter freundii, *Listeria monocytogenes*, and *Providencia* species have shown amikacin to be effective against a wide range of gram-negative and gram-positive organisms.

*Not commercially available in the U.S. as a single entity.

†Not commercially available in Canada as a single entity.

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gentamicin and other aminoglycosides by *Salmonella* species\textsuperscript{[R-113; 117–119]}, but the strains tested are still susceptible to amikacin\textsuperscript{[R-118; 199; 250]}

Apramycin is an aminocyclitol antibiotic with a chemical structure very similar to that of the aminoglycosides but different enough to leave it unaffected by many aminoglycoside inactivating enzymes \textsuperscript{[R-245]}. At low concentrations, apramycin is more effective in inhibiting bacterial protein synthesis than kanamycin A, streptomycin, amikacin, or gentamicin \textsuperscript{[R-96]}. Apramycin is active against *Staphylococcus aureus*, many gram-negative organisms, and some mycoplasma strains \textsuperscript{[R-163]}. Apramycin has been reported to be effective in vitro against *E. coli* and *Salmonella* species \textsuperscript{[R-96; 164]} that are resistant to streptomycin and neomycin \textsuperscript{[R-167; 173]}.

Resistance to aminoglycosides is produced primarily by enzymes encoded by genes located on bacterial plasmids \textsuperscript{[R-116; 168]}. The enzymes act inside the bacterium to modify the aminoglycoside, thereby preventing it from binding to ribosomes \textsuperscript{[R-116; 168]}. This type of plasmid-associated resistance is transferable between bacteria. A single type of plasmid may confer cross-resistance to multiple aminoglycosides \textsuperscript{[R-116; 117; 120–145]} and also resistance to other unrelated antimicrobials \textsuperscript{[R-7; 114; 115; 120; 145; 168]}. In some cases, a single plasmid gene encoding for one enzyme, an acetyltransferase, may confer resistance to several aminoglycosides \textsuperscript{[R-171]}. For example, the enzyme aminoglycoside 3-

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**Bacteremia (treatment); or**

**Septicemia (treatment)—** *Cats and dogs:* Kanamycin sulfate injection \textsuperscript{[R-93]}, amikacin injection \textsuperscript{[R-264]}, and gentamicin injection \textsuperscript{[R-7]} are indicated in the treatment of bacteremia or septicemia caused by susceptible organisms.

**Bone and joint infections (treatment)\textsuperscript{[1]}—** *Cats and dogs:* Kanamycin sulfate injection \textsuperscript{[R-93]}, amikacin injection \textsuperscript{[1][R-264]}, and gentamicin injection \textsuperscript{[R-264]} are indicated in the treatment of bone and joint infections caused by susceptible organisms \textsuperscript{[R-93]}.

**Enteritis (treatment)—** The primary treatment for enteritis in many cases is aggressive fluid replacement. Treatment of enteritis with antimicrobials should rely on a specific diagnosis and knowledge of pathogen susceptibility.

**Calves:** Neomycin sulfate for medicated feed is indicated in the control and treatment of enteritis caused by susceptible *Escherichia coli* \textsuperscript{[R-94]}. Streptomycin oral solution \textsuperscript{[R-181; 182]} is indicated in the treatment of bacterial enteritis caused by susceptible organisms.

**Cattle and sheep:** Neomycin sulfate for medicated feed \textsuperscript{[1]}, neomycin sulfate powder for oral solution \textsuperscript{[R-97; 104]} and neomycin sulfate oral solution \textsuperscript{[R-98; 103]} are indicated in the control and treatment of bacterial enteritis caused by susceptible *Escherichia coli*. If systemic signs develop, medications that are well absorbed systemically should be considered for addition to or substitution for therapy with this medication \textsuperscript{[R-98]}.

**Chickens:** [Neomycin oral powder\textsuperscript{[R-104]}, neomycin oral solution\textsuperscript{[R-103]}] and streptomycin \textsuperscript{[R-181; 182]} are indicated in the control and treatment of bacterial enteritis in chickens.

**Goats:** Neomycin sulfate for medicated feed, neomycin sulfate powder for oral solution \textsuperscript{[R-97; 104]} and neomycin sulfate oral solution \textsuperscript{[R-98; 103]} are indicated in the control and treatment of bacterial enteritis caused by susceptible *Escherichia coli*.

**Horses:** Neomycin sulfate powder for oral solution \textsuperscript{[R-95]}, gentamicin injection \textsuperscript{[R-7; 125]}; gentamicin powder for oral solution \textsuperscript{[R-15]}, gentamicin oral solution \textsuperscript{[R-11; 14]}; neomycin sulfate for medicated feed \textsuperscript{[R-94]; neomycin sulfate oral solution \textsuperscript{[R-96; 103]}; neomycin sulfate powder for oral solution \textsuperscript{[R-97; 104]; [dihydrostreptomycin\textsuperscript{[R-106]} and streptomycin \textsuperscript{[R-181; 182]} are indicated in the control and treatment of enteritis (weaning pig scours) in piglets caused by susceptible *E. coli*. If systemic signs develop, medications that are well absorbed systemically should be considered \textsuperscript{[R-98]}.

**Pigs:** Neomycin sulfate for medicated feed is indicated in the control and treatment of enteritis (weaning pig scours) in piglets caused by susceptible *E. coli* \textsuperscript{[R-94]}.

**Pigs:** Neomycin sulfate powder for oral solution \textsuperscript{[R-97; 104]} and neomycin sulfate oral solution \textsuperscript{[R-98; 103]} are indicated in the control and treatment of bacterial enteritis caused by susceptible *Escherichia coli*. If systemic signs develop, medications that are well absorbed systemically should be considered for addition to or substitution for therapy with this medication \textsuperscript{[R-98]}.

**Pigs:** Neomycin sulfate powder for oral solution \textsuperscript{[R-97; 104]} and neomycin sulfate oral solution \textsuperscript{[R-98; 103]} are indicated in the control and treatment of bacterial enteritis in turkeys.

**E. coli infection (treatment)—**

**Chicks:** 1-day-old: Gentamicin injection \textsuperscript{[R-7; 8]} is indicated in the prevention of early mortality in chicks caused by susceptible *E. coli*. **Turkey:** growing \textsuperscript{[1]}: Neomycin sulfate powder for oral solution is indicated in the control of mortality associated with susceptible *E. coli* in growing turkeys \textsuperscript{[R-2]}.

**Paracolon (treatment)—** *Turkey poults, 1- to 3-day-old:* Gentamicin injection \textsuperscript{[R-7; 8]} is indicated in the treatment of infections in turkeys caused by susceptible *Salmonella arizonae*.

**Pseudomonas aeruginosa infection (treatment); or**

*Salmonella typhimurium* infection (treatment)—*Chicks, 1-day-old:* Gentamicin injection \textsuperscript{[R-7; 8]} is indicated in the prevention of early mortality...
in chicks caused by susceptible *Pseudomonas aeruginosa*, and *Salmonella typhimurium*.

Respiratory tract infections, bacterial (treatment)—*Cats and dogs: Gentamicin injection*[^4-7] and *kanamycin injection*[^93], and [amikacin injection[^264]] are indicated in the treatment of susceptible respiratory tract infections, including pneumonia and upper respiratory tract infections.

Skin and soft tissue infections, bacterial (treatment)—

*Cats: Gentamicin injection[^4-7; 123] and kanamycin injection[^93], and [amikacin injection[^119; 140; 264]] are indicated in the treatment of susceptible skin and soft tissue infections.*

*Dogs: Amikacin injection[^4-7], gentamicin injection[^4-7], and kanamycin injection[^93] are indicated in the treatment of susceptible skin and soft tissue infections. In the case of staphylococcal dermatitis, although the *in vitro* susceptibility of canine *Staphylococcus intermedius* to gentamicin is persistently high[^109–111], practical administration and toxicity considerations with long-term therapy have limited the usefulness of aminoglycosides[^9].


Urinary tract infections, bacterial (treatment)—

*Cats: Gentamicin injection[^4-7] and kanamycin injection[^93], and [amikacin injection[^119; 140; 264]] are indicated in the treatment of urinary tract infections, such as cystitis, caused by susceptible organisms.*

*Dogs: Amikacin injection[^4-7], gentamicin injection[^4-7], and kanamycin injection[^93] are indicated in the treatment of urinary tract infections caused by susceptible organisms.*

Uterine infections, bacterial (treatment)—

*Cats: Kanamycin injection[^93], [amikacin injection[^119; 140; 264]], and [gentamicin injection[^264]] are indicated in the treatment of endometritis in cats[^93].

*Dogs: Kanamycin injection[^93], [gentamicin injection[^7]], and [amikacin injection[^264]] are indicated in the treatment of uterine infections (metritis) in dogs caused by susceptible organisms.*

*Horses: Amikacin uterine solution[^1], gentamicin uterine infusion[^11], and gentamicin injection[^4-7] are indicated in the control of bacterial infections of the uterus caused by susceptible organisms.*

**ACCEPTANCE NOT ESTABLISHED**

Distemper, canine (treatment)—*Dogs: U.S. product labeling includes the use of kanamycin in the treatment of bacterial complications of canine distemper[^93]. This use may be appropriate for bacterial infections that are susceptible to kanamycin; however, it is not considered more appropriate or more generally accepted than other antimicrobials in the treatment of bacterial infections associated with viral infections.*

Gastrointestinal infections (treatment[^1]):

*Mastitis (treatment[^1]):

Otitis media (treatment[^1]): or

Pancreatitis (treatment)—*Cats and dogs: U.S. product labeling includes use in the treatment of gastrointestinal infections, mastitis, otitis media, and pancreatitis in cats and dogs[^93]; however, based on current knowledge about tissue penetration and pathogen susceptibility, there are more appropriate antibiotics for use in the treatment of these infections.*

Infections, bacterial (treatment)—

*Calves[^1] and [cattle[^2]]: The extralabel use of aminoglycosides in cattle has been strongly discouraged because of the long duration of drug residues in some tissues (see the Regulatory Considerations section). However, in the case of bacterial infections susceptible to gentamicin in cattle that will not be used for food production, there are pharmacokinetic data available to estimate dosing for amikacin in calves[^141; 144] and gentamicin in calves and cattle[^21; 22; 25]. Use of aminoglycosides should be restricted to susceptible bacterial infections caused by pathogens resistant to antimicrobials that are less likely to produce prolonged residues.*

*Donkeys[^1], [foals[^1]], [horses[^1]], and [ponies[^1]]: Although the safety and efficacy have not been established, amikacin has been recommended in the treatment of susceptible bacterial infections in donkeys, foals, horses (systemic administration), and ponies, based on pharmacokinetic studies[^110–112; 136; 137] and *in vitro* antimicrobial susceptibility of common pathogens[^159; 253]. Although the safety and efficacy have not been established, gentamicin has been recommended in the treatment of susceptible bacterial infections in foals and horses, based on pharmacokinetic studies[^115],[^40–52; 54; 55] and *in vitro* antimicrobial susceptibility of common pathogens[^159; 253].

*Minor species[^1]: Although the safety and efficacy have not been established, amikacin has been suggested for the treatment of susceptible bacterial infections in *African gray parrots[^150]*, *ball pythons[^155]*, *goats that will not be used for food production[^151]*, *gopher snakes[^154]*, *gopher tortoises[^156]*, *guinea pigs[^152]*, and *red-tailed hawks[^147]*, based on pharmacokinetic studies. Although the safety and efficacy have not been established, gentamicin has been suggested for the treatment of susceptible bacterial infections in the following species, if not used for food production: *baboons[^76]*, *badgers[^86]*, *buffalo calves[^78]*, *eagles[^88]*, *geese[^40]*, *hawks[^88]*, *llamas[^82]*, *owls[^88]*, and *pythons[^89]*, based on pharmacokinetic studies.*

Panleukopenia (treatment[^1]): or

Pneumonitis (treatment)—*Cats: U.S. product labeling includes the use of gentamicin in the treatment of secondary bacterial infections associated with panleukopenia in cats[^94] and the use of kanamycin in the treatment of bacterial complications of feline pneumonitis[^93]. These uses may be appropriate for bacterial infections that are susceptible to these medications; however, they are not considered more appropriate or more generally accepted than other antimicrobials in the treatment of bacterial infections associated with viral infections.*

*Leptospirosis (treatment)—*Cattle, dogs, and pigs: Canadian product labeling includes the use of dihydrostreptomycin in the treatment of leptospirosis in cattle, dogs, and pigs[^106]. Studies have shown that, while shedding of leptospires in the urine of cattle can be halted for at least 2 months by the administration of a single dose of dihydrostreptomycin, carriers are not necessarily eliminated[^244]. Equally effective alternative medicines exist.*

**UNACCEPTED**

*Mastitis (treatment)—*Cattle and pigs: Although some Canadian product labeling has listed the use of dihydrostreptomycin in the treatment of mastitis in cows and sows, there is no published evidence that this treatment is effective. Dihydrostreptomycin is irregularly distributed into milk when administered at the labeled dose[^247]. Another member of this drug family, gentamicin, has
been shown in some studies to be ineffective in the treatment of coliform mastitis[^R-259–260].

[Pneumonia (treatment)]—Calves and cattle: Although Canadian product labeling includes the use of dihydrostreptomycin in the treatment of bacterial pneumonia in calves[^R-106], there is no published evidence available pertaining to efficacy of this therapy. Such use is not recommended by the USP Veterinary Medicine Advisory Panel[^R-258] due to the lack of efficacy data and the potential for extended tissue withdrawal times.

[Uterine infections (treatment)]—

**Cattle:** Although Canadian product labeling has included the use of gentamicin uterine solution or gentamicin injection administered by the intrauterine route in the treatment of uterine infections in cattle[^R-7], this use is not recommended. Intrauterine gentamicin dosage regimens necessary to produce therapeutic concentrations in uterine tissue other than the endometrium can lead to significant systemic drug distribution and a risk of long-term tissue residues of gentamicin[^R-28–30].

**Dogs:** Although Canadian product labeling includes the use of gentamicin injection administered by the intrauterine route in the treatment of uterine infections in dogs, such use is not recommended[^R-258].

[^R-258]: Not included in Canadian product labeling or product not commercially available in Canada.

**REGULATORY CONSIDERATIONS**

**U.S.—**

Because drug residues can persist in some tissues for many months, the extralabel use of aminoglycosides in food-producing animals should be avoided when there are no established scientific data on residue depletion. A voluntary resolution against the administration of aminoglycosides to cattle has been instituted by the Academy of Veterinary Consultants, the American Association of Bovine Practitioners, the National Cattlemen’s Beef Association, and the American Veterinary Medical Association (AVMA)[^R-257]. The AVMA resolution states that, “Until further scientific information becomes available, aminoglycoside antibiotics should not be used in cattle, except as specifically approved by the FDA[^R-257].” At issue is the need for a clearer understanding of the complexity of aminoglycoside residue depletion for food-producing animals[^R-25; 32; 34; 36]. Drug residues can persist in some tissues for many months.

Gentamicin is not labeled for use in horses intended for food production. Neomycin is not labeled for use in veal calves.

Withdrawal times have been established for the use of apramycin sulfate powder for oral solution, gentamicin sulfate oral solution, and gentamicin sulfate powder for oral solution in pigs; dihydrostreptomycin injection in cattle and pigs; gentamicin injection in chickens, cows, piglets, and turkey poults; and neomycin sulfate oral solution and neomycin sulfate powder for oral solution in cattle, chickens, pigs, sheep, and turkeys. See the Dosage Forms section.

**CHEMISTRY**

**Source:**

Amikacin—Semi-synthetic; derived from kanamycin[^R-91].

Apramycin—Produced by fermentation of Streptomyces tenebrarius[^R-18; 96].

Gentamicin—Created from fermentation of Micromonospora purpurea[^R-1:5; 18].

Kanamycin—Produced through fermentation by Streptomyces kanamyceticus[^R-91].

Neomycin—The sulfate of an antibacterial substance produced by Streptomyces fradiae[^R-256].

Streptomycin—Prepared from fermentation of Streptomyces griseus, an actinomycete organism isolated from soil[^R-256].

**Chemical group:**

Amikacin, dihydrostreptomycin, gentamicin, kanamycin, neomycin, and streptomycin—Aminoglycoside antibiotics.

Apramycin—Aminocyclitol.

Note: The aminoglycosides are defined by their mechanism of action, binding with the 30S ribosomal subunit[^R-251]. The term aminocyclitol describes the structure of both the aminoglycosides and apramycin; however, the structure of apramycin differs just enough from other aminoglycosides that it may be listed as an aminocyclitol rather than specifically an aminoglycoside. It is very similar physicochemically to other aminoglycosides[^R-164].

**Chemical name:**

Amikacin sulfate—[(S)-3-amino-3-deoxy-alpha-D-glucopyranosyl-(1 → 6)-O-[6-amino-6-deoxy-alpha-D-glucopyranosyl(1 → 4)]-N^3(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy, (S)-, sulfate (1:2) (salt)[^R-18].

Apramycin—[(S)-3-amino-3-deoxy-alpha-D-glucopyranosyl(1 → 6)-O-[6-amino-6-deoxy-alpha-D-glucopyranosyl(1 → 4)]-2-deoxy, sulfate (1:1) (salt)[^R-18].

Dihydrostreptomycin sulfate—[Dihydrostreptomycin sulfate (2:3) (salt)][^R-18].

Gentamicin sulfate—A complex antibiotic substance formulated as sulfate salts, including aminosugars[^R-24]. Three major components, sulfates of gentamicin C1, gentamicin C2, and gentamicin C1A[^R-18] and minor components that are sometimes present, called A, B, B1, and X.

Kanamycin sulfate—[(S)-3-amino-3-deoxy-alpha-D-glucopyranosyl(1 → 6)-O-[6-amino-6-deoxy-alpha-D-glucopyranosyl(1 → 4)]-2-deoxy, sulfate (1:1) (salt)[^R-18].

Neomycin sulfate—Neomycin sulfate[^R-18].

Streptomycin sulfate—[(S)-3-amino-3-deoxy-alpha-D-glucopyranosyl(1 → 6)-O-[6-amino-6-deoxy-alpha-D-glucopyranosyl(1 → 4)]-N,N-bisaminominomethyl]-sulfate (2:3) (salt)[^R-18].

**Molecular formula:**

Amikacin sulfate—C_{27}H_{43}N_{6}O_{11}·2H_{2}SO_{4}[^R-18].

Apramycin—C_{21}H_{43}N_{6}O_{13}[^R-18].

Dihydrostreptomycin sulfate—[(C_{21}H_{43}N_{6}O_{12})_{2}·3H_{2}SO_{4}[^R-18].

Gentamicin—

Gentamicin C1: C_{21}H_{43}N_{6}O_{12}[^R-17].

Gentamicin C2: C_{20}H_{41}N_{6}O_{12}[^R-17].

Gentamicin C1A: C_{19}H_{39}N_{5}O_{12}[^R-17].
Kanamycin sulfate—C_{18}H_{36}N_{4}O_{11} \cdot \text{H}_{2}SO_{4} [R-18].
Streptomycin sulfate—(C_{21}H_{39}N_{7}O_{12})_{2} \cdot 3 \text{H}_{2}SO_{4} [R-18].

**Molecular weight:**
- Amikacin sulfate—781.76 [R-18].
- Apramycin—539.58 [R-19].
- Dihydrostreptomycin sulfate—1461.42 [R-18].
- Gentamicin—8.8 [R-254].

**Gentamicin sulfate—**
Gentamicin—781.76
Gentamicin C1: 477.61 [R-17].
Gentamicin C2: 463.59 [R-17].
Gentamicin C1a: 449.56 [R-17].

Kanamycin—7.2 [R-256].
Kanamycin sulfate—582.58 [R-18].

**Solubility:**
- Amikacin Sulfate USP—Freely soluble in water [R-19].
- Apramycin sulfate—Highly soluble in water and slightly soluble in the lower alcohols [R-96].
- Dihydrostreptomycin Sulfate USP—Freely soluble in water; practically insoluble in acetone, in chloroform, and in methanol [R-19].
- Gentamicin Sulfate USP—Freely soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether [R-19].
- Kanamycin Sulfate USP—Freely soluble in water; insoluble in acetone and in ethyl acetate [R-19].
- Neomycin Sulfate USP—Its solutions are dextrorotatory. Freely soluble in water; very slightly soluble in alcohol; insoluble in acetone, in chloroform, and in ether [R-19].
- Streptomycin Sulfate USP—Freely soluble in water, very slightly soluble in alcohol; practically insoluble in chloroform [R-19].

**PHARMACOLOGY/PHARMACOKINETICS**

**Note:** See also **Tables I and II** for this monograph.

**Mechanism of action/effect:**
Aminoglycosides—**Bactericidal** [R-107; 116]. Aminoglycosides enter susceptible bacteria by oxygen-dependent active transport (making anaerobes impervious to them) [R-107] and by passive diffusion [R-17]. Once the antibiotic has gained access, it binds irreversibly to a receptor protein on the 30S ribosomal subunit [R-5; 107] and blocks the formation of a complex that includes mRNA, formylmethionine, and tRNA [R-107]. As a result, the tRNA is translated incorrectly, producing a nonfunctional protein [R-107]. Aminoglycosides also disrupt protein synthesis by disruption of polysomes and may prevent the initiation of DNA replication [R-107].

Aminocyclitols—Apramycin is bactericidal. It also acts against bacteria by inhibiting protein synthesis at the ribosome level [R-96]. Like the aminoglycosides, it inhibits the translocation step of protein synthesis and induces translation errors [R-96].

**Absorption:**
- Intramammary administration—In cows with mastitis, gentamicin is well absorbed systemically following intramammary administration. With a single dose (1.1 mg per kg of body weight), concentrations of antibiotic in the serum (measured in one study up to 1.09 ± 0.15 mcg per mL) could result in prolonged tissue residues [R-26].
- Intramuscular or subcutaneous administration—Amikacin, dihydrostreptomycin, gentamicin, and kanamycin generally are rapidly and well absorbed from intramuscular and subcutaneous routes of administration [R-177; 230: 247].
- Intrauterine administration—Cows: In healthy cows, 39% of a total intrauterine dose of 2500 mg, administered once a day for 3 days, was absorbed systemically and produced serum concentrations of up to 6.6 mcg/mL [R-283]. In cows with endometritis, absorption was similar, with 36% of an intrauterine dose of 4 mg/kg of body weight administered once a day for 3 days absorbed systemically, producing peak serum concentrations of 6 to 11 mcg/mL [R-29]. A smaller total intrauterine dose of 225 to 275 mg produced plasma concentrations of 0 to 2.5 mcg/mL [R-30], while 70% of the dose administered remained in the lumen of the uterus [R-17; 10]. Because of the demonstrated intrauterine absorption of aminoglycosides, some clinicians have warned that intrauterine administration is likely to result in residues above regulatory limits in food-producing animals [R-60].

Oral administration—In general, aminoglycosides and apramycin are very poorly absorbed from oral administration in adult animals, including cattle, chickens, and pigs [R-46; 96; 166; 230]. However, 11% of an oral neomycin dose of 30 mg per kg of body weight (mg/kg) was absorbed in 3-day-old calves and 1 to 2% of the dose was absorbed by 2-month-old calves, regardless of ruminant status [R-238]. In very young calves, this absorption can be significant. When neomycin was administered orally to 2- to 4-day-old calves at a dose of 33 mg/kg for 14 days, absorption was significant enough to produce relatively high concentrations of drug in the kidneys (approximately 300 mcg per gram of tissue) [R-240]. Some absorption of apramycin has also been shown to occur in neonatal pigs [R-296]. Damage to the gastrointestinal mucosa can also lead to increased aminoglycoside absorption [R-166; 230]. Moderate enteritis from induction of coccidial infection in chickens caused a significant increase in absorption of a 43 mg/kg dose of apramycin for 5 days [R-166]. Serum concentrations were increased from 0.04 to 0.06 mcg/mL and tissue concentrations were also increased [R-166].

**Distribution:** Aminoglycosides are distributed primarily into the extracellular space [R-46] and over time accumulate in tissues [R-25]. The amount of antibiotic in most tissues appears to be dependent on the total dose administered over time rather than the size of each individual dose [R-25; 134]. Aminoglycosides do not distribute well across membrane barriers and, therefore, are not found at high concentrations in brain tissue, cerebrospinal fluid, ocular fluid, or respiratory secretions [R-20; 153; 230].
**AMINOGLYCOSIDES Veterinary—Systemic**

Systemic administration—

Otic tissue: Aminoglycosides concentrate in the perilymph of the inner ear. The damage to the ciliated cells can result in deafness; vestibular nerve injury may result as well.\(^{R-261}\)

Renal tissue: When aminoglycosides are administered systemically, the predominant site of drug accumulation is the renal cortex in most species tested, including cats, cattle, pigs, and sheep.\(^{R-20; 25; 34; 42; 67; 230}\) Therapeutic concentrations are also reached in other tissues and slow depletion from some tissues may prolong the presence of residues.\(^{R-25; 34; 42; 67; 230}\) For cats, cattle, pigs, and sheep, the following general relative gentamicin concentrations are reached over time with repeated doses, from highest to lowest concentrations: renal cortex: renal medulla: liver/lung/spleen: skeletal muscle.\(^{R-25; 34; 42; 67; 230}\) Renal proximal tissues actively take up and accumulate aminoglycosides by pinocytosis.\(^{R-265}\) Once within the tubular cells, the drug may cause dysfunction in lysosomes, mitochondria, proximal tubule cell plasma membrane phospholipids and enzymes, and glomerular filtration.\(^{R-17}\)

Other tissues:

**Cats:** Amikacin is distributed into uterine tissue so that tissue concentrations are about 25% of the current serum concentration.\(^{R-140}\)

**Horses:**

Amikacin—Amikacin is distributed into peritoneal fluid and synovial fluid in the horse with a peak of 13.7 ± 3.2 mcg/mL and 16.8 ± 8.8 mcg/mL, respectively, at the first sample, 1 hour after an intravenous dose of 6.6 mg per kg of body weight.\(^{R-117}\)

Gentamicin—Gentamicin is distributed into endometrial tissue so that tissue concentration is higher than plasma concentrations reached after 7 days of intramuscular therapy with a dose of 5 mg/kg every 8 hours.\(^{R-51}\)

Gentamicin is distributed into synovial fluid in normal horses to produce a peak of 6.4 mcg/mL at 2 hours with a single 4.4 mg/kg intravenous dose. However, local inflammation may increase drug concentrations in the joint and concentrations may increase with repeated doses.

Gentamicin is distributed into jejunal and colonic tissue with a maximum gentamicin concentration of 4.13 ± 1.8 mcg/mL measured in the colon at 0.5 hour after administration and 2.26 ± 1.35 mcg/mL measured in jejunum at 0.33 hour.\(^{R-59}\)

Intra-articular administration—**Horses:** Intra-articular administration of 150 mg of gentamicin resulted in a peak synovial concentration of 1828 ± 240 mcg/mL 15 minutes after administration.\(^{R-61}\) The intra-articular administration of buffered gentamicin produced more synovitis and higher gentamicin concentrations (2680 ± 1069 mcg/mL) than unbuffered gentamicin.\(^{R-61}\) However, synovial concentrations 12 hours later were very similar for buffered and unbuffered gentamicin. Synovial concentrations remained >10 mcg/mL for at least 24 hours.\(^{R-61}\) A peak plasma concentration of 0.69 mcg/mL at 15 minutes after intra-articular administration was measured; gentamicin was no longer detectable in plasma at 6 hours.

Intrauterine administration—**Horses:**

Amikacin—Intrauterine administration of a total dose of 2 grams produces a peak of greater than 40 mcg per gram of endometrial tissue within 1 hour after infusion.\(^{R-92}\) Twenty-four hours after infusion, 2 to 4 mcg of amikacin per gram of endometrial tissue is still present.\(^{R-92}\)

Gentamicin—Intrauterine administration of 2.5 grams of gentamicin once daily for 5 days resulted in endometrial tissue concentrations of 41.65 ± 17 mcg/gram 24 hours after the last dose.\(^{R-60}\) The addition of progesterone, administered concurrently, increased the sample to 100.33 ± 19.27 and the administration of estradiol concurrently with gentamicin increased the sample to 74.09 ± 8.6 mcg/gram.\(^{R-60}\) At the same time, measured serum concentrations of gentamicin peaked at 0.64 ± 0.06 for gentamicin administered alone; the concurrent administration of progesterone or estradiol increased gentamicin serum concentrations to a peak of 8.34 ± 1.34.\(^{R-60}\)

Regional limb perfusion—**Horses:** Amikacin—Regional intravenous perfusion of amikacin (125 mg diluted in 60 mL of electrolyte solution) into the distal limb of horses produced sufficiently high concentrations of antibiotic in local joint fluid, bone, and serum in the limb to be effective in the treatment of most susceptible organisms.\(^{R-267}\)

**Protein binding:**

Amikacin—Cows: 6% at a concentration of 5 to 150 mcg per mL of serum (mcg/mL).\(^{R-141}\)

Dihydrostreptomycin—

Cows: 8%, at a concentration of 2.5 to 5 mcg/mL.\(^{R-129}\)

Ewes: 12%, at a concentration of 2.5 to 5 mcg/mL.\(^{R-129}\)

Gentamicin—Horses and foals: < 30%.\(^{R-1; 47}\)

Kanamycin—Ewes: 0 to 4%, at a concentration of 2.5 to 5 mcg/mL.\(^{R-129}\)

Neomycin—

Cows: 45%, at a concentration of 5 to 10 mcg/mL.\(^{R-129}\)

Ewes: 50%, at a concentration of 5 to 10 mcg/mL.\(^{R-129}\)

Spectinomycin—Cows: 6%, at a concentration of 12.5 to 25 mcg/mL.\(^{R-129}\)

**Biotransformation:** In many species, aminoglycosides are eliminated in the form of the administered drug.\(^{R-96; 143; 150; 177; 180; 218}\) That is, they are not biotransformed.

**Elimination:** Parenterally administered aminoglycosides are predominantly excreted unchanged in the urine.\(^{R-96; 164; 177; 180}\) Only a small amount is excreted in the bile in some species, such as cattle.\(^{R-1}\)

For amikacin in dogs and gray parrots, gentamicin in calves, cows, horses, and sheep, and kanamycin in dogs, 75 to 100% of the dose is eliminated unchanged in the urine in the first 8 to 24 hours.\(^{R-1; 7; 20; 22; 32; 143; 150; 178; 204}\)

Because the kidney is the site of predominant accumulation and elimination of drug, the analysis of elimination seems straightforward. However, researchers have described a dose-dependent slow elimination phase (gamma phase) many times longer than the initial elimination phase.\(^{R-12}\) It is postulated that gentamicin is bound to tissues by one of at least two different processes so that some gentamicin is released quickly and gentamicin bound by another process is released more slowly.\(^{R-25; 32; 34; 36}\) It is not known if these processes are tissue-specific.

**PRECAUTIONS TO CONSIDER**

**PREGNANCY/REPRODUCTION**

Amikacin—

Dogs: Reproductive studies have not been performed in dogs.\(^{R-91}\)
**Horses:** No evidence was found of impaired fertility in mares given an intrauterine dose of 2 grams of amikacin 8 hours before natural breeding\(^{[R-92]}\). In *in vitro* studies, equine sperm exposed to 0.1 mg of benzethonium chloride per mL of solution, present in some amikacin products, showed impaired viability\(^{[R-92]}\). Product labeling recommends that mares not be bred for 8 hours after intrauterine treatment with amikacin\(^{[R-92]}\).

**Apramycin—** No adverse effects have been observed in laboratory animals pertaining to mutagenicity, teratology, or reproduction\(^{[R-90]}\).

**Dihydrostreptomycin—** *Bulls:* No effect was noted on spermatogenesis, seminal pH, ejaculate volume, percentage of motile spermatozoa, rate of spermatozoal motility, or concentration of spermatozoa from nine beef bulls on the third or seventh days after the second dose of 22 mg of dihydrostreptomycin per kg of body weight every 12 hours for two doses\(^{[R-242]}\).

**Gentamicin—**

- **Cats and dogs:** Reproductive studies have not been performed with gentamicin in cats and dogs\(^{[R-4]}\).
- **Horses:** Intrauterine treatment of mares with gentamicin is not recommended the day of breeding\(^{[R-4]}\).
- **Rats:** Otoxicity has been shown to be a risk even before the auditory organs have begun to function in developing rats\(^{[R-188]}\).

**LACTATION**

Because of poor lipid solubility, aminoglycosides have relatively poor penetration from plasma into milk\(^{[R-22; 26]}\). In general, parenteral administration of gentamicin has not been shown to produce therapeutic milk concentrations (greater than 3 to 5 mcg/mL) for the treatment of most gram-negative, non-mammary pathogens\(^{[R-22; 23; 25]}\). At any one time, approximately 10 to 15% of plasma gentamicin levels may appear in milk\(^{[R-22; 26]}\). Intramammary administration of gentamicin to cows with experimental mastitis results in significant systemic absorption (88%), leading to long persistence of drug residues in some tissues, such as renal tissue\(^{[R-23; 26]}\).

**Apramycin—**

- **Cows, goats, and sheep:** Apramycin has limited distribution from parenteral administration into milk in healthy glands\(^{[R-163]}\). It is distributed into bovine milk at higher concentrations during acute clinical mastitis, but it is not known if concentrations would be high enough to have clinical effect without significant residue and toxicity considerations\(^{[R-163]}\).

**Dihydrostreptomycin—**

- **Cows:** When administered at an intramuscular dose of 11 mg/kg, dihydrostreptomycin is irregularly distributed into the milk for at least 18 hours\(^{[R-242]}\).

**Gentamicin—**

- **Cows:** With an intramuscular dose of 5 mg/kg, a peak concentration of 1.5 to 1.8 mcg/mL is measured 2 to 6 hours after administration\(^{[R-22; 26]}\).

**PEDIATRICS**

The susceptibility of young animals to toxicity from aminoglycosides may be species-specific and drug-specific. Young dogs, rabbits, and rats have shown resistance to gentamicin nephrotoxicity in some studies\(^{[R-219; 268]}\), while 2- to 3-month-old foals may be more susceptible than adults to toxicity\(^{[R-208; 219]}\). The renal function of young rats, 21-days old, was more strongly affected by the administration of amikacin than was the renal function of adults given the same dose\(^{[R-192]}\).

Young animals typically have a higher percentage of extracellular water and, therefore, have a higher volume of distribution compared with adults. Higher doses may be necessary in animals less than 6 weeks old compared with adults\(^{[R-266]}\).

Very young animals may absorb significant amounts of orally administered apramycin or neomycin. See Absorption, above in this monograph.

**GERIATRICS**

In a case report study of dogs, advanced age of more than 8 years appeared to be a risk factor in susceptibility to gentamicin nephrotoxicity\(^{[R-215]}\). However, it is not known if these dogs had subclinical renal compromise, which is known to increase the nephrotoxicity of gentamicin\(^{[R-217]}\), or some other dysfunction associated with aging.

**DRUG INTERACTIONS AND/OR RELATED PROBLEMS**

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):

**Note:** Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Aminoglycosides, two or more concurrently\(^{[R-4; 91]}\) (concurrent administration may increase the risk of ototoxicity, nephrotoxicity, or neuromuscular blockade\(^{[R-4]}\))

**Calcium**

- Intravenous calcium supplementation may decrease nephrotoxicity associated with aminoglycosides in horses; 20 mg of intravenous calcium gluconate per kg of body weight administered every 12 hours decreased nephrotoxicity of high dose gentamicin [20 mg/kg every 8 hours for 14 days] administered to adult ponies\(^{[R-223]}\).

**Calcium channel blocker**\(^{[R-212]}\)

- (an increased risk of neuromuscular blockade may occur with concomitant administration with an aminoglycoside\(^{[R-212]}\))

**Halothane anesthesia**

- (horses administered gentamicin, 4 mg/kg, while under halothane anesthesia have significant changes in the pharmacokinetics of gentamicin; total body clearance and volume of distribution decrease while half-life of elimination increases; a longer gentamicin dosing interval after anesthesia may help correct for the changes, but serious consideration should be given to choice of another antimicrobial\(^{[R-204]}\))

**Iron, supplemental**

- (the risk of auditory and renal toxicity might be increased when aminoglycosides are administered with iron supplements; guinea pigs administered gentamicin at 100 mg/kg a day for 30 days showed a more rapid and profound hearing loss within the treatment period with concurrent administration of supplemental iron at a dose of 2 to 6 mg/kg a day; the effect was iron dose-dependent\(^{[R-198]}\); a study in rats showed increased renal tubular damage when gentamicin was administered at a dose of 100 mg/kg a day to rats given iron supplementation\(^{[R-202]}\))

**Ketorolac**\(^{[R-224]}\)

**Phenylbutazone**\(^{[R-203]}\), or Nonsteroidal anti-inflammatory drugs (NSAIDs), other (in the horse, concurrent administration of phenylbutazone with gentamicin affects the pharmacokinetics of gentamicin by decreasing the half-life of elimination by 23% and decreasing the volume of...
In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monograph, *Aminoglycosides (Systemic)* in *USP DI Volume I*: these drug interactions are intended for informational purposes only and may or may not be applicable to the use of aminoglycosides in the treatment of animals:

**Antimyasthenics**
(concurrent use of medications with neuromuscular blocking action may antagonize the effect of antimyasthenics on skeletal muscle; temporary dosage adjustments of antimyasthenics may be necessary to control symptoms of myasthenia gravis during and following use of medications with neuromuscular blocking action)

**Beta-lactam antibiotics**
(aminoglycosides can be inactivated by many beta-lactam antibiotics [cephalosporins, penicillins] *in vitro* and *in vivo* in patients with significant renal failure; degradation depends on the concentration of the beta-lactam agent, storage time, and temperature)

**Indomethacin, intravenous**
(when aminoglycosides are administered concurrently with intravenous indomethacin in the premature neonate, renal clearance of aminoglycosides may be decreased, leading to increased plasma concentrations, increased elimination half-lives, and risk of aminoglycoside toxicity; dosage adjustment of aminoglycosides based on measurement of plasma concentrations and/or evidence of toxicity may also be required)

**HUMAN LABORATORY VALUE ALTERATIONS**
In addition to the above laboratory value alterations, the following alterations have been reported in humans, and are included in the human monograph *Aminoglycosides (Systemic)* in *USP DI Volume I*: these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of aminoglycosides in animals:

**MEDICAL CONSIDERATIONS/CONTRAINDICATIONS**
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance).

*Except under special circumstances, this medication should not be used when the following medical problems exist:*

- Dehydration, hypovolemic
(concurrent and/or sequential use of these medications with aminoglycosides should be avoided since the potential for nephrotoxicity and/or neuromuscular blockade may be increased; neuromuscular blockade may result in skeletal muscle weakness and respiratory depression or paralysis [apnea]; caution is also recommended when methoxyflurane or polymyxins are used concurrently with aminoglycosides during surgery or in the postoperative period)
aminoglycoside to treat life-threatening infections while rehydration is in progress;[R-262]
» Hypersensitivity to aminoglycosides:[R-7; 92; 93]
  (a previous reaction to one aminoglycoside may contraindicate use of
  the same or other aminoglycosides due to cross-sensitivity)
» Renal dysfunction:[R-4; 91]
  (alternative antimicrobials should be considered in animals with
  severe renal compromise and/or renal azotemia:[R-4; 5]; because they
  lack the ability to compensate, even dogs with subclinical renal
dysfunction can develop nonreversible acute renal failure from a dose
that produces only mild polyuria in dogs with healthy kidneys:[R-213; 214]; if an aminoglycoside must be given, increasing the dosing interval
is more effective in preventing toxicity than decreasing the dose.[R-217]

Risk-benefit should be considered when the following medical problems exist:
Cardiac dysfunction:[R-5]
  (gentamicin may exacerbate a decreasing heart rate or depression of
  blood pressure:[R-5])
Endotoxemia
  (even a low serum concentration of endotoxin may increase the
toxicity of the aminoglycosides by increasing their concentration in
the kidneys:[R-184]; the administration of an aminoglycoside to treat
gram-negative bacterial infections may also increase the amount of
endotoxin released:[R-184]; see the Veterinary Dosing Information
section)
Hypocalemia
  (although the clinical impact is not clear, aminoglycosides, including
dihydrostreptomycin and neomycin, have been shown to decrease
the total blood calcium concentration in cattle through decreasing
the protein-bound calcium:[R-187]; this effect caused signs of hypo-
calemia in 77% of lactating cows treated with 4.5 mg of
intravenous neomycin per kg of body weight:[R-187])
Potential risk factors for acute renal failure:[R-185; 215], other, including
Acidosis
  Advanced age
  Diabetes mellitus
  Dirofilarial infection:[R-91]
  Electrolyte imbalances
  Fever
  Sepsis
  Hepatic dysfunction
  Hyperviscosity syndromes
  Hypoalbuminemia
  Hypotension
  Septicemia
  Trauma, severe
  (level of risk of nephrotoxicity with administration of aminogly-
cosides can be difficult to assess, but caution is indicated in
animals with one or several factors associated with increased risk,
such as those affecting renal perfusion)
Pyelonephritis:[R-226]
  (rats with infected kidneys are more susceptible to gentamicin
toxicity than healthy rats:[R-226])

PATIENT MONITORING
The following may be especially important in patient monitoring (other
tests may be warranted in some patients, depending on condition; *=
major clinical significance):

Aminoglycoside, serum concentration
  (because of the risk of nephrotoxicity and the wide variability in drug
disposition, it is recommended that, whenever possible, serum amino-
glycoside concentration should be monitored in animals receiving
repeated doses, and dosage adjustments made:[R-55; 56]; when multiple
dosing is done in a 24-hour period, peak and trough concentrations have
been considered the most helpful with the least number of tests:[R-57].
With once-daily dosing, serum concentrations are more typically
measured at 1 and 2 hours or 2 and 4 hours after the daily dose:[R-266].
Many sources recommend serum concentrations be allowed to drop
below 1 mcg/mL for gentamicin and below 2.5 to 5 mcg/mL for amikacin
or kanamycin for an extended period within a dosing interval to reduce
the risk of toxicity.[R-47; 51; 63; 148; 185; 209; 210]

Renal function tests:[R-4; 91]
  (serial urinalyses may be the most sensitive tests for renal toxicosis in
spite of the fact that no early urinary test has been developed that can
consistently warn clinicians when serious renal toxicity occurs; serial
urinalyses may be monitored for decreased specific gravity in the
absence of fluid therapy or appearance of casts, protein, albumin,
glucose, or blood in the absence of leukocytes and bacteria:[R-4; 208];
proteinuria may be seen within 24 hours with extremely high toxic
doses:[R-206]; early indication of nephrotoxicity may be possible with
the ratio of urinary gamma glutamyltranspeptidase to urinary creatinine excretion [UGGT/UCr]; this enzyme concentration ratio is
increased to three times the baseline within 2 to 3 days of a
nephrototoxic gentamicin dose of 30 mg/kg[R-206; 209; 210; 211],
however, because even a single dose of gentamicin can cause some
renal tubule changes, elevations in the UGGT/UCr ratio may occur
without subsequent severe kidney damage; therefore, some clinicians
believe that other tests may be needed to decide if gentamicin therapy
must be discontinued:[R-210; 220; 221]; serum creatinine, creatinine
clearance tests, specific gravity, blood urea nitrogen and/or clinical
signs of nephrotoxicity may not be diagnostic of severe kidney damage
for at least 7 days:[R-4; 206; 210; 216]

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their
potential clinical significance (possible signs and, for humans, symp-
toms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence more frequent
All species
Nephrotoxicity:[R-7; 212]; ototoxicity, auditory; ototoxicity, vestibular
Note: Evidence of physiological effects on the kidneys has been demon-
strated with a single dose of gentamicin at 15 mg per kg of body
weight (mg/kg) in 5-month-old beagles, although clinical disease is not
necessarily produced.[R-209; 212] It is assumed that renal damage
associated with aminoglycoside administration runs a range from
mild, subclinical changes to more severe nephrotoxicity, to acute renal
failure:[R-4; 209; 212]. The animal’s ability to recover most likely
depends on the type of medication exposure and the amount of healthy
renal tissue remaining to compensate:[R-213]. Neomycin is considered
the most nephrotoxic aminoglycoside, dihydrostreptomycin and
streptomycin the least nephrotoxic, and the other common aminogly-
cosides included in this monograph are considered somewhere
between those three drugs in their toxicity.[R-254]. Aminoglycoside

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administration is, as a rule, immediately withdrawn when evidence of renal damage is found; however, many signs of toxicity may be delayed for some time after significant damage has occurred.

Although renal toxicity is dependent on the concentration of aminoglycoside in the renal cortex, many variables can affect how much of the medication reaches the cortex and how serious the effects will be, making it difficult to consistently predict which animal is likely to develop clinical toxicity with a particular therapeutic dosage regimen.

Aminoglycosides cause nephrotoxicity by accumulating in the proximal tubular cells and, once there, interfering with cellular metabolism and transport processes.\(^{[R-218; 225]}\) The tubular changes can progress to proximal tubular necrosis with increasing exposure to the drug. Fairly late in the process, glomerular filtration rate is affected and azotemia appears.\(^{[R-225]}\) These changes may simultaneously occur at different rates in different parts of the renal cortex, making it possible to have both reabsorption defects and glomerular filtration rate reduction at the same time.\(^{[R-225]}\)

The toxic renal changes caused by gentamicin and other aminoglycosides will decrease elimination of the antibiotic and increase serum antibiotic concentrations, thereby increasing the potential toxicity.\(^{[R-57; 209]}\) Elimination half-lives of 24 to 45 hours have been reported in the horse with renal toxicity, prolonging the toxic exposure to the drug.\(^{[R-57]}\) While peritoneal dialysis is useful in lowering creatinine and blood urea nitrates, it may not be effective in significantly speeding the elimination of the accumulating aminoglycoside.\(^{[R-57]}\) If there is enough healthy tissue remaining in the kidneys, acute renal failure may be reversible by regeneration and hypertrophy of remaining tissue.\(^{[R-191; 213]}\) Dogs with subclinical renal dysfunction are more sensitive to the toxicity of gentamicin; they develop oliguria and acute renal failure that may not be reversible from a high gentamicin dose that produces only mild polyuria in dogs with healthy kidneys.\(^{[R-213; 214]}\) Therefore, merely adjusting dosage regimens to compensate for renal dysfunction may not be sufficient to avoid toxicity. Careful selection of candidates for aminoglycoside therapy and a dosage regimen designed to minimize risk of nephrotoxicity is recommended.

Some aminoglycosides are more likely to cause auditory ototoxicity and others are more likely to cause vestibular ototoxicity.\(^{[R-4; 7]}\) This may be due to the distribution characteristics of each drug and its ability to concentrate in each sensory organ.\(^{[R-183]}\) As demonstrated in studies on guinea pigs,\(^{[R-183; 190]}\) amikacin, kanamycin, and dihydrostreptomycin are more toxic to the cochlea than to vestibular organs.\(^{[R-183; 190; 191; 233]}\) Neomycin causes severe cochlear toxicity.\(^{[R-233]}\) Studies in guinea pigs have shown that auditory toxicity is often delayed,\(^{[R-189]}\) requiring at least 4 days after administration of a toxic dose for hearing loss to be measurable.\(^{[R-189]}\) This period of delay may shorten with higher doses.\(^{[R-189]}\) Vestibular toxicity is more often seen than auditory toxicity with streptomycin.\(^{[R-233]}\)

Incidence less frequent or rare

**Neuromuscular blockade**\(^{[R-7]}\)

Note: Neuromuscular paralysis is considered rare compared with the nephrotoxic and otoxic effects of aminoglycosides.\(^{[R-232]}\) The neuromuscular blocking effects of dihydrostreptomycin, gentamicin, kanamycin, neomycin, and streptomycin at a dose of 14 to 43 mg per kg of body weight have been demonstrated during pentobarbital anesthesia (28 to 32 mg per kg of body weight [mg/kg]) in nonhuman primates.\(^{[R-186]}\) However, respiratory depression and apnea occurred only at the highest antibiotic dosages.\(^{[R-186]}\) Neuromuscular blockade and respiratory paralysis have been reported in response to high doses of gentamicin (40 mg/kg) in the cat.\(^{[R-7]}\) The postsynaptic blocking component of this effect can be reversed by a cholinesterase inhibitor, such as neostigmine, and the apparent presynaptic effect can be antagonized by the administration of calcium.\(^{[R-186]}\)

**Diarrhea**\(^{[R-91]}\) with amikacin,\(^{[R-91]}\) vomiting with amikacin

Incidence unknown

**Calves and pigs**

**Diarrhea**—seen in animals given oral doses of apramycin or neomycin that are higher than the label dose.\(^{[R-96; 241]}\)

**Cats**

**Local tissue trauma, mild**—at site of intramuscular injection with amikacin.\(^{[R-93; 139]}\)

**Dogs**

**Local tissue trauma, mild**—at site of injection, with amikacin or gentamicin.\(^{[R-5; 91; 93]}\)

**HUMAN SIDE/ADVERSE EFFECTS**\(^{[R-255]}\)

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Aminoglycosides (Systemic) in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of aminoglycosides in the treatment of animals:

Incidence more frequent

**Nephrotoxicity; neurotoxicity; otoxicity, auditory; otoxicity, vestibular; peripheral neuritis**—only with streptomycin

Incidence less frequent

**Hypersensitivity; optic neuritis**—only with streptomycin

Incidence rare

**Endotoxin-like reaction**—gentamicin only; neuroparalytic blockade

Note: Neuromuscular blockade, respiratory paralysis, otoxicity, and nephrotoxicity may occur following local irritation or topical application of aminoglycosides during surgery. Because of its potential toxicity, use of parenteral neomycin is not recommended.

**OVERDOSE**

For more information on the management of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888–426–4435 or 900–443–0000; a fee may be required for consultation) and/or the drug manufacturer.
GENERAL CONSIDERATIONS

When systemically absorbed, the aminoglycosides have the potential to cause nephrotoxicity, neurotoxicity, or ototoxicity. This includes absorption through irrigation of tissues in surgery and sometimes from topical application. Because of the narrow therapeutic index, the margin between therapeutic concentrations and toxic concentrations, for aminoglycosides used in animals, toxicity is a potential risk in the best of circumstances. The minimum gentamicin dose required to produce nephrotoxicity is variable between species and between animals and the data listed in this section cannot clearly define the dose that will produce serious toxicity in a particular animal.

Toxic dose—Information about toxicity of the aminoglycosides has been drawn primarily from human therapeutic literature. It has been reported that minimum serum concentrations within a dosing interval of greater than 2 mcg/mL for gentamicin and greater than 2.5 to 5 mcg/mL for amikacin or kanamycin significantly increase the risk of toxicity. Persistent peak serum concentrations of gentamicin greater than 10 to 12 mcg/mL and of amikacin or kanamycin greater than 30 to 40 mcg/mL are also considered to increase the risk of toxicity.

Amikacin:

**Dogs**—Renal toxicity: Minimal to mild renal changes are seen with a dose of 45 mg per kg of body weight (mg/kg) a day for 2 weeks or 30 mg/kg a day for 90 days.

**Guinea pigs:** Auditory and vestibular ototoxicity—Marked hearing loss—150 to 225 mg/kg a day in divided doses every 8 hours for 1 week. Hearing loss, less pronounced—When the 150 mg/kg dose was administered every 24 hours for 7 to 21 days, there was a significant decrease in vestibular and auditory damage.

**Apramycin:**

**Chickens**—

No effect: With a dose of 50 mg per kg of feed, fed as the only ration, no toxic signs are noted.

With a dose of 150 to 250 mg per kg of feed, a reduction in serum hemoglobin and erythrocytes may be noted, as well as dystrophic changes in the internal organs.

**Dogs**—No effect: Chronic administration yielded no toxicity with 50 parts per million (ppm) fed to dogs for 1 year.

**Pigs**—

No effect: With a dose of up to 300 mg per liter of drinking water for 15 days, no signs of toxicity were noted.

With a dose of 500 to 1000 mg per liter of drinking water (5 to 10 times the label dose) for more than 15 days, some animals developed a drop in the percentage of neutrophils and an increase in lymphocyte percentage in the complete blood count.

**Rats**—No effect: Chronic administration yielded no toxicity with 10,000 ppm fed to rats for 2 years.

Gentamicin: Renal—

**Cats**—

No significant effect—A dose of 4.4 mg/kg every 12 hours for 12 days produced no significant effects.

Toxic effect—Only mild nephritis was produced by 20 mg/kg a day administered subcutaneously for 70 days.

**Dogs**—Toxic effect—A parenteral dose of 30 mg/kg a day for 10 days (or 10 mg/kg every 8 hours for 8 days) produced evidence of renal toxicity, including elevated serum urea nitrogen concentration, elevated serum creatinine, proteinuria, decreased urine specific gravity, decreased exogenous creatinine clearance, decreased glomerular filtration rate, and histological evidence of renal toxicity.

**Foals**—Toxic effect—Nephrotoxicity occurred in one of twelve foals given 17.6 mg/kg every 12 hours and one of twelve given 8.8 mg/kg every 12 hours for 15 days.

**Hawks, red tailed**—Toxic effect—An intravenous dose of 10 mg/kg every 12 hours for 4 days caused significantly increased serum uric acid concentrations.

**Lambs**—Toxic effect—An intravenous dose of 80 mg/kg a day for up to 20 days produced renal tubular necrosis and dilation.

Serum creatinine concentrations of up to 132 micromoles per liter were measured beginning 14 days, on average, after initiation of therapy.

**Kanamycin:**

**Dogs**—Toxic effect: A single dose of 100 mg/kg administered to three dogs caused a transient decrease in auditory perception in one dog as measured by auditory brain stem responses. Administration of 100 mg/kg daily for 9 weeks caused a complete loss of hearing for high-frequency tone, although changes did not begin until about 2 weeks after the beginning of therapy.

**Streptomycin:**

**Cats**—

No effect: A dose of 25 mg/kg a day, administered for 9 to 28 days, did not cause signs of toxicity.

Toxic effect: An intramuscular dose of 50 mg/kg a day, divided into doses administered every 8 hours for 9 to 28 days, produced nonreversible hearing loss in most cats. A dose of 200 mg/kg produced both permanent hearing loss and vestibular impairment.

**Lethal dose**

Note: These doses have been reported as lethal but are not necessarily the minimum lethal dose in a particular animal. No effect is listed if the research was intended to define a lethal dose.

**Amikacin:** LD₅₀—**Dogs:** Intramuscular or intravenous, >250 mg/kg.

**Mice**—In mice, greater than 5200 mg/kg as a single dose produced no mortality.

**Gentamicin:**

**Cats**—40 to 70 mg/kg a day administered subcutaneously caused renal necrosis and death within 10 days.

**Hawks, red-tailed**—An intravenous dose of 20 mg/kg every 12 hours was lethal for all five birds in 2 to 6 days; predominant signs were indicative of neuromuscular blockade.

**CLINICAL EFFECTS OF OVERDOSE**

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: The following overdose effects mirror the side/adverse effects listed in this monograph because of the small therapeutic index for
aminoglycosides. These effects may occur in some animals with therapeutic doses so that most animals treated should be monitored for adverse effects. These are also dose-related effects, however, with risk increasing as the dose rises above recommended levels.[87]

**All species**

**Nephrotoxicity**[87; 212]; **neuromuscular blockade; ototoxicity; auditory; ototoxicity, vestibular**

### TREATMENT OF OVERDOSE

Recommended treatment consists of the following:

**Note:** Some experts suggest that administration of a beta-lactam antibiotic that binds an aminoglycoside (ticarcillin, for example) will decrease the toxicity after accidental overdose of aminoglycosides.[86]

For **neuromuscular blockade**

- Administration of edrophonium, 0.5 mg/kg, will reverse neuromuscular blocking effects[200; 201]. Administration of calcium chloride at 10 to 20 mg/kg, calcium gluconate at 30 to 60 mg/kg, or neostigmine at a dose of 100 to 200 mcg per kg of body weight can also reverse muscle response depression and associated dyspnea.[186]

For **renal toxicity**

- Aminoglycoside administration should be immediately discontinued[200].
- Polyionic electrolyte fluid therapy should be initiated to stimulate diuresis[208].

**Note:** Three or more weeks of therapy may be required for recovery in animals with sufficient remaining renal tissue to compensate. Oliguria may be a poor prognostic sign.[215].

### CLIENT CONSULTATION

There are reports that aminoglycosides, such as neomycin or streptomycin, can cause contact dermatitis in human beings.[236]. Direct contact with skin should be avoided by people handling these products.[236].

### VETERINARY DOSING INFORMATION

**Resistance:** Reports of antimicrobial resistance support recommendations to culture pathogens to be sure the use of an aminoglycoside is warranted. There is also some evidence that limiting the use of aminoglycosides and, in particular, limiting administration at subtherapeutic concentrations to a population of animals may limit the increase in E. coli resistance that is seen with more intense antimicrobial use.[234].

### FOR PARENTERAL DOSAGE FORMS ONLY

Systemic aminoglycosides are generally dosed to achieve a high peak serum concentration followed by a period of subtherapeutic serum concentration. This strategy is built on several factors:

1. **Aminoglycosides kill bacteria by a concentration-dependent mechanism**[80] rather than dependence on the length of time the organism is exposed to the antibiotic.[160]. A spike in concentration[80; 232] or, in some situations, a plateau[155; 157] above the minimum inhibitory concentration is neccessary for effective bacterial killing.

2. **A high peak of antibiotic will cause the most killing of bacteria and will also cause the most prolonged postantibiotic effect (PAE), in which pathogen growth is inhibited after the serum concentration falls below minimum inhibitory concentrations.[80].** The PAE has been shown to occur when amikacin or gentamicin is administered to treat gram-negative infections.[174]. Postantibiotic effect may be evidence that exposure to a high concentration of antimicrobial causes cellular changes in the pathogen that will inevitably cause death after drug concentrations have dropped below the MIC.[158]. The PAE may be shortened in neutropenic animals but prolonged in animals with renal impairment.[174].

3. **An extended period of serum drug concentrations below a minimum amount is expected to decrease the risk of aminoglycoside toxicity.** Dosing is usually designed to produce peaks above the MIC and troughs below a minimum concentration to prevent adverse effects, regardless of the frequency of dosing within a 24-hour period. Many sources recommend serum concentrations be allowed to drop below 2 mcg/mL for gentamicin and to less than 2.5 to 5 mcg/mL for amikacin or kanamycin for an extended period within a dosing interval to reduce the risk of toxicity.[47; 51; 63; 148; 185; 209; 210] A plasma or serum concentration of at least 8 to 10 times the MIC of the organism has been recommended for the aminoglycoside antibiotics to be effective.[155].

**Individualized dosing/Patient monitoring:** Even within the same species, individual animals can differ widely in the serum concentrations produced from the same dosage regimen[83; 89; 211; 230]. When this relative unpredictability is combined with the often small difference between therapeutic and toxic serum concentrations of aminoglycosides, the determination of serum concentrations in a particular animal becomes very valuable. When it is economically possible to measure plasma or serum concentrations during aminoglycoside therapy, the information can be used to maximize efficacy and minimize toxicity[110; 132].

**Note:** There can be up to a fourfold difference between avian species in the elimination of gentamicin.[85]. It is recommended that species-specific pharmacokinetic data be used to develop dosing for birds, if at all possible.[148].

**Once daily dosing:** The continuing effort to maximize therapeutic effect and minimize toxic effect of aminoglycosides has led to ongoing research on the efficacy of a 24-hour dosing interval.[160; 232; 252]. Dosing once a day is considered by some clinicians to be a rational use of aminoglycosides in specific situations.[232]. The supporting arguments include that use of the highest safe single dose has been linked to increased efficacy in human studies, greater bacterial killing and a longer postantibiotic effect are expected with a higher peak concentration, and once-a-day dosing allows for the longest period of low serum concentration to minimize toxicity.[160; 232; 252].

Concern has been expressed that dosing once every 24 hours may be less effective than repeated daily dosing in some situations, such as in immunocompromised patients.[158]. Studies with guinea pigs have demonstrated no significant difference in bacterial killing between gentamicin administered subcutaneously at 6 mg/kg every 24 hours versus 2 mg/kg every 8 hours.[80]. However, once-a-day dosing has been less effective in treating some infections in neutropenic animals.[158; 232]. Some researchers have demonstrated a potential for development of resistance with dosing once a day[232], but others have described an adaptive resistance to aminoglycosides in *Pseudomonas* species that occurs with doses repeated within 16 hours in animal models but that is reduced by longer dosing intervals in the first 3 days.[160]. Some clinicians have expressed reservations about once-daily dosing when intestinal damage allows continued exposure to...
bacteria that may replicate during the prolonged periods of subtherapeutic aminoglycoside concentration\textsuperscript{[R-263]}. Desired benefits include reduction of toxicity. If the total daily dose of aminoglycoside is kept constant, less frequent dosing per day is associated with decreasing renal toxicity\textsuperscript{[R-232, 212]}. The same is true for gentamicin ototoxicity in guinea pigs but, while the single daily dose has not been shown to be more toxic for amikacin or kanamycin, the benefit in reducing ototoxicity is less clear for amikacin or kanamycin in guinea pigs\textsuperscript{[R-190, 191, 212]}. 

**Renal dysfunction:** Treatment with gentamicin every 8 hours is not recommended in patients with subclinical renal disease\textsuperscript{[R-72]}. Because drug clearance may be slowed with gentamicin treatment, the risk of nephrotoxicity may be increased. Trough serum concentrations can be reduced by increasing the dosing interval and decreasing the dose\textsuperscript{[R-185]}. Some clinicians have developed methods to calculate an increased dosing interval based on the creatinine clearance concentration; however, the most prudent course may be to avoid use of aminoglycosides if it is necessary to significantly reduce the aminoglycoside dose because of poor renal function\textsuperscript{[R-72]}. 

**Endotoxemia:** Producing high serum and tissue concentrations of aminoglycoside as early as possible in animals with gram-negative sepsis is important\textsuperscript{[R-72]}. The release of endotoxin by gram-negative organisms may be enhanced by administration of the antibiotic\textsuperscript{[R-184]}. The systemic effects of endotoxemia will also increase the risk of concentrating aminoglycosides in the renal tissue and causing acute renal failure\textsuperscript{[R-185]}. 

**Diabetes mellitus:** It appears that diabetic dogs may have increased clearance of gentamicin and reduced volume of distribution (V\textsubscript{D(app)}) of gentamicin, which make them less susceptible to nephrotoxicity at therapeutic doses of the medication\textsuperscript{[R-71]}; however, the possibility of subclinical renal disease should also be considered. 

**Concurrent fluid administration:** In horses, the administration of therapeutic fluids, similar to those that are used in the treatment of colic, does not significantly change the pharmacokinetics of concurrently administered gentamicin\textsuperscript{[R-45]}. 

**Gastrointestinal microflora:** Parenterally administered amikacin appears to have minimal effect on gastrointestinal microflora in horses\textsuperscript{[R-116]}. 

**Gastrointestinal surgery:** When gentamicin administration (4 to 6.6 mg/kg every 24 hours) is begun immediately after abdominal surgery for naturally occurring colic, the pharmacokinetics of the gentamicin has been measured to be within the reference range for normal healthy horses\textsuperscript{[R-266]}. 

**FOR ORAL DOSAGE FORMS ONLY** 

**Chickens:** Because poultry litter may contain bacteria with multiple antibiotic resistance, treatment of litter to prevent contamination before reutilization in soil or bedding is recommended\textsuperscript{[R-121]}. 

**DIET/NUTRITION** 

**Dogs:** Dogs with normal renal function consuming a higher protein diet (26%) for 3 weeks before treatment have a faster gentamicin clearance and a larger volume of distribution than dogs fed a medium (13%) or low (9%) protein diet\textsuperscript{[R-73]}. 

**Horses:** Horses fed an alfalfa diet rather than oats alone have a smaller degree of nephrotoxicosis from administration of gentamicin\textsuperscript{[R-222]}. Likewise, horses administered supplemental calcium gluconate, 20 mg/kg every 12 hours, have a decreased risk of acute renal failure from gentamicin overdose compared with horses not receiving calcium\textsuperscript{[R-223]}. 

**Sheep:** Sheep fed a low protein diet (straw and barley) have a significantly lower total clearance and volume of distribution at steady state than sheep fed a high protein diet (alfalfa and barley). This results in an increased serum concentration of gentamicin in the group fed a low protein diet\textsuperscript{[R-18]}.

**AMIKACIN**

**SUMMARY OF DIFFERENCES** 

**Category:** Aminoglycoside 

**Indications:** General considerations—Has the broadest spectrum of activity of the aminoglycosides and is considered effective against strains not susceptible to other aminoglycosides. 

**Side/adverse effects:** Intermediate renal toxicity. More toxic to the cochlea than to vestibular organs. Diarrhea and vomiting in dogs. Mild local tissue trauma in cats and dogs. 

**MUCOSAL DOSAGE FORMS** 

**AMIKACIN SULFATE UTERINE SOLUTION** 

**Usual dose:** Uterine infections—**Horses:** Intrathecal, 2 grams, administered every twenty-four hours for three days\textsuperscript{[R-92, 105, 118]}. The medication should be mixed with 200 mL of 0.9% sodium chloride injection before administration\textsuperscript{[R-92]}. 

**Note:** Product labeling recommends that mares not be bred for eight hours after intrauterine treatment with amikacin\textsuperscript{[R-92]}. 

**Strength(s) usually available**\textsuperscript{[R-231]; U.S.—} 

**Veterinary-labeled product(s):** 

250 mg per mL (Rx) \textsuperscript{[R-92]}; Amikacin E Solution; AmTech AmiMax E Solution; EquiGlide; Phar EquiGlide; generic. 

**Note:** These products contain 0.1 mg benzethonium chloride per mL as a preservative\textsuperscript{[R-92]}. 

**Canada—** 

**Veterinary-labeled product(s):** 

250 mg per mL (Rx) \textsuperscript{[Amikase-V]}. 

**Withdrawal times:** U.S. and Canada—Product is not labeled for use in horses to be used for food production\textsuperscript{[R-92]}. 

**Stability:** A change from a colorless solution to pale yellow in color does not indicate a decrease in potency of the antimicrobial\textsuperscript{[R-92]}. 

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. 

**USP requirements:** Not in USP\textsuperscript{[R-19]}. 

**PARENTERAL DOSAGE FORMS** 

**Note:** Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.
AMIKACIN SULFATE INJECTION USP

Note: Intravenous administration—When amikacin is administered by the intramuscular or subcutaneous route, it is rapidly and completely absorbed. Although not always listed on product labeling, this medication is also commonly administered intravenously. An indwelling catheter is used for convenience and to minimize the discomfort of repeated dosing.\[263\]. To further decrease the risk of neuromuscular blockade, it is recommended that the drug be diluted in saline or administered slowly.\[263\].

**Usual dose:**

- **Bacteremia**\[1\];
- **Bone and joint infections**\[1\];
- **Respiratory tract infections**\[1\];
- **Septicemia**\[1\];
- **Skin and soft tissue infections**\[1\];
- **Urinary tract infections**\[1\]; or
- **Uterine infections**\[1\]—**Dogs:**
  - Intramuscular or subcutaneous, 10 mg per kg of body weight every eight to twelve hours.\[R-91; 143\].
  - Once-daily dosing—Intramuscular or subcutaneous, 15 to 30 mg per kg of body weight every twenty-four hours.\[R-266\].
- **Bacteremia**\[1\];
- **Bone and joint infections**\[1\];
- **Respiratory tract infections**\[1\];
- **Septicemia**\[1\];
- **Skin and soft tissue infections**\[1\];
- **Urinary tract infections**\[1\]; or
- **Uterine infections**\[1\]—**Cats:**
  - Intramuscular or subcutaneous, 10 mg per kg of body weight every eight hours.\[R-139; 140; 264\].
  - Once-daily dosing—Intramuscular or subcutaneous, 10 to 15 mg per kg of body weight every twenty-four hours.\[R-266\].

Note: **Calves**\[1\]—Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations should be considered before the extra-label use of aminoglycosides in food-producing animals: Although the safety and efficacy of amikacin have not been established, a dose of 12 mg per kg of body weight every twelve hours has been suggested for use in the treatment of susceptible bacterial infections.\[R-134; 144\].

- **Donkeys**\[1\] and **ponies**\[1\]—Although the safety and efficacy of amikacin have not been established, a dose of 6 mg per kg of body weight every six hours, administered intravenously, has been recommended in the treatment of bacterial infections in donkeys and ponies.\[R-136\].
- **Foals, less than 30 days of age**\[1\]—Although the safety and efficacy of amikacin have not been established, a dose of 20 to 25 mg per kg of body weight every twenty-four hours, administered by the intramuscular or intravenous route, has been recommended in the treatment of susceptible bacterial infections in foals.\[R-110; 112; 134; 266; 271\].
- **Goats**\[1\]—AMDUCA regulations should be considered before the extra-label use of aminoglycosides in food-producing animals: Although the safety and efficacy of amikacin have not been established, a subcutaneous dose of 8 mg per kg of body weight every twelve hours has been suggested in the treatment of susceptible bacterial infections in goats.\[R-151\]. In one study, this was predicted to provide peak serum concentrations of 32.3 mcg/mL.\[R-151\].
- **Guinea pigs**\[1\]—Although the safety and efficacy of amikacin have not been established, an intramuscular dose of 15 mg per kg of body weight every twelve hours has been suggested for the treatment of susceptible bacterial infections in guinea pigs.\[R-152\].
- **Hawks, red-tailed**\[1\]—Although the safety and efficacy of amikacin have not been established, a dose of 15 to 20 mg per kg of body weight every twenty-four hours or 7 to 10 mg per kg of body weight every twelve hours, administered intramuscularly, has been suggested for the treatment of susceptible bacterial infections in red-tailed hawks.\[R-147\]. This recommendation is based on pharmacokinetic data. In this study, it was also noted that larger birds tended to develop lower peak serum drug concentrations than smaller birds in response to the same dose.\[R-147\].
- **Horses**\[1\] and **foals, more than 30 days of age**\[1\]—Although the safety and efficacy have not been established, an intramuscular or intravenous dose of 10 mg per kg of body weight every twenty-four hours has been recommended in the treatment of susceptible bacterial infections, based on pharmacokinetic data.\[R-6\]. For some infections in horses, dosing more than once a day may still be necessary and, in those cases, an intravenous dose of 6 mg per kg of body weight every eight hours has been recommended.\[R-146\].
- **Parrots, African gray**\[1\]—Although the safety and efficacy of amikacin have not been established, an intramuscular or intravenous dose of 10 to 20 mg per kg of body weight every eight to twelve hours has been recommended in the treatment of susceptible bacterial infections, based on pharmacokinetic data.\[R-150\].
- **Pythons, ball**\[1\]—Although the safety and efficacy of amikacin have not been established, an intramuscular dose of 3.48 mg per kg of body weight as a single dose has been recommended in the treatment of susceptible bacterial infections in ball pythons.\[R-155\]. It has also been recommended that snakes be kept at the high end of their preferred temperature range (37 °C to maximize distribution of drug in the body).\[R-154\].
- **Snakes, gopher**\[1\]—Although the safety and efficacy of amikacin have not been established, an intramuscular loading dose of 5 mg per kg of body weight, followed by 2.5 mg per kg of body weight every seventy-two hours has been suggested in the treatment of susceptible bacterial infections in gopher snakes.\[R-154\].
- **Tortoises, gopher**\[1\]—Although the safety and efficacy of amikacin have not been established, an intramuscular dose of 5 mg per kg of body weight (including shell), administered every forty-eight hours, has been suggested for the treatment of susceptible bacterial infections in gopher tortoises.\[R-156\].

**Strength(s) usually available**\[R-231\]:

- **Veterinary-labeled product(s):**
  - 50 mg per mL (Rx) Amiglyde-V Injection.\[R-91\]; Amiject D; Amikacin C Injection; AmTech AmiMax C Injection; CaniGlide; GENERIC.
  - Note: These products contain 0.1 mg benzethonium chloride per mL.\[R-92\].

**Withdrawal times:**

U.S.—This product is not labeled for use in food-producing animals and should not be administered to such animals because of the risk of long-term antibiotic residues.\[R-258\].
Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass. A sterile solution of Amikacin Sulfate in Water for Injection, or of Amikacin in Water for Injection prepared with the aid of Sulfuric Acid. Contains an amount of amikacin sulfate equivalent to the labeled amount of amikacin, within –10% to +20%. Meets the requirements for Identification, Bacterial endotoxins, pH (3.5–5.5), and Particulate matter, and for Injections\textsuperscript{R-19}.

\textsuperscript{1}Not included in Canadian product labeling or product not commercially available in Canada

APRAMYCIN

SUMMARY OF DIFFERENCES
Category: Aminocyclitol.
Indications: General considerations—Apramycin is active against Staphylococcus aureus, many gram-negative organisms, and some mycoplasma. It has been reported to be effective \textit{in vitro} against \textit{Escherichia coli} and \textit{Salmonella} species\textsuperscript{R-96; 164} that are resistant to streptomycin and neomycin\textsuperscript{R-167; 173}.

Side/adverse effects: This medication produces minimal side/adverse effects and toxicity when administered by the oral route.

ORAL DOSAGE FORMS

APRAMYCIN SULFATE POWDER FOR ORAL SOLUTION
Usual dose: Enteritis, \textit{E. coli}—Piglets: Oral, 12.5 mg per kg of body weight a day for seven days (375 mg per gallon or 100 mg per liter), administered in the only source of water\textsuperscript{R-95; 96}.

Note: Water consumption should be monitored closely and adjusted to avoid overdose.

Strength(s) usually available\textsuperscript{R-231};

U.S.—Veterinary-labeled product(s):

- 48 grams per packet (OTC) \textit{[Apralan Soluble]}.

Canada—Veterinary-labeled product(s):

- 48 grams per packet (OTC) \textit{[Apralan]}.

Withdrawal times:

\begin{tabular}{ll}
Species & Withdrawal time \\
\textit{Pigs} & 28 \\
\end{tabular}

\textsuperscript{R-95}

\textsuperscript{R-96}

DIHYDROSTREPTOMYCIN

SUMMARY OF DIFFERENCES
Category: Aminoglycoside.
Indications: General considerations—Active against mycobacteria, \textit{Leptospira}\textsuperscript{R-243; 244}, \textit{Francisella tularensis}, and \textit{Yersinia pestis}, but only some mycoplasma, gram-negative organisms, and \textit{Staphylococcus} species\textsuperscript{R-116}. The introduction of newer aminoglycosides has eclipsed the significance of dihydrostreptomycin in the face of increasing bacterial resistance.

Lactation: Irregularly distributed into the milk of cows for 18 hours or more.

Side/adverse effects: Less nephrotoxic than other aminoglycosides. Unlike streptomycin, dihydrostreptomycin is associated with more auditory than vestibular toxicity\textsuperscript{R-233}.

ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

DIHYDROSTREPTOMYCIN INJECTION USP
Usual dose:

Note: [Cattle], [dogs], and [pigs]—Although Canadian product labeling includes a dose of 25 mg per kg of body weight for three to five days in the treatment of \textit{leptospirosis} in cattle, dogs, and pigs, studies have shown that while shedding of leptospires will be halted for at least 2 months, carriers are not necessarily eliminated\textsuperscript{R-243; 244}.

Although Canadian product labeling includes the use of dihydrostreptomycin in the treatment of \textit{bacterial pneumonia} in \textit{calves}, there is no published evidence available pertaining to efficacy of this therapy. Such use is not recommended by the USP Veterinary Medicine Advisory Panel\textsuperscript{R-258} due to the lack of efficacy data and the potential for extended tissue withdrawal times.

Strength(s) usually available\textsuperscript{R-231};

U.S.—Veterinary-labeled product(s):

Not commercially available.

Canada—Veterinary-labeled product(s):

- 500 mg per mL (OTC) \textit{[Ethamycin}\textsuperscript{R-106]}.

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**Withdrawal times:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, pigs</td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td>Cattle</td>
<td>30</td>
<td>96</td>
</tr>
</tbody>
</table>

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**USP requirements:** Preserve in single-dose or in multiple-dose containers, preferably of Type I glass. A sterile solution of Gentamicin Sulfate in Water for Injection. Label Uterine Infusion to indicate that it is for veterinary use only. The label states that it must be diluted with 0.9% Sodium Chloride Irrigation before aseptic uterine infusion. May contain suitable buffers, preservatives, and sequestering agents. Contains the labeled amount, within –10 to +25%. Meets the requirements for Identification, Sterility, and pH (5.0–8.0)\(^{(R-19)}\).

**GENTAMICIN**

**SUMMARY OF DIFFERENCES**

Category: Aminoglycoside.

Indications: General considerations—Gentamicin has been widely used in the treatment of gram-negative organisms and some gram-positive organisms. As with other aminoglycosides, use is limited by risk of toxicity.

Side/adverse effects: Intermediate nephrotoxicity. It is considered to be equally toxic to the cochlea and to vestibular organs.

**MUCOSAL DOSAGE FORMS**

**GENTAMICIN UTERINE INFUSION USP**

**Usual dose:**

Uterine infections, bacterial—Horses: Intrauterine, 2 to 2.5 grams as a total dose a day for three to five days during estrus\(^{(R-1)}\). Before administration, the dose should be diluted with 200 to 500 mL of sterile physiological saline\(^{(R-1)}\).

**Strength(s) usually available\(^{(R-231)}\):**

U.S.—Veterinary-labeled product(s):

- 50 mg per mL (Rx) [Gentocin Solution\(^{(R-1)}\)].
- 100 mg per mL (Rx) [AmTech GentaMax 100; GentaMax 100; Gentavet 100; Gentocin Solution; Gentocin; Legacy; Generic\(^{(R-3)}\)].

Canada—Veterinary-labeled product(s):

- Not commercially available.

**Withdrawal times:**

U.S.—This product is not labeled for use in food-producing animals in the U.S., including horses intended for food production\(^{(R-11)}\).

**Packaging and storage:** Store between 2 and 30 °C (36 and 86 °F)\(^{(R-11)}\), unless otherwise specified by manufacturer.

**ORAL DOSAGE FORMS**

**GENTAMICIN ORAL SOLUTION**

**Usual dose:**

Enteritis, *E. coli*—

- *Piglets*, 1 to 3 days of age: Oral, 5 mg as a total dose, administered once at the onset of signs\(^{(R-13; 14)}\).
  - Note: The above dose is for “pig pump” solutions, administered at the strength provided in metered dose packaging\(^{(R-13; 14)}\); see manufacturer’s product labeling.

- *Piglets*, weanling\(^1\): Oral, 25 mg per gallon of water (approximately 1.1 mg per kg of body weight), administered as the sole source of drinking water for three consecutive days\(^{(R-11)}\).

Swine dysentery\(^1\)—Pigs: Oral, 50 mg per gallon of water (approximately 2.2 mg per kg of body weight), administered as the sole source of drinking water for three consecutive days\(^{(R-11)}\).

**Strength(s) usually available\(^{(R-231)}\):**

U.S.—Veterinary-labeled product(s):

- 4.35 mg per mL (OTC) [Garacin Pig Pump\(^{(R-13)}\)].
- 5 mg per mL (OTC) [AmTech Gentamicin Sulfate Pig Pump Oral Solution].

Canada—Veterinary-labeled product(s):

- 4.35 mg per mL (OTC) [Garasol Pig Pump Oral Solution\(^{(R-14)}\)].

**Withdrawal times:**

U.S.\(^{(R-13)}\)—

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piglets</td>
<td>14</td>
</tr>
</tbody>
</table>

Canada\(^{(R-14)}\)—

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piglets</td>
<td>11</td>
</tr>
</tbody>
</table>

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing\(^{(R-13)}\).

**Preparation of dosage form:** This medication is dispensed in a “pig pump.” Medication is administered by one plunger depression to deliver 5 mg into each pig’s mouth\(^{(R-12)}\).
Stability:
Contents of “pig pump” medication bottle should be destroyed 90 days after opening, if unused{R-12}. Medicated drinking water should be prepared daily{R-11}.

Incompatibilities: To prevent inactivation of the drug, medicated drinking water should not be stored in rusty containers{R-11}.

USP requirements: Not in USP{R-19}.

GENTAMICIN POWDER FOR ORAL SOLUTION

Usual dose:
Enteritis, E. coli¹—Piglets: Oral, 25 mg per gallon of water (approximately 1.1 mg per kg of body weight), administered as the sole source of drinking water for three consecutive days{R-15}.
Swine dysentery¹—Pigs: Oral, 50 mg per gallon of water (approximately 2.2 mg per kg of body weight), administered as the sole source of drinking water for three consecutive days{R-15}.
Note: Under extreme hot or cold weather conditions, product labeling recommends that the concentration of medication be adjusted, based on expected changes in water consumption{R-14}.

Strength(s) usually available{R-231}:
U.S.—
Veterinary-labeled product(s):
66.7 mg of gentamicin per gram of powder (OTC) [Garacin Soluble Powder].
333.3 mg of gentamicin per gram of powder (OTC) [Gen-Gard].

Canada—
Not commercially available.

Withdrawal times:
U.S.{R-14}—

<table>
<thead>
<tr>
<th>Species</th>
<th>Meas (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs, piglets</td>
<td>10</td>
</tr>
</tbody>
</table>

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. To avoid degradation of medication, this product should not be stored in rusty containers{R-15}.

Preparation of dosage form: Prepare daily according to manufacturer’s recommendation{R-15}.

USP requirements: Not in USP{R-19}.

¹Not included on Canadian product labeling or product not commercially available in Canada.

PARENTERAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are not commercially available in the U.S.

GENTAMICIN INJECTION USP

Note: Intravenous administration—When gentamicin is administered by the intramuscular or subcutaneous route, it is rapidly and completely absorbed. Although not always listed on product labeling, this medication is also commonly administered intravenously. An indwell- ing catheter is used for convenience and to minimize the discomfort of repeated dosing{R-261}. To further decrease the risk of neuromuscular blockade, it is recommended that the drug be diluted in saline or administered slowly{R-263}.

Usual dose:
[Bacteremia]:
[Bone and joint infections]¹;
Respiratory tract infections;
[Septicemia]:
Skin and soft tissue infections;
Urinary tract infections; or
[Uterine infections]¹—
Cats:
Intramuscular, intravenous, or subcutaneous, 3 mg per kg of body weight every eight hours{R-63; 64}.
Once-daily dosage—Intramuscular, intravenous, or subcutaneous, 5 to 8 mg per kg of body weight every twenty-four hours{R-266}.

Dogs:
Intramuscular or subcutaneous, 4.4 mg per kg of body weight every eight hours{R-4; 7}.
Once-daily dosage—Intramuscular or subcutaneous, 10 to 15 mg per kg of body weight every twenty-four hours{R-266}.

Note: Authors of a study of obese cats considered to be approximately 45% overweight (4.6 to 6.6 kg body weight) recommended an intramuscular, intravenous, or subcutaneous dose of 2.5 mg per kg of body weight every eight hours to compensate for pharmacokinetic differences from normal-weight cats{R-68}.

Treatment of urinary tract infections with aminoglycosides should be reserved for those cases in which resistance exists to safer alternative antibiotics. Despite label directions to limit treatment duration to 7 days{R-4}, most urinary tract infections will require extended therapy. This is possible with the aminoglycosides, provided careful monitoring is performed (see Patient monitoring). According to product labeling, treatment with gentamicin injection should not exceed 7 days{R-4}.

Enteritis, Escherichia coli—Piglets, 1- to 3-day-old: Intramuscular, 5 mg as a single total dose{R-7; 9}.
E. coli infection;
Pseudomonas aeruginosa infection; or
Salmonella typhimurium infection—Chicks, 1-day-old: Subcutaneous, 0.2 mg as a total single dose{R-7; 8}.

Enterocolitis, Enteritis, Enteritis coli—Turkey poults, 1- to 3-day-old: Subcutaneous, 1 mg as a total single dose{R-7; 8}.

Paracolon—Turkey poults, 1- to 3-day-old: Subcutaneous, 2.5 mg of gentamicin dissolved in 5 to 8 mL of sterile physiological saline{R-4; 7}.

Note: The following recommendations have been suggested based on pharmacokinetic studies:
[Baboons]¹—Although the safety and efficacy of gentamicin have not been established, an intramuscular dose of 3 mg per kg of body weight every six to eight hours has been suggested in the treatment of Pseudomonas aeruginosa infections in baboons{R-76}.

[Buffalo calves]¹—Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations should be considered before the extra label
use of aminoglycosides in food-producing animals: Although the safety and efficacy of gentamicin have not been established, an intramuscular dose of 3.25 mg per kg of body weight as an initial dose, followed by 2 to 3 mg per kg of body weight every twelve hours has been recommended in the treatment of susceptible bacterial infections in buffalo calves\(^{[R-77; 78]}\).

[Budgerigars]\(^{1}\)—Although the safety and efficacy of gentamicin have not been established, an intramuscular dose of 5 mg per kg of body weight every eight hours for three days has been suggested in the treatment of susceptible bacterial infections in budgerigars\(^{[R-86]}\).

[Calves, less than 2 weeks of age]\(^{1}\)—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy have not been established, an intramuscular dose of 12 to 15 mg per kg of body weight every twenty-four hours has been recommended in the treatment of susceptible bacterial infections, based on pharmacokinetic data\(^{[R-21; 266]}\).

[Cattle]\(^{1}\)—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy have not been established, an intramuscular dose of 5 to 6 mg per kg of body weight every twenty-four hours has been recommended in the treatment of susceptible bacterial infections, based on pharmacokinetic data\(^{[R-22; 25; 261; 266]}\).

[Eagles]\(^{1}\), [hawks]\(^{1}\), or [owls]\(^{1}\)—Although the safety and efficacy of gentamicin have not been established, an intramuscular or intravenous dose of 2.5 mg per kg of body weight every eight hours has been recommended in the treatment of susceptible bacterial infections in eagles, hawks, and owls\(^{[R-88]}\). Caution is advised in extrapolating dosage recommendations from one avian species to another, as pharmacokinetics can vary widely.

[Goats]\(^{1}\)—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy of gentamicin have not been established, an intravenous dose of 4 mg per kg of body weight every eight hours has been recommended for use in the treatment of susceptible bacterial infections in goats\(^{[R-40]}\).

[Horse foals]\(^{1}\) and [pony foals]\(^{1}\), less than 30 days of age—Although the safety and efficacy have not been established, some researchers suggest that dosing of gentamicin for horse and pony foals less than 30 days of age should be an intramuscular or intravenous dose of 10 to 14 mg per kg of body weight every twenty-four hours\(^{[R-6; 266]}\).

[Horses]\(^{1}\) and [foals, more than 30 days of age]\(^{1}\)—Although the safety and efficacy of gentamicin have not been established, an intramuscular or intravenous dose of 4 to 6.8 mg per kg of body weight every twenty-four hours has been suggested for the treatment of susceptible bacterial infections in horses and foals more than 30 days of age\(^{[R-6; 46; 50; 52; 53; 55; 252; 264; 266]}\).

[Llamas]\(^{1}\)—AMDUCA regulations should be considered before the extra label use of aminoglycosides in food-producing animals: Although the safety and efficacy of gentamicin have not been established, a dose of 2.5 mg per kg of body weight every eight hours for six days has been suggested in the treatment of bacterial infections in llamas\(^{[R-82]}\).

[Pythons]\(^{1}\)—Although the safety and efficacy of gentamicin have not been established, an intramuscular dose of 2.5 mg per kg of body weight as an initial dose, followed by 1.5 mg per kg of body weight at ninety-six-hour intervals has been suggested in the treatment of susceptible bacterial infections in pythons\(^{[R-89]}\).

**Strength(s) usually available**\(^{[R-231]}\):

**U.S.—** Veterinary-labeled products:
- 5 mg per mL (Rx) [Garacin Piglet Injection\(^{[R-9]}\)]
- 50 mg per mL (Rx) [GentaVed 50; Gentocin\(^{[R-4]}\)]
- 100 mg per mL (OTC) [AmTech Gentapoul; Garasol Injection\(^{[R-8]}\); Genta-fuse; Generic]

**Canada—**
- Veterinary-labeled products:
  - 5 mg per mL (Rx) [Garasol Solution Injectable\(^{[R-10]}\)]
  - 50 mg per mL (Rx) [Gentocin Solution Injectable\(^{[R-7]}\)]
  - 100 mg per mL (Rx) [Gentocin Solution Injectable]

### Withdrawal times:

**U.S.—** This product is not labeled for use in horses to be used in food production\(^{[R-4]}\).

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat, days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicks</td>
<td>35</td>
</tr>
<tr>
<td>Piglets</td>
<td>40</td>
</tr>
<tr>
<td>Turkey poults</td>
<td>63</td>
</tr>
</tbody>
</table>

**Canada—** This product is not labeled for use in horses to be used in food production\(^{[R-7]}\).

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat, days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicks</td>
<td>35</td>
</tr>
<tr>
<td>Piglets</td>
<td>42</td>
</tr>
<tr>
<td>Turkey poults</td>
<td>63</td>
</tr>
</tbody>
</table>

Note: The administration of gentamicin to cattle in the treatment of uterine infections is included in Canadian product labeling. However, gentamicin is not labeled for use in food-producing animals in the U.S. and the USP Veterinary Medicine Advisory Panel does not recommend use in the treatment of uterine infections in cattle. Therefore, the labeled intrauterine dose and withdrawal time for cattle are not listed in this monograph.

**Packaging and storage:** Store between 15 and 30 °C (59 and 86 °F)\(^{[R-4]}\), unless otherwise specified by manufacturer. Keep from freezing\(^{[R-4]}\).

**USP requirements:** Preserve in single-dose or in multiple-dose containers, preferably of Type I glass. May contain suitable buffers, preservatives, and sequestering agents, unless it is intended for intrathecal use, in which case it contains only suitable toxicity agents. Contains an amount of gentamicin sulfate equivalent to the labeled amount of gentamicin, within –10% to +25%. Meets the requirements for Identification, Bacterial endotoxins, pH (3.0–5.5), and Particulate matter, and for Injections\(^{[R-19]}\).

\(^{1}\)Not included on Canadian product labeling or product not commercially available in Canada.
KANAMYCIN

SUMMARY OF DIFFERENCES
Category: Aminoglycoside.
Indications: General considerations—Spectrum of activity focuses primarily on gram-negative organisms and a few gram-positive organisms.
Side/adverse effects: Intermediate nephrotoxicity. More toxic to the cochlea than to vestibular organs.

PARENTERAL DOSAGE FORMS

KANAMYCIN INJECTION USP

Usual dose:
- Bacteremia or septicemia
- Bone and joint infections
- Otitis media
- Pancreatitis
- Respiratory tract infections
- Skin and soft tissue infections
- Urinary tract infections
- Uterine infections—Cats and dogs: Subcutaneous, 5.5 mg per kg of body weight every twelve hours. According to product labeling, this medication may also be given by intramuscular injection, if necessary.
Note: Another source recommends a dose of 10 mg per kg of body weight every six hours in the dog, based on pharmacokinetic data.

Strength(s) usually available:
- Veterinary-labeled product(s):
  - 200 mg per ml. (Rx) [Kantrim].
- U.S.—Veterinary-labeled product(s):
  - Not commercially available.
- Canada—Veterinary-labeled product(s):
  - Not commercially available.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Stability: Unopened vials may darken in color during storage, but potency is unaffected.

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass. Contains suitable buffers and preservatives. Contains an amount of Kanamycin Sulfate equivalent to the labeled amount of kanamycin, within –10% to +15%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH (3.5–5.0), and Particulate matter and for Injections.

Side/adverse effects: High risk of nephrotoxicity and severe cochlear toxicity when parenterally administered.

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are not commercially available in the U.S.

NEOMYCIN SULFATE FOR MEDICATED FEED

Usual dose: Enteritis, Escherichia coli (treatment)—Cattle, goats, pigs, and sheep: Oral, 22 mg per kg of body weight a day for up to a maximum of fourteen days.
Note: This product is labeled for use in the preparation of Type B or Type C medicated feeds; Type C medicated feeds may be either medicated solid feeds or milk replacers. To administer the recommended dosage, adjustments must be made in the concentration of neomycin in feed or milk replacer, based on factors altering consumption, such as age and weight of the animal, disease signs, and environmental factors.

Strength(s) usually available:
- U.S.—Veterinary-labeled product(s):
  - 715 grams per kg [Neomix AG 325 Medicated Premix].
- Canada—Veterinary-labeled product(s):
  - Not commercially available.

Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle and ruminating calves</td>
<td>1</td>
</tr>
<tr>
<td>Goats and kids, pigs and piglets</td>
<td>3</td>
</tr>
<tr>
<td>Sheep and lambs</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Products are not labeled for use in preruminating calves to be processed for veal or for lactating dairy cattle or goats producing milk for human consumption.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tightly closed container, unless otherwise specified by manufacturer.

Store in a dry place, securely closing packaging to prevent caking of contents.

Preparation of dosage form: Prepare solutions daily according to manufacturer’s instructions.

USP requirements: Not in USP.

NEOMYCIN SULFATE ORAL SOLUTION USP

Usual dose: Enteritis, E. coli—Cattle, goats, [horses], pigs, and sheep: Oral, 22 mg per kg of body weight a day, administered in the only source of drinking water for fourteen days.
Note: For many of these products, individual animal treatment is also possible by dividing the daily dose and administering as a drench with milk or water or by mixing in an individual animal’s only water supply. Consult the manufacturer’s product labeling.
Canadian product labeling lists the dose of neomycin in terms of mL per liter of drinking water and an incrementally increasing dose from 2 weeks to adult, or 2 weeks to 26 weeks of age, for chickens and turkeys, respectively. See product labeling for specific dosing directions.

**Strength(s) usually available**: U.S.—Veterinary-labeled product(s):
- 200 mg per mL (OTC) [AmTech Neomycin Oral Solution; Biosol Liquid; Neomycin 200; Neosol 200; Neovet Neomycin Oral Solution; generic].

Canada—Veterinary-labeled product(s):
- 200 mg per mL (OTC) [Biosol Liquid].

**Withdrawal times**:

#### U.S.—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>1</td>
</tr>
<tr>
<td>Goats, pigs</td>
<td>3</td>
</tr>
<tr>
<td>Sheep</td>
<td>2</td>
</tr>
</tbody>
</table>

#### Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>30</td>
</tr>
<tr>
<td>Pigs, sheep</td>
<td>20</td>
</tr>
</tbody>
</table>

**Note**: Products are not labeled for use in preruminating calves to be processed for veal or for lactating dairy cattle or goats producing milk for human consumption.

**Packaging and storage**: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Preparation of dosage form**: Prepare solutions daily according to manufacturer’s instructions. When administered in the drinking water, adjustments must be made in concentration, based on factors altering water consumption, such as age, disease signs, and environmental factors.

**USP requirements**: Preserve in tight, light-resistant containers, preferably at controlled room temperature. Contains an amount of neomycin sulfate equivalent to the labeled amount of neomycin, within –10 to +25%. Meets the requirements for Identification and pH (5.0–7.5).

**NEOMYCIN SULFATE POWDER FOR ORAL SOLUTION**

**Usual dose**:

- E. coli infection—Turkeys, growing: Oral, 22 mg per kg of body weight a day, administered in the only source of drinking water for five days.
- Enteritis, E. coli—Cattle, goats, horses, pigs, and sheep: Oral, 22 mg per kg of body weight a day for fourteen days, administered in the only source of drinking water.

**Strength(s) usually available**: U.S.—Veterinary-labeled product(s):
- 715 mg per gram of powder (OTC) [Neo-325; Neomix 325; Neomix AG 325; Neomycin 325; Neo-Sol 50; Neosol Soluble Powder; Neovet 325/100].

Canada—Veterinary-labeled product(s):
- 715 mg per gram of powder (OTC) [Neomix Soluble Powder].
- 813 mg per gram of powder (OTC) [Neomed 325; Neomycin 325].

**Withdrawal times**:

#### U.S.—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>1</td>
</tr>
<tr>
<td>Goats, pigs</td>
<td>3</td>
</tr>
<tr>
<td>Sheep</td>
<td>2</td>
</tr>
<tr>
<td>Turkeys, growing</td>
<td>0</td>
</tr>
</tbody>
</table>

**Note**: Products are not labeled for use in preruminating calves to be processed for veal or for lactating dairy cattle or goats producing milk for human consumption.

**Packaging and storage**: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Preparation of dosage form**: Prepare solutions daily according to manufacturer’s instructions. When administered in the drinking water, adjustments must be made in concentration, based on factors altering water consumption, such as age, disease signs, and environmental factors.
Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meats (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>30</td>
</tr>
<tr>
<td>Chickens, broiler</td>
<td>7</td>
</tr>
<tr>
<td>Chickens, laying, pigs, sheep, turkeys</td>
<td>14</td>
</tr>
</tbody>
</table>

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: Prepare solutions daily according to manufacturer’s instructions. When administered in the drinking water, adjustments must be made in concentration, based on factors altering water consumption, such as age, disease signs, and environmental factors.[R-98]

USP requirements: Not in USP[R-19].

Note: Strength of administered solution may be adjusted to compensate for variations in age or weight, the severity of disease signs, and environmental factors that may affect water consumption[R-182].

Strength(s) usually available[R-231]:

U.S.—

Veterinary-labeled product(s):

- 250 mg per mL (OTC) [GENERIC].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meats (days)</th>
</tr>
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<tr>
<td>Calves</td>
<td>2</td>
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<tr>
<td>Chickens</td>
<td>4</td>
</tr>
<tr>
<td>Pigs</td>
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</table>

Note: Product labeling listing the above withdrawal times states that they are not labeled for use in chickens producing eggs for human consumption.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: Prepare according to manufacturer’s instruction.

USP requirements: Not in USP[R-19].

Note: Not included in Canadian product labeling or product not commercially available in Canada.

STREPTOMYCIN

SUMMARY OF DIFFERENCES

Category: Aminoglycoside.

Indications: General considerations—First aminoglycoside introduced. Active against mycobacteria, *Leptospira*[R-243; 244], *Francisella tularensis*, and *Yersinia pestis*, but only some mycoplasma, gram-negative organisms, and *Staphylococcus* species[R-116]. The introduction of newer aminoglycosides has eclipsed the significance of streptomycin in the face of increasing bacterial resistance.

Side/adverse effects: Less nephrotoxic than other aminoglycosides.

Vestibular toxicity is more often seen than auditory toxicity.

ORAL DOSAGE FORMS

STREPTOMYCIN SULFATE ORAL SOLUTION

Usual dose: Enteritis, bacterial[R-181; 182].—Calves, chickens, and pigs: Oral, 22 to 33 mg per kg of body weight, administered in the only source of drinking water[R-181; 182].

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<table>
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<tr>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>Number of doses</th>
<th>Vol₀ area (L/kg)</th>
<th>Vol₀ steady state (L/kg)</th>
<th>Clearance (mL/min/kg)</th>
<th>Elimination half-life, initial phase (hour)</th>
<th>Elimination half-life, gamma phase* (hour)</th>
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<td>0.23 ± 0.02</td>
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<td><strong>Buffalo calves, 3 to 4 months of age (Murrah)</strong></td>
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<td><strong>Camels</strong></td>
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<td>2 ± 0.17</td>
<td>5.19 ± 0.3</td>
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<tr>
<td>Piglets[R-42]</td>
<td>2</td>
<td>Every 8 hours for 7 days</td>
<td>0.32 ± 0.32</td>
<td>0.24 ± 0.03</td>
<td>1.66 ± 0.12</td>
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<td>Rabbits[R-75]</td>
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<td>Single</td>
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<td>Rabbits, [R-76]</td>
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<td>Rabbits, [R-74]</td>
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Table 1. (Contd.)

<table>
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<tr>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>Number of doses</th>
<th>VolD area (L/kg)</th>
<th>VolD steady state (L/kg)</th>
<th>Clearance (mL/min/kg)</th>
<th>Elimination half-life, initial phase (hour)</th>
<th>Elimination half-life, gamma phase* (hour)</th>
</tr>
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<tbody>
<tr>
<td>Sheeps [R-31]</td>
<td>2.2 Single</td>
<td>0.19 ± 0.06</td>
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<td>57.5 ± 26.2</td>
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<td>[R-15]</td>
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<td>41.9 ± 18.5</td>
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<td>[R-16: 57]</td>
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<td>57.5 ± 26.2</td>
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<td>[R-16]</td>
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<td>0.16</td>
<td>1.03</td>
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<td>2.4 ± 0.5</td>
<td>30.4 ± 18.9</td>
<td>88.9 ± 19.8</td>
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<td>[R-11]</td>
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<td>[R-36: 37]</td>
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<td>0.24 ± 0.03</td>
<td>0.81 ± 0.32</td>
<td>41.9 ± 18.5</td>
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<td>2.4</td>
<td>30.4 ± 18.9</td>
<td>88.9 ± 19.8</td>
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<tr>
<td>[R-16: 57]</td>
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<td>0.38 ± 0.2</td>
<td>88.9 ± 19.8</td>
<td>106</td>
<td>0.97</td>
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<tr>
<td>[R-36: 37]</td>
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<td>0.71 ± 0.75</td>
<td>167.2 ± 42.7</td>
<td>106</td>
<td>0.97</td>
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<td>[R-16]</td>
<td>3 Every 8 hours for 7 days</td>
<td>0.16</td>
<td>1.03</td>
<td>1.75</td>
<td>2.4 ± 0.5</td>
<td>30.4 ± 18.9</td>
<td>88.9 ± 19.8</td>
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<tr>
<td>Chickens, 18-day-old [R-16: 57]</td>
<td>10 Single</td>
<td>0.671 ± 0.045</td>
<td>4.78 ± 0.26</td>
<td>1.6</td>
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<td>Chickens [R-16: 57]</td>
<td>10 Single</td>
<td>0.294 ± 0.004</td>
<td>1.4 ± 0.1</td>
<td>2.4</td>
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<td>Pigeons [R-16: 57]</td>
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<tr>
<td>Days [R-177]</td>
<td>10 Single</td>
<td>0.255 ± 0.030</td>
<td>0.97 ± 0.31</td>
<td>0.97 ± 0.31</td>
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<tr>
<td>[R-16: 57]</td>
<td>10 Every 8 hours for 7 doses</td>
<td>0.252 ± 0.018</td>
<td>0.98 ± 0.18</td>
<td>0.98 ± 0.18</td>
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<tr>
<td>Goats [R-16: 57]</td>
<td>10 Single</td>
<td>0.263 ± 0.022</td>
<td>1.5 ± 0.18</td>
<td>1.5 ± 0.18</td>
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<tr>
<td>Horses [R-176]</td>
<td>10 Single</td>
<td>0.228 ± 0.023</td>
<td>1.8 ± 0.17</td>
<td>1.8 ± 0.17</td>
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<tr>
<td>Rabbits [R-16: 57]</td>
<td>10 Single</td>
<td>0.254 ± 0.017</td>
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<tr>
<td>Calves [R-180]</td>
<td>2 days of age</td>
<td>0.356 ± 0.042</td>
<td>2.26 ± 0.61</td>
<td>2.12 ± 0.39</td>
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<tr>
<td>[R-180]</td>
<td>1 week of age</td>
<td>0.472 ± 0.085</td>
<td>3.62 ± 0.58</td>
<td>1.5 ± 0.03</td>
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<tr>
<td>[R-180]</td>
<td>2 weeks of age</td>
<td>0.322 ± 0.056</td>
<td>2.31 ± 0.31</td>
<td>1.59 ± 0.08</td>
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<td>[R-180]</td>
<td>4 weeks of age</td>
<td>0.462 ± 0.065</td>
<td>2.63 ± 0.24</td>
<td>1.9 ± 0.01</td>
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<tr>
<td>[R-180]</td>
<td>5 weeks of age</td>
<td>0.355 ± 0.073</td>
<td>2.03 ± 0.54</td>
<td>2.04 ± 0.19</td>
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<tr>
<td>Calves, 3 months of age [R-257]</td>
<td>12 Single</td>
<td>1.17 ± 0.23</td>
<td>4.16 ± 0.67</td>
<td>7.48 ± 2.02</td>
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<tr>
<td>Horses [R-176]</td>
<td>10 Single</td>
<td>0.232 ± 0.06</td>
<td>2.1 ± 0.97</td>
<td>2.1 ± 0.97</td>
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<tr>
<td>Sheep [R-248]</td>
<td>10 Single</td>
<td>0.304 ± 0.08</td>
<td>1.98 ± 0.5</td>
<td>1.98 ± 0.5</td>
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<td>Streptomycin</td>
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<tr>
<td>Horses [R-176]</td>
<td>10 Single</td>
<td>0.231 ± 0.04</td>
<td>0.79 ± 0.13</td>
<td>3.40 ± 0.42</td>
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</table>

*Researchers have described a dose-dependent slow elimination phase (gamma) many times longer than the initial elimination phase [R-32]. It is postulated that gentamicin is bound to tissues by one of at least two different processes so that some gentamicin is released quickly and gentamicin bound to tissue by another process is more gradually eliminated [R-25; 12; 14; 16].

†Clearance was the only pharmacokinetic value that differed with statistical significance for amikacin between 3 and 5 days of age [R-130]. Another study showed no pharmacokinetic differences for amikacin between foals of 1 and 7 days of age [R-133].

IC = Intracardiac

Table 2. Pharmacology/pharmacokinetics—other systemic data.

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg); Route</th>
<th>Number of doses</th>
<th>Absorption half-life (hour)</th>
<th>Peak serum concentration (mcg/mL)</th>
<th>Time to peak concentration (hour)</th>
<th>Bioavailability (%)</th>
<th>Terminal half-life, initial phase (hours)</th>
<th>Terminal half-life, gamma phase* (hours)</th>
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</thead>
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<td>Birds</td>
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<tr>
<td>Chickens [R-157]</td>
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<td>19.9</td>
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<td>[R-146]</td>
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<td>Cockatiels [R-148]</td>
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<td>Hawks, red tailed [R-147]</td>
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<td>56 ± 8.8</td>
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<td>Parrots, African gray [R-150]</td>
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<td>10.8 ± 0.63</td>
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</tbody>
</table>

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<table>
<thead>
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<th>Species</th>
<th>Dose (mg/kg); Route</th>
<th>Number of doses</th>
<th>Absorption half-life (hour)</th>
<th>Peak serum concentration (mcg/mL)</th>
<th>Time to peak concentration (hour)</th>
<th>Bioavailability (%)</th>
<th>Terminal half-life, initial phase (hours)</th>
<th>Terminal half-life, gamma phase* (hours)</th>
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<td>Calves</td>
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<td>57.7 ± 3.6</td>
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<td>1.17 ± 0.75</td>
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<td>7.5; IM Single</td>
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<td>Horse foals, 3- to 5-day old</td>
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<td>34.17 ± 3.54</td>
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<tr>
<td>Pong foals, 2- to 11-day old</td>
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<td>14.7 ± 1.14</td>
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<td>Snakes, gopher</td>
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<td>5.58 ± 2.77</td>
<td>71.9 ± 10</td>
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<td>75.4 ± 30.1</td>
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<th>Species</th>
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<th>Absorption half-life (hour)</th>
<th>Peak serum concentration (mcg/mL); Time to peak concentration (hour)</th>
<th>Bioavailability %</th>
<th>Terminal half-life, initial phase (hours)</th>
<th>Terminal half-life, gamma phase* (hours)</th>
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</table>
Researchers have described a slow elimination phase (gamma) many times longer than the initial elimination phase by one of at least two different processes so that some gentamicin is released quickly and gentamicin bound to tissue by another process is more gradually eliminated.

The major pharmacokinetic values for intraosseus administration of amikacin did not significantly differ from those measured for intravenous administration.

Table 2. (Contd.)

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<tr>
<th>Species</th>
<th>Dose (mg/kg); Route</th>
<th>Number of doses</th>
<th>Absorption half-life (hour)</th>
<th>Peak serum concentration (mcg/mL)</th>
<th>Time to peak concentration (hour)</th>
<th>Bioavailability (%)</th>
<th>Terminal half-life, initial phase (hours)</th>
<th>Terminal half-life, gamma phase* (hours)</th>
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<td>Dogs</td>
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<td>37.75 ± 1.32</td>
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<td>Horses</td>
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<td>0.32 ± 0.04</td>
<td>12.55 ± 1.89</td>
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<td>0.31 ± 0.13</td>
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<td>4.14 ± 21.4</td>
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*Researchers have described a slow elimination phase (gamma) many times longer than the initial elimination phase. It is postulated that gentamicin is bound to tissues by one of at least two different processes so that some gentamicin is released quickly and gentamicin bound to tissue by another process is more gradually eliminated.† The major pharmacokinetic values for intraosseus administration of amikacin did not significantly differ from those measured for intravenous administration.‡ Although the half-lives of absorption and elimination were similar at different temperatures, the estimated volume of distribution and clearance were significantly higher at the warmer temperature.

IM = intramuscular, IO = intraosseous, SC = subcutaneous

REFERENCES

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6. Committee comment, Rec 7/29/02.
7. Gentamicin package insert (Gentocin, Schering-Plough—Canada), Rec 12/10/97.
10. Gentamicin package insert (Garasol, Schering-Plough—Canada), Rec 12/10/97.
14. Gentamicin product information (Garasol Pig Pump, Schering-Plough—Canada), Downloaded from Schering-Plough Animal Health Product Label Retrieval Service on 2/21/03.


110. Amikacin package insert (Amiglyde-V [250 mg/mL], Fort Dodge—US), Rev 3/93, Rec 2/15/96.


266. Panel comment, Rec 8/7/99.


**AMINOPENICILLINS Veterinary—Intramammary-Local†**

This monograph includes information on the following: Amoxicillin; Hetacillin.

Some commonly used brand names for veterinary-labeled products are: Amoxi-Mast and Hetacin-K Intramammary Infusion.

**Note:** For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

†Not commercially available in Canada.

**CATEGORY:**
Antibacterial (intramammary-local).

**INDICATIONS**

**GENERAL CONSIDERATIONS**

Aminopenicillins have activity against penicillin-sensitive gram-positive bacteria as well as some gram-negative bacteria. Aminopenicillins are susceptible to destruction by beta-lactamases and therefore are not effective against bacteria that produce these enzymes.{[R-1-3] Most strains of Klebsiella, Proteus, Pseudomonas, and Staphylococcus{[R-17] are resistant.}{[R-1-4]}

**ACCEPTED**

Mastitis (treatment){[R-9]—Cows, lactating: Amoxicillin and hetacillin are indicated in the treatment of mastitis caused by susceptible organisms such as Streptococcus agalactiae.}([R-8; 6.4] Intramammary therapy alone is indicated only in the treatment of subacute or subclinical mastitis manifested by mild changes in the milk or udder. Acute or purulent mastitis, in which gross inflammatory changes in the milk or udder or systemic signs appear, requires administration of other medications also, which may include systemic antibiotics and/or supportive therapy.){[R-7]}

1Not included in Canadian product labeling or product not commercially available in Canada.

**REGULATORY CONSIDERATIONS**

U.S.—Withdrawal times have been established. See the Dosage Forms section.

**CHEMISTRY**

**Source:**

Amoxicillin—Semisynthetic derivative of ampicillin.([R-8])

Hetacillin—Derived from the penicillin nucleus, 6-aminopenicillanic acid and chemically related to ampicillin.([R-6])

**Chemical group:** Beta-lactam antibiotics.

**Chemical name:**

Amoxicillin—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate [25S-[2alpha,5alpha,6beta(S)*]]—([R-9])

Hetacillin potassium—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)-3,3-dimethyl-7-oxo-, monopotassium salt, [25S-[2alpha,5alpha,6beta(S)*]]—([R-9])

**Molecular formula:**

Amoxicillin—C_{16}H_{19}N_{3}O_{5}S·3H_{2}O.([R-9])

Hetacillin potassium—C_{14}H_{22}KN_{3}O_{2}S.([R-9])

**Molecular weight:**

Amoxicillin—419.45.([R-9])

Hetacillin potassium—427.56.([R-9])

**Description:**

Amoxicillin USP—White, practically odorless, crystalline powder.([R-10])

Hetacillin potassium—White to light buff, crystalline powder.

**Solubility:**

Amoxicillin USP—Slightly soluble in water and in methanol; insoluble in carbon tetrachloride and in chloroform.([R-10])

Hetacillin potassium—Freely soluble in water; soluble in alcohol.

**PHARMACOLOGY/PHARMACOKINETICS**

**Mechanism of action/effects:** Like other penicillins, the aminopenicillins produce their bactericidal effect by inhibiting bacterial cell wall synthesis.([R-11] These antibiotics must penetrate the cell wall to attach to specific proteins on the inner surface of the bacterial cell membrane. In actively growing cells, the binding of ampicillin or amoxicillin within the cell wall leads to interference with production of cell wall peptidoglycans and subsequent lysis of the cell in an isoosmotic environment.([R-11–13])

**Distribution:** Medications infused into a teat are considered to be fairly evenly distributed in that quarter of the healthy mammary gland; however, in an udder affected by moderate to severe mastitis, the presence of edema, blockage of milk ducts, and reduced blood circulation causes uneven distribution.([R-14])

**PRECAUTIONS TO CONSIDER**

**PATIENT MONITORING**

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

Bacteriologic pathogens in milk

(milk samples should be tested 3 weeks after treatment is discontinued; mastitis is not considered bacteriologically cured until samples show an absence of the mastitis-causing organisms)

Clinical signs of mastitis

(although a resolution of clinical signs of mastitis is not an indication that a bacteriologic cure has been achieved, monitoring of the clinical condition of the mammary gland, teat, and milk produced can aid in diagnosis of a recurrence of mastitis or initial diagnosis of mastitis in another cow in the herd)

Somatic cell count

(somotic cell counts performed on milk to monitor the dairy herd are used primarily to maintain milk quality, but they are also used to assess the approximate overall effectiveness of mastitis control programs, which may include antibiotic treatment of cows.)([R-7])

**SIDE/ADVERSE EFFECTS**

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:
THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
Cows
Allergic reactions—local or systemic

OVERDOSE
For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

CLIENT CONSULTATION
Treatment of mastitis in dairy cattle is best achieved by a comprehensive mastitis control program in which herd management is the primary focus. The program should include good maintenance of milking equipment and constant evaluation of milking procedures and teat health as well as strategic treatment of clinical cases of mastitis.

VETERINARY DOSING INFORMATION
The choice of antibiotic for the treatment of mastitis should be based on knowledge of culture and sensitivity of pathogens causing mastitis in the cow and the dairy herd. The available intramammary aminopenicillin products are formulated for use in the lactating cow only.

Before administration of intramammary amoxicillin or hetacillin, the following steps should be performed:

- The udder should be milked out completely and the teats and udder washed with warm water and a disinfectant. Care should be taken to avoid washing excess dirt down from the udder onto the teat ends. The area should be dried thoroughly and each teat wiped with a separate cotton ball soaked with an antiseptic such as 70% isopropyl alcohol.
- Persons performing the treatment should wash and dry their hands before each treatment.
- The tip of the syringe should be inserted into the teat end as little as possible and the contents of the syringe should be injected into each streak canal while the teat is held firmly. The medication should then be gently massaged up the teat canal into the udder.

A teat dip is recommended on all teats following treatment.

AMOXICILLIN

INTRAMAMMARY DOSAGE FORMS

**AMOXICILLIN INTRAMAMMARY INFUSION USP**

**Usual dose:** Mastitis—Cows, lactating: Intramammary, 62.5 mg into each affected quarter of the udder every twelve hours for a maximum of three doses.

**Strength(s) usually available:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows, lactating</td>
<td>12</td>
<td>60</td>
</tr>
</tbody>
</table>

**USP requirements:** Preserve in well-closed disposable syringes. A suspension of Amoxicillin in a suitable vegetable oil vehicle. Label it to indicate that it is intended for veterinary use only. Contains the labeled amount, within -10% to +20%. Contains a suitable dispersing agent and preservative. Meets the requirements for Identification and Water (not more than 1.0%).

**Strength(s) usually available:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows, lactating</td>
<td>10</td>
<td>72</td>
</tr>
</tbody>
</table>

**Withdrawal times:**

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Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

USP requirements: Not in USP.

REFERENCES

17. Panel comment, 2/20/95.
18. Manufacturer comment, 2/28/95.
AMINOPENICILLINS Veterinary—Systemic

This monograph includes information on the following: Amoxicillin; Ampicillin.

Some commonly used brand names are:

For veterinary-labeled products—

- Amoxicillin
- Amoxi-Inject
- Amoxi-Tablets
- Amoxi-Tabs
- Biomax Oral Suspension
- Biomax Tablets
- Moxil-50 Suspension
- Polypen

For human-labeled products—

- Ampicin
- Ampicin-N
- Apo-Ampicillin
- Nu-Ampicillin
- Ormipen
- Ormipen-N
- Principen
- Penbritin
- Polycillin-N
- Robanox-V
- Robanox-V Oral Suspension
- Robanox-V Tablets
- Moxilean-50 Suspension
- Robamox-V Oral Suspension
- Robamox-V Tablets
- Robamox-V Oral Suspension
- Robantin
- Totacillin

CATEGORY: Antibacterial (systemic).

INDICATIONS

Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

GENERAL CONSIDERATIONS

The aminopenicillins have activity against penicillin-sensitive gram-negative bacteria as well as some gram-negative bacteria. Ampicillin is effective against alpha- and beta-hemolytic streptococci, including Streptococcus equi, non–penicillinase-producing Staphylococcus species, some Bacillus anthracis, and most strains of Clostridia. Amoxicillin has the same spectrum of activity as ampicillin, but has slightly better activity against some gram-negative bacteria, including E. coli, and Salmonella species. Most anaerobic bacteria, except beta-lactamase-producing strains of Bacteroides, are sensitive to amoxicillin. The aminopenicillins are subject to destruction by beta-lactamases and therefore are not effective against some bacteria that produce these enzymes. Most strains of Klebsiella, Proteus, and Pseudomonas are resistant.

ACCEPTED

Dermatitis, bacterial (treatment)—Dogs: Amoxicillin is indicated in the treatment of bacterial dermatitis caused by susceptible organisms; however, amoxicillin is not the treatment of choice because bacteria that cause dermatitis are often resistant to this medication. Gastroenteritis, bacterial (treatment)—Cats and dogs: Amoxicillin and parenteral ampicillin are indicated in the treatment of bacterial gastrointestinal tract infections caused by susceptible organisms. Genitourinary tract infections, bacterial (treatment)—Cats and dogs: Amoxicillin and parenteral ampicillin are indicated and [oral] ampicillin is used in the treatment of genitourinary tract infections, including cystitis and urethritis, caused by susceptible organisms.

Pneumonia, bacterial (treatment)—Calves, nonruminating: Parenteral ampicillin is indicated for the treatment of respiratory tract infections caused by susceptible organisms, including some bacterial pneumonias associated with shipping fever complex. Cats and dogs: Parenteral ampicillin and [amoxicillin] are indicated in the treatment of pneumonia caused by susceptible organisms. Cattle: Parenteral amoxicillin and parenteral ampicillin are indicated for the treatment of respiratory tract infections caused by susceptible organisms, including some bacterial pneumonias associated with shipping fever complex.

Pododermatitis, necrotic, acute (treatment)—Cattle: Parenteral amoxicillin is indicated in the treatment of acute necrotic pododermatitis caused by susceptible Fasobacterium necrophorum if administered early in the course of the disease, amoxicillin may reduce the severity of lesions.

Skin and soft tissue infections (treatment)—Cats and dogs: Amoxicillin and parenteral ampicillin are indicated in the treatment of soft tissue infections and wounds caused by susceptible organisms. Horses: Parenteral ampicillin is used in the treatment of skin and soft tissue infections, including abscesses and wounds, caused by susceptible organisms.

Strangles (treatment)—Horses: Parenteral ampicillin may be used in the treatment of strangles caused by susceptible Streptococcus equi.

Tonsillitis, bacterial (treatment); or Tracheobronchitis, bacterial (treatment); or Upper respiratory tract infections (treatment)—Cats and dogs: Amoxicillin and parenteral ampicillin are indicated in the treatment of tonsillitis, tracheobronchitis, and upper respiratory tract infections caused by susceptible organisms.

ACCEPTANCE NOT ESTABLISHED

Bacterial infections (treatment)—Calves, nonruminating: Until recently, amoxicillin tablets were labeled in the United States for use in the treatment of infections in calves caused by susceptible E. coli. Although the labeled product is no longer available, oral amoxicillin may be used in the treatment of susceptible infections in calves.

Leptospirosis (treatment)—Dogs: Although the efficacy has not been established, amoxicillin is used in therapy of leptospirosis in dogs. Penicillin and penicillin derivatives (including amoxicillin) are considered to be effective for eliminating leptospiremia, but it is not known if they are effective in terminating the carrier state.

REGULATORY CONSIDERATIONS

U.S.—Ampicillin is not labeled for use in horses to be used for food production. Withdrawal times have been established for amoxicillin and ampicillin. See the Dosage Forms section.
The aminopenicillins penetrate gram-negative bacterial cell walls more rapidly than do the natural penicillins such as penicillin G and therefore are more efficient in destroying those organisms. Amoxicillin enters the gram-negative cell more easily than does ampicillin; this is considered to be the basis for the greater activity of amoxicillin against some gram-negative bacteria.\[^{[19]}\]

**Absorption:**

The aminopenicillins are stable in gastric fluid.\[^{[8]}\] One of the primary differences between ampicillin and amoxicillin is the difference in absorption after oral administration. A higher percentage of amoxicillin than of ampicillin is absorbed after oral administration to cats, dogs, pigs, and preruminant calves.\[^{[25–28; 46]}\] In people, the more complete oral absorption of amoxicillin leaves less drug remaining in the intestinal tract than does ampicillin; therefore amoxicillin is associated with a lower incidence of diarrhea as a side effect; however, amoxicillin is also less effective than ampicillin in the treatment of some intestinal bacterial infections in people.\[^{[20]}\]

In horses, amoxicillin sodium is well absorbed following intramuscular or subcutaneous administration; however, oral dosage forms are poorly absorbed by adult horses\[^{[84]}\]. Oral absorption of amoxicillin has been reported to be between 5.3 and 10.4\%\[^{[42; 86]}\]. Ampicillin trihydrate administered intramuscularly produces lower ampicillin blood concentrations that extend over a longer period of time than does amoxicillin sodium\[^{[27–49]}\].

Note: There is evidence that giving amoxicillin and clavulanate concurrently has little effect on the pharmacokinetics of either medication\[^{[82]}\]. Therefore, the following information based on dosing with amoxicillin and clavulanate combination may be useful in predicting the absorption of amoxicillin alone.

**Calves—**

Preruminant calves (2 weeks old): Absorption of amoxicillin when administered orally in combination with clavulanate at doses of 10 to 20 mg per kg of body weight (mg/kg) is 34 to 36\%.

Early ruminant calves (6 weeks old): Absorption of amoxicillin and clavulanate combination is much poorer than in preruminant calves given the same oral dose; therapeutic serum amoxicillin concentrations are not achieved in early ruminant calves.

**Distribution:**

The aminopenicillins are rapidly and widely distributed into most body fluids with the exception of fluids of the eye and the prostate gland; also, distribution into cerebrospinal fluid is low unless the meninges are inflamed.\[^{[8]}\] Penetration into synovial fluid is high.\[^{[87–89]}\]

**Volume of distribution—**

- **Ampicillin:**
  - **Horses—**
    - **Adult:**
      - Area—325 mL per kg of body weight (mL/kg)\[^{[42]}\].
      - Steady state—192 mL/kg\[^{[86]}\].
    - **Foal (6 to 7 days of age):**
      - Area—369 mL/kg\[^{[41]}\].
      - Steady state—263 mL/kg\[^{[41]}\].
- **Ampicillin:**
  - **Cats—** Area: 116 mL/kg\[^{[40]}\].
  - **Horses—** Steady state: 180 mL/kg\[^{[23; 86]}\]; 263 mL/kg\[^{[85]}\].

**Mechanism of action/effect:** Like other penicillins, the aminopenicillins produce their bactericidal effect by inhibiting bacterial cell wall synthesis.\[^{[18]}\] These antibiotics must penetrate the cell wall to attach to specific proteins within the bacterial cell membrane. In actively growing cells, the binding of ampicillin or amoxicillin within the cell wall leads to interference with production of cell wall peptidoglycans and subsequent lysis of the cell in an iso-osmotic environment.\[^{[18–20]}\]
Ampicillin—

Cattle: Low (18%).1 [R-43; 44]
Horses: Very low (6.8 to 8%).3 [R-48]
Rabbits: Low (17.5%).3 [R-44]
Sheep: Low (13.8%).3 [R-43; 44]

Half-life:

Distribution—Ampicillin:

Cats—13 minutes.4 [R-40]
Pigs—5 to 7 minutes.3 [R-19]

Elimination—

Ampicillin:

Goats—67 minutes.5 [R-47]
Horses—

Adult: 39 minutes,4 [R-42]; 85 minutes.4 [R-45; 86].
Foal (6 to 7 days of age): 44 minutes.3 [R-41]
Sheep—46 minutes.4 [R-47]

Ampicillin:

Cats—73 minutes.4 [R-40]
Dogs—20 minutes.4 [R-44]
Horses—37 minutes.4 [R-21]; 42 minutes.4 [R-85]; 93 minutes.4 [R-48]; 103 minutes.4 [R-86].
Pigs—30 to 35 minutes.3 [R-19]
Rabbits—24 minutes.4 [R-44]

Peak serum concentration: Ampicillin—Horses:

6.2 to 9.7 mcg/mL at 16 minutes (intramuscular dose of 10 mg of ampicillin sodium per kg of body weight).4 [R-84]
21.6 mcg/mL in nonpregnant mares (intramuscular dose of 22 mg of ampicillin sodium per kg of body weight).4 [R-87]
8.9 mcg/mL in pregnant mares (intramuscular dose of 22 mg of ampicillin sodium per kg of body weight).4 [R-87]

Elimination: Amoxicillin and ampicillin are primarily excreted unchanged in the urine. Ten to twenty-five percent of the administered dose of amoxicillin is excreted in the form of penicilloic acid.

Total clearance—

Amoxicillin:

Goats—11.4 mL per minute per kg of body weight (mL/min/kg).4 [R-47]
Horses and foals, 6 to 7 days of age—5.7 mL/min/kg.4 [R-41; 42]
Sheep—10.1 mL/min/kg.4 [R-47]
Ampicillin: Horses—3.5 mL/min/kg.6 [R-89].

PRECAUTIONS TO CONSIDER

CROSS-SENSITIVITY AND/OR RELATED PROBLEMS

Animals allergic to one penicillin may be allergic to other penicillins also.3 [R-49]

SPECIES SENSITIVITY

Calves—In neonatal calves, ampicillin administered orally at 12 mg per kg of body weight (mg/kg) every eight hours has been shown to cause diarrhea and malabsorption. Aminopenicillins are not recommended for treatment of enteritis in calves unless secondary complications, such as septicemia or bacterial arthritis, are present.3 [R-9; 10]

Guinea pigs, hamsters, and rabbits—Oral ampicillin often disturbs the normal microflora; the severity of this side effect makes the use of aminopenicillins in these species contraindicated.3 [R-58; 73]

Horses—Large oral doses of the aminopenicillins can disturb the normal cecal microflora and are generally contraindicated.3 [R-49; 58]

Ruminants—Oral ampicillin administration disrupts the rumen flora.

PREGNANCY/REPRODUCTION

The safety of amoxicillin and ampicillin in the treatment of infections during pregnancy has not been established.3 [R-13]
Penicillins have been shown to cross the placenta; however, laboratory animal reproduction studies have shown no evidence of adverse effects in the fetus.3 [R-28; 33; 36]

LACTATION

In humans, penicillins are distributed into milk.3 [R-11; 17]. Amoxicillin has been shown to be distributed into the milk of cows and ewes.3 [R-50]

DRUG INTERACTIONS AND/OR RELATED PROBLEMS

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Antibacterials, bacteriostatic, such as:

Tetracycline (because the aminopenicillins act only on cells that are actively reproducing, bacteriostatic antibiotics may decrease the efficacy of amoxicillin and ampicillin by depressing the activity of target cells; however, the clinical significance of this interference is not well documented)

Probenecid (probenecid is a competitive inhibitor of renal tubular secretion and slows the body clearance of aminopenicillins in horses, calves, pigs, and possibly other species, resulting in increased serum concentrations and longer elimination half-life)3 [R-51; 52; 55]

LABORATORY VALUE ALTERATIONS

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Laboratory value alterations relating specifically to use of aminopenicillins in animals appear to be rarely described. Human laboratory value alterations have been reported and are included in this section.

HUMAN LABORATORY VALUE ALTERATIONS3 [R-2]

The following laboratory value alterations have been reported in humans, and are included in the human monograph Penicillins (Systemic) in USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of amoxicillin or ampicillin in the treatment of animals:
MEDICAL CONSIDERATIONS/CONTRAINDICATIONS
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (∗ = major clinical significance).

Risk-benefit should be considered when the following medical problems exist:

Congestive heart failure or Renal function impairment or Electrolyte imbalance due to other causes (the sodium content of ampicillin sodium administered at high doses may contribute to electrolyte imbalances associated with congestive heart failure, renal function impairment, or other causes; also, because the aminopenicillins are excreted primarily by the kidneys, the dosage regimen should be adjusted to avoid unnecessary accumulation of medication in the plasma and tissues of animals with renal function impairment[∗•∗])

Patient monitoring
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; ∗ = major clinical significance):
Culture and pathogen susceptibility, in vitro, and Minimum inhibitory concentration (MIC) (in vitro cultures and MIC tests should be done on samples collected prior to aminopenicillin administration to determine pathogen susceptibility)

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence more frequent

Calves

Diarrhea and malabsorption[∗•∗]
Note: In healthy neonatal calves, oral administration of 12 mg of ampicillin per kg of body weight (mg/kg) every eight hours has been shown to cause diarrhea and malabsorption.[∗•∗]

Incidence unknown

All species[∗; 6; 8; 11; 49]

Hypersensitivity reactions, specifically acute anaphylaxis; hypersensitivity (urticaria, fever)

Horses

Diarrhea—primarily with oral dosage forms[∗•∗]

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME
Incidence more frequent

Horses

Injection site reaction (mild to moderate heat, pain, or swelling)—with ampicillin trihydrate[∗•∗; 67]

Incidence less frequent[∗•∗; 61]

Cats and dogs

Anorexia[∗•∗], diarrhea[∗•∗], vomiting[∗•∗]

HUMAN SIDE/ADVERSE EFFECTS[∗•∗]
In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Penicillins (Systemic) in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of amoxicillin or ampicillin in the treatment of animals:

Incidence more frequent

Gastrointestinal reactions; headache; oral candidiasis; vaginal candidiasis

Incidence less frequent

Allergic reactions, specifically anaphylaxis; exfoliative dermatitis; serum sickness–like reactions; skin rash, hives, or itching

Incidence rare

Clostridium difficile colitis; interstitial nephritis; leukopenia or neutropenia; pain at site of injection; thrombocytopenia; seizures

Note: Clostridium difficile colitis may occur up to several weeks after discontinuation of these medications.

Interstitial nephritis is seen primarily with methicillin, and to a lesser degree with nafcillin and oxacillin, but may occur with any penicillin. Seizures are more likely to occur in patients receiving high doses of a penicillin and/or patients with severe renal function impairment.

OVERDOSE
For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

VETERINARY DOSING INFORMATION
All species: Beta-lactam antibiotics are believed to produce time-dependent bacterial killing; that is, efficacy is related to the time the
serum concentrations are maintained above the minimum inhibitory concentration (MIC) of the pathogen. As such, in critical cases frequent dosings (short dosage intervals) may be preferred.

FOR ORAL DOSAGE FORMS ONLY
Calves—Both amoxicillin and ampicillin are more bioavailable in calves when administered in a glucose-glycine-electrolyte solution than when administered with water or milk; however, unlike ampicillin, the bioavailability of amoxicillin is not significantly altered by administration with milk as compared with water.[R-60]

Dogs—There is some decrease in systemic availability when oral amoxicillin or ampicillin is administered after a standard meal instead of on an empty stomach.[R-25] However, because amoxicillin has twice the oral bioavailability of ampicillin in dogs, the therapeutic efficacy of amoxicillin may be less affected than that of ampicillin by administration with food.[R-60]

Horses—Oral ampicillin is not recommended in adult horses because of poor oral bioavailability (5%) and the risk of disturbing gastrointestinal bacterial balance, thus causing diarrhea.[R-49] Amoxicillin trihydrate is also poorly absorbed following oral administration, with a fractional absorption of 10%; oral amoxicillin trihydrate should be used to treat only highly susceptible pathogens.[R-42]

Sheep—In adult sheep, oral administration of ampicillin does not provide therapeutically significant ampicillin plasma concentrations.[R-61]

FOR TREATMENT OF ADVERSE EFFECTS
Treatment includes the following:
For anaphylaxis:
- Administration of parenteral epinephrine.[R-6]
- Oxygen administration and respiratory support.
- Parenteral fluid administration as needed.

AMOXICILLIN

SUMMARY OF DIFFERENCES
Pharmacology/pharmacokinetics: Absorption—Cats, dogs, pigs, and preruminant calves: A higher percentage of amoxicillin than of ampicillin is absorbed after oral administration.[R-25–28; 46] In dogs, orally administered amoxicillin is about 70% absorbed.[R-46]

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

AMOXICILLIN FOR ORAL SUSPENSION USP

Usual dose: Antibacterial—Cats and dogs: Oral, 10 to 22 mg per kg of body weight every eight, twelve, or twenty-four hours.[R-14; 26; 69]

Note: Although the efficacy has not been established, amoxicillin is used in the treatment of [leptospirosis][1] in dogs at an intravenous or oral dose of 22 mg per kg of body weight every six to eight hours.[R-91; 92]. It is not known if this therapy will eliminate the carrier state.

Note: As beta-lactams appear to have time-dependent bacterial killing properties, shorter dosing intervals, whenever possible, are recommended to improve efficacy. Once daily dosing should be used only when organisms with very low MICs are suspected.[R-80]

Strength(s) usually available:

- When reconstituted according to manufacturer’s instructions—
  - U.S.:[R-6; 11; 21; 18]
    - Veterinary-labeled product(s)—
      - 50 mg per mL (Rx) [Amoxi-Drop; Biomox Oral Suspension; Robamox-V Oral Suspension].
  - Canada:[R-18]
    - Veterinary-labeled product(s)—
      - 50 mg per mL (Rx) [Moxilean-50 Suspension].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a tight container.

Preparation of dosage form: To reconstitute, add the amount of water recommended by the manufacturer and shake vigorously. Before each use, shake well to resuspend.[R-6; 21]

Stability: After reconstitution, the suspension retains potency for 14 days. Some products require refrigeration.[R-6; 21]

USP requirements: Preserve in tight containers, at controlled room temperature. Contains the labeled amount, within −10% to +20%. Contains one or more suitable buffers, colors, flavorens, preservatives, stabilizers, sweeteners, and suspending agents. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume (multiple-unit containers), pH (5.0–7.5 in the suspension constituted as directed in the labeling), and Water (not more than 3%).[R-17]

AMOXICILLIN TABLETS USP

Usual dose: Antibacterial—Cats and dogs: See Amoxicillin For Oral Suspension USP.

Note: [Calves, nonruminating][1]—An oral dose of 10 to 22 mg per kg of body weight every eight, twelve, or twenty-four hours has been used in the treatment of susceptible bacterial infections.[R-69]

As beta-lactams appear to have time-dependent bacterial killing properties, shorter dosing intervals, whenever possible, are recommended to improve efficacy. Once daily dosing should be used only when organisms with very low MICs are suspected.[R-80]

Strength(s) usually available:

- U.S.:[R-7; 8; 13; 14; 38]
  - Veterinary-labeled product(s):—
    - 50 mg (Rx) [Amoxi-Tabs; Biomox Tablets; Robamox-V Tablets].
    - 100 mg (Rx) [Amoxi-Tabs; Biomox Tablets; Robamox-V Tablets].
    - 150 mg (Rx) [Amoxi-Tabs].
    - 200 mg (Rx) [Amoxi-Tabs; Biomox Tablets; Robamox-V Tablets].
    - 400 mg (Rx) [Amoxi-Tabs; Biomox Tablets; Robamox-V Tablets].
  - Canada:[R-29; 38]
    - Veterinary-labeled product(s):—
      - 50 mg (Rx) [Amoxil Tablets].
      - 100 mg (Rx) [Amoxil Tablets; Cavan].
      - 200 mg (Rx) [Amoxil Tablets].
      - 400 mg (Rx) [Amoxil Tablets].
Withdrawal times: There are no established withdrawal times for food-producing animals in the United States or Canada because products labeled for this use are not available. Based on previously available U.S. product labeling, if oral amoxicillin is administered to nonruminating calves at a dose of 8.8 mg per kg of body weight every twelve hours for five days or less, a meat withdrawal time of 20 days should be sufficient to avoid residues{[R-8].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a tight container.

USP requirements: Preserve in tight containers, at controlled room temperature. Label chewable Tablets to indicate that they are to be chewed before swallowing. Tablets intended solely for veterinary use are so labeled. Contain the labeled amount, within –10% to +20%. Meet the requirements for Thin-layer chromatographic identification test and Dissolution (80% in 90 minutes in water in Apparatus 2 at 75 rpm; and for products labeled as Chewable Tablets: 70% in 90 minutes in water in Apparatus 2 at 75 rpm).{[R-17]

Strength(s) usually available: When reconstituted according to manufacturer’s instructions—
U.S.:{[R-11; 18; 64]
Veterinary-labeled product(s)—
100 mg per mL (Rx) [Amoxi-Inject (3-gram vial labeled for cats and dogs)].
250 mg per mL (Rx) [Amoxi-Inject (3-gram vial labeled for cats and dogs or 25-gram vial labeled for cattle)].
Canada:
Veterinary-labeled product(s)—
Not commercially available.{[R-18]

Withdrawal times:{[R-11]}

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>25</td>
<td>96</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that the recommended withdrawal times are based on a dose of 6.6 mg per kg of body weight every twenty-four hours and a course of therapy not exceeding five days.{[R-11]

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: Dosage form is reconstituted by adding the amount of sterile water for injection recommended by the manufacturer.{[R-11]

Stability: After reconstitution, the suspension retains potency for twelve months when refrigerated or for three months when stored at room temperature (72 °F).{[R-11]

USP requirements: Preserve in Containers for Sterile Solids. A sterile mixture of Amoxicillin and one or more suitable buffers, preservatives, stabilizers, and suspending agents. Label it to indicate that it is for veterinary use only. Contains the labeled amount, within –10% to +20%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH (5.0–7.0, in the suspension constituted as directed in the labeling), and Water (11.0–14.0%).{[R-17]

AMPICILLIN

SUMMARY OF DIFFERENCES

Pharmacology/pharmacokinetics: Absorption—Calves, nonruminating, cats, dogs, and pigs: With oral administration, ampicillin is more poorly absorbed than is amoxicillin; the dosage is adjusted to compensate. In dogs, orally administered ampicillin trihydrate is only about 35% absorbed; in cats, oral anhydrous ampicillin is about 20 to 40% absorbed.

ADDITIONAL DOSING INFORMATION

See also Veterinary Dosing Information.

Pharmacology/pharmacokinetics: Horses—There is evidence that administering ampicillin concurrently with either gentamicin or kanamycin does not alter the pharmacokinetics of either of the medications.

Parenteral dosage forms—Ampicillin sodium produces higher plasma concentrations than does ampicillin trihydrate; ampicillin trihydrate produces relatively low plasma concentrations but maintains measurable concentrations for a longer period of time. All rights reserved
ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

AMPICILLIN CAPSULES USP

Usual dose: Antibacterial—

Cats: Oral, 10 to 20 mg per kg of body weight every eight to twenty-four hours.\(^{[R-40; 69]}\)

Dogs: Oral, 20 to 40 mg per kg of body weight every eight to twelve hours.\(^{[R-12; 69]}\)

Note: As beta-lactams appear to have time-dependent bacterial killing properties, shorter dosing intervals, whenever possible, are recommended to improve efficacy. Once daily dosing should be used only when organisms with very low MICs are suspected.\(^{[R-80]}\)

Strength(s) usually available:

U.S.—\(^{[R-16; 17]}\)

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [Omnipen; Principen; Totacillin; \(\text{Gen").}\)]

500 mg (Rx) [Omnipen; Principen; Totacillin; \(\text{Gen").}\)]

Canada—\(^{[R-16; 17]}\)

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [Apo-Ampli; Novo-Ampicillin; Nu-Ampli; Penbrittin].

500 mg (Rx) [Apo-Ampli; Novo-Ampicillin; Nu-Ampli; Penbrittin].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Label Capsules to indicate whether the ampicillin therein is in the anhydrous form or is the trihydrate. Contain an amount of ampicillin (anhydrous or as the trihydrate) equivalent to the labeled amount of ampicillin, within −10% to +20%. Meet the requirements for Identification, Dissolution (75% in 45 minutes in water in Apparatus 1 at 100 rpm), Uniformity of dosage units, and Loss on drying (not more than 4.0% for the anhydrous and 10.0–15.0% for the trihydrate).\(^{[R-17]}\)

\(^{[1]}\)Not included in Canadian product labeling or product not commercially available in Canada.

PARENTERAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of ampicillin free acid (not the sodium salt).

AMPICILLIN FOR INJECTABLE SUSPENSION USP

Usual dose: Antibacterial—

Cats: Intramuscular or subcutaneous, 10 to 20 mg per kg of body weight every twelve to twenty-four hours.\(^{[R-40]}\)

Dogs: Intramuscular or subcutaneous, 10 to 50 mg per kg of body weight every twelve hours.\(^{[R-32]}\)

Cattle and calves, including nonruminating calves: Intramuscular, 4.4 to 11 mg per kg of body weight every twenty-four hours.\(^{[R-3]}\)

Note: As beta-lactams appear to have time-dependent bacterial killing properties, shorter dosing intervals, whenever possible, are recommended to improve efficacy. Once daily dosing should be used only when organisms with very low MICs are suspected.\(^{[R-80]}\)

Size(s) usually available:

U.S.—\(^{[R-3; 38]}\)

Veterinary-labeled product(s):

10 grams (Rx) [Polyflex].

25 grams (Rx) [Polyflex].

Canada—\(^{[R-5; 38]}\)

Veterinary-labeled product(s):

10 grams (Rx) [Polyflex].

25 grams (Rx) [Polyflex].

Withdrawal times: \(^{[R-3]}\)

U.S.—\(^{[R-3]}\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>6</td>
<td>48</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that treatment should not exceed seven days for withdrawal times to apply.\(^{[R-1]}\)

Canada—\(^{[R-5]}\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>Withdrawal time</td>
</tr>
<tr>
<td>Pigs</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>48</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that the recommended withdrawal times are based on a dose of 6 mg per kg of body weight every twenty-four hours and a course of therapy not exceeding seven days.\(^{[R-5]}\)

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form:

The sizes may be reconstituted according to manufacturer’s directions to one of the following strengths: 100, 200, 250, 300, or 400 mg per mL. Before each use, shake well to resuspend.\(^{[R-5]}\)

Stability: After reconstitution, the solution retains potency for twelve months when refrigerated and for three months when stored at 25 °C.\(^{[R-3]}\)

USP requirements: Preserve in Containers for Sterile Solids. A dry mixture of ampicillin trihydrate and one or more suitable buffers,
preservatives, stabilizers, and suspending agents. Contains the equivalent of the labeled amount of ampicillin, within -10% to +20%. Meets the requirements for identification, Bacterial endotoxins, Sterility, pH (5.0–7.0, in the suspension constituted as directed in the labeling), and Water (11.4–14.0%), and for Uniformity of dosage units, and Labeling under Injections.\textsuperscript{[R-17]}

**AMPICILLIN FOR INJECTION USP**

**Usual dose: [Antibacterial]\textsuperscript{1—}**

- **Cats and dogs:** Intramuscular or intravenous, 10 to 20 mg (free acid) per kg of body weight every six to eight hours.\textsuperscript{[R-32; 40]}
- **Horses:** Intramuscular or intravenous, 10 to 20 mg (free acid) per kg of body weight every six to eight hours.\textsuperscript{[R-78; 79]}
- **Note:** The dose of 10 to 20 mg per kg of body weight every six to eight hours is sufficient for most sensitive bacteria; however, for infections due to moderately resistant organisms or infections associated with natural tissue barriers, such as those of the central nervous system, doses of up to 25 to 40 mg per kg of body weight every six to eight hours have been used.\textsuperscript{[R-81]}
- A possible increased risk of gastrointestinal side effects with increasing dose should be considered.

**Size(s) usually available:**

**U.S.—**\textsuperscript{[R-1; 18; 76]}

- Veterinary-labeled product(s):
  - Not commercially available.
- Human-labeled product(s):
  - 125 mg (free acid) (Rx) [Omnipen-N; Polycillin-N; GENERIC].
  - 250 mg (free acid) (Rx) [Omnipen-N; Polycillin-N; Totacillin-N; GENERIC].
  - 500 mg (free acid) (Rx) [Omnipen-N; Polycillin-N; Totacillin-N; GENERIC].
  - 1 gram (free acid) (Rx) [Omnipen-N; Polycillin-N; Totacillin-N; GENERIC].
  - 2 grams (free acid) (Rx) [Omnipen-N; Polycillin-N; Totacillin-N; GENERIC].
  - 10 grams (free acid) (Rx) [Omnipen-N; Polycillin-N; GENERIC].
- Canada—\textsuperscript{[R-77]}
  - Veterinary-labeled product(s):
    - Not commercially available.
  - Human-labeled product(s):
    - 125 mg (free acid) (Rx) [Ampicin; Penbritin].
    - 250 mg (free acid) (Rx) [Ampicin; Penbritin].
    - 500 mg (free acid) (Rx) [Ampicin; Penbritin].
    - 1 gram (free acid) (Rx) [Ampicin; Penbritin].
    - 2 grams (free acid) (Rx) [Ampicin; Penbritin].

**Packaging and storage:** Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect the reconstituted solution from freezing.

**Preparation of dosage form:** Dosage form should be reconstituted according to manufacturer’s directions.\textsuperscript{[R-1]}

**Stability:**

- After reconstitution, the solution retains potency for 1 hour at room temperature (70 to 75 °C).\textsuperscript{[R-1]}
- After reconstitution for intravenous infusion, solutions with concentrations of up to 30 mg per mL retain at least 90% of their potency for 2 to 8 hours at room temperature or up to 72 hours if refrigerated in suitable diluents (see manufacturer’s package insert).\textsuperscript{[R-75]}

Concentrated solutions (100 mg per mL) prepared from pharmacy bulk vials retain their potency for 2 hours at room temperature or 4 hours if refrigerated.\textsuperscript{[R-75]}

Diluted solutions (20 mg per mL or less) in 5% dextrose injection retain their potency for 2 hours at room temperature or 3 hours if refrigerated.\textsuperscript{[R-75]}

**Incompatibilities:** Extemporaneous admixtures of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation. These types of antibacterial agents should not be mixed in the same intravenous bag, bottle, or tubing.

**Additional information:** This product contains approximately 3 milliequivalents (mEq; millimoles [mmol]) of sodium per gram of ampicillin and could result in electrolyte overload in some animals.\textsuperscript{[R-54]}

**USP requirements:** Preserve in Containers for Sterile Solids. Protect the constituted solution from freezing. Contains an amount of Ampicillin Sodium equivalent to the labeled amount of ampicillin within -10% to +15%. Meets the requirements for Constituted solution, Bacterial endotoxins, Particulate matter, Uniformity of dosage units, and for Identification tests, Crystallinity, pH, and Water under Ampicillin Sodium, and for Sterility tests, and Labeling under Injections.\textsuperscript{[R-17]}

\textsuperscript{1Not included in Canadian product labeling or product not commercially available in Canada.}

Developed: 07/25/95
Revised: 06/30/02
Interim revision: 07/18/96; 06/02/97; 05/27/98; 10/12/99; 04/04/03

**REFERENCES**

44 AMINOPENICILLINS Veterinary—Systemic

54. Panel comment, Rec 2/23/95.
55. Panel comment, Rec 3/9/95.
56. Panel comment, Rec 2/22/95.
57. Panel comment, Rec 3/16/95.
59. Panel comment, Rec 2/17/95.
60. Committee comment, Rec 2/27/95.
64. Panel comment, Rec 6/22/95.
66. Committee comment, Rec 1/15/02.
92. Committee comment, 1/22/02.
AMOXICILLIN AND CLAVULANATE Veterinary—Systemic

A commonly used brand name for a veterinary-labeled product is Clavamox.

Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:
Antibacterial (systemic).

INDICATIONS
Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in Canada.

GENERAL CONSIDERATIONS
Amoxicillin has activity against penicillin-sensitive gram-positive bacteria as well as some gram-negative bacteria. The gram-positive spectrum of activity includes alpha- and beta-hemolytic streptococci, some Staphylococci species, Clostridia species, and some Bacillus anthracis.[R-2] Amoxicillin is also effective against gram-negative bacteria, including Escherichia coli (E. coli), many strains of Salmonella, and Pasteurella multocida.[R-2] Amoxicillin is sensitive to destruction by beta-lactamases and therefore when administered by itself is not effective against bacteria, such as Klebsiella and Proteus, that produce these enzymes.[R-2]

Clavulanate is a naturally occurring noncompetitive inhibitor of beta-lactamase produced by gram-positive, and also many gram-negative, bacteria.[R-3; 4] Although it has a beta-lactam chemical structure, clavulanic acid has little antibacterial activity of its own. However, when clavulamic acid is administered concurrently with amoxicillin, it extends the activity of amoxicillin by preventing its destruction by bacterial enzymes. Beta-lactamase inhibitors will only assist in the destruction of bacteria that produce beta-lactamase enzymes; other forms of resistance, such as alteration of penicillin-binding protein, are not affected. Also, the beta-lactam structure of amoxicillin and clavulanate may stimulate some bacteria to produce more beta-lactamase; it is easier for clavulanate to protect amoxicillin against a small amount of enzyme than against a large amount.

Clavulanate extends the spectrum of activity of amoxicillin to include some Staphylococcus species.[R-4; 6] Most anaerobes, including Bacteroides fragilis, are susceptible to the combination of clavulanic acid and amoxicillin.[R-5] However, some beta-lactamase enzymes, including those produced by Enterobacter and Pseudomonas, are unaffected by clavulanate.[R-6]

ACCEPTED
Periodontal infections (treatment)—Dogs: Amoxicillin and clavulanate combination is indicated in the treatment of periodontal infections caused by susceptible strains of aerobic and anaerobic bacteria.[R-1; 11]

Skin and soft tissue infections (treatment)—Cats and dogs.[R-7; 8]
Amoxicillin and clavulanate combination is indicated in the treatment of skin and soft tissue infections caused by susceptible Staphylococcus species, E. coli, Pasteurella species, and Streptococcus species.

Urinary tract infections, bacterial (treatment)—Cats[R-7] and [dogs]:[R-9–11] Amoxicillin and clavulanate combination is indicated in the treatment of urinary tract infections, including those caused by susceptible E. coli.

ACCEPTANCE NOT ESTABLISHED
[Osteomyelitis (treatment)]—Cats and dogs: There are insufficient data to show that amoxicillin and clavulanate combination is effective in the treatment of osteomyelitis in cats and dogs; however, in vitro studies show that the bacteria causing this type of infection are often susceptible.[R-12–14; 17]

Not included in Canadian product labeling or product not commercially available in Canada.

CHEMISTRY
Source:
Amoxicillin—Semisynthetic derivative of ampicillin.[R-12]
Clavulanate—A fermentation product of the actinomycete Streptomyces clavuligerus.[R-7; 8]

Chemical name:
Amoxicillin—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[3-(hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate[2S-[2alpha,5alpha,6beta(S'')]]—.[R-11]
Clavulanate potassium—4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, [2R-(2alpha,3Z,5alpha)]]—.[R-13]

Molecular formula:
Amoxicillin—C16H19N3O5S.[R-7; 8]
Clavulanate potassium—C18H22N4O6S2K.[R-13]

Molecular weight:
Amoxicillin—419.45, [R-13]
Clavulanate potassium—237.25.[R-13]

Description:
Amoxicillin USP—White, practically odorless, crystalline powder.[R-14]
Clavulanate Potassium USP—White to off-white powder. Is moisture-sensitive.[R-14]

pKa:
Amoxicillin—2.8 and 7.2.[R-16]
Clavulanate—2.7.[R-17]

Solubility:
Amoxicillin USP—Slightly soluble in water and in methanol; insoluble in carbon tetrachloride, and in chloroform.[R-14]
Clavulanate Potassium USP—Freely soluble in water, but stability in aqueous solution is not good; optimum stability at a pH of 6.0 to 6.3; soluble in methanol, with decomposition.[R-14]

PHARMACOLOGY/PHARMACOKINETICS
Note: There is evidence that giving amoxicillin with clavulanate has little effect on the pharmacokinetics of either medication.[R-17; 24]

Mechanism of action/effect:
Amoxicillin—Bactericidal. Amoxicillin must reach and bind to the penicillin-binding proteins on the inner membrane of the bacterial...
cell wall. In actively growing cells, the binding of amoxicillin within the cell wall leads to interference with production of cell wall peptidoglycans and subsequent lysis of the cell in an iso-osmotic environment.[R-18-20]

Clavulanate—Binds irreversibly to susceptible beta-lactamase enzymes, preventing hydrolysis of the amoxicillin beta-lactam ring. When clavulanate binds with the enzyme, a chemical complex is formed, which destroys the clavulanate and inactivates the beta-lactamase.[R-3, 4, 6]

Absorption:

Cats and dogs—Both amoxicillin and clavulanate are stable in gastric fluid and, therefore, are well absorbed after oral administration.[R-6; 7, 21-23]

Calves—

Perruminant calves (2 weeks old): Absorption of amoxicillin when administered in combination with clavulanate at doses of 10 to 20 mg per kg of body weight (mg/kg) is 34 to 36%.

Early ruminant calves (6 weeks old): Absorption of amoxicillin and clavulanate combination is much poorer than in preruminant calves given the same dose; early ruminant calves do not develop therapeutic serum amoxicillin concentrations.[R-26]

Horses—Orally administered amoxicillin is only 10% absorbed in adult horses.[R-16]

Peak serum concentration: Amoxicillin—

Calves, preruminant:

Oral, 10 mg/kg dose—2 mcg per mL (mcg/mL) at 78 minutes.[R-26]

Oral, 20 mg/kg dose—3.3 mcg/mL at 64 minutes.[R-26]

Dogs: Oral, 12.5 mg/kg dose—5 to 6 mcg/mL at 60 minutes.[R-38]

Distribution: Cats and dogs—Amoxicillin and clavulanate diffuse into most body tissues and fluids; however, distribution of amoxicillin into cerebrospinal fluid is low unless the meninges are inflamed.[R-7, 8]

Elimination: Amoxicillin—Primarily excreted unchanged in the urine. 10 to 25% is excreted in the form of penicilloic acid.[R-25]

PRECAUTIONS TO CONSIDER

CROSS-SENSITIVITY AND/OR RELATED PROBLEMS

Animals allergic to one penicillin or cephalosporin may also be allergic to amoxicillin or clavulanate.[R-9]

SPECIES SENSITIVITY

Horses and rabbits—This medication is generally contraindicated in these species because of the potential for disturbance of the normal gastrointestinal microflora.[R-6]

PREGNANCY/REPRODUCTION

The safety of administration of amoxicillin and clavulanate to pregnant or breeding animals is unknown.[R-8, 9] Penicillins have been shown to cross the placenta; however, laboratory animal reproduction studies have shown no evidence of adverse effects on the fetus.[R-17]

LACTATION

In humans, penicillins are distributed into milk, and the same is true for many animals.[R-27, 28]

DRUG INTERACTIONS AND/OR RELATED PROBLEMS

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Probenecid

(probenecid decreases tubular secretion and slows the body clearance of amoxicillin, resulting in increased serum concentrations and longer elimination half-lives in many species[R-24, 29]; however, clavulanic acid is unlikely to be affected because it is cleared primarily by glomerular filtration[R-17])

LABORATORY VALUE ALTERATIONS

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):

Note: Laboratory value alterations relating specifically to use of amoxicillin and clavulanate in animals appear to be rare. Human laboratory value alterations have been reported and are included in this section.

HUMAN LABORATORY VALUE ALTERATIONS[R-15]

The following laboratory value alterations have been reported in humans, and are included in the human monograph Penicillins and Beta-lactamase Inhibitors (Systemic) in USP DI Volume 1; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of amoxicillin and clavulanate combination in the treatment of animals:

With diagnostic test results

Glucose, urine

(high urinary concentrations of a penicillin may produce false-positive or falsely elevated test results with copper-reduction tests [Benedict’s, Clinistix, or Fehling’s]; glucose enzymatic tests [Clinistix or Testape] are not affected)

Direct antiglobulin (Coombs’) tests

(false-positive result may occur during therapy with any penicillin)

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) and Alkaline phosphatase and Aspartate aminotransferase (AST [SGOT]) and Lactate dehydrogenase (LDH), serum

(values may be increased)

Bilirubin, serum

(concentrations may be increased)

Estradiol or Estriol-glucuronide or Estriol, total conjugated, or Estrone, conjugated

(concentrations may be transiently decreased in pregnant women following administration of amoxicillin)
White blood count
(leukopenia or neutropenia is associated with the use of all penicillins; the effect is more likely to occur with prolonged therapy and severe hepatic function impairment)

PATIENT MONITORING
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; *= major clinical significance):
Culture and susceptibility, in vitro, and
Minimum inhibitory concentration (MIC)
*(in vitro cultures and MIC test should be done on samples collected prior to amoxicillin and clavulanate administration to determine pathogen susceptibility)*

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
All species
*Hypersensitivity reactions, specifically acute anaphylaxis, fever, or urticaria*

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME
Incidence less frequent
Cats and dogs
*Anorexia; diarrhea; vomiting*

HUMAN SIDE/ADVERSE EFFECTS
In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Penicillins and Beta-lactamase Inhibitors (Systemic) in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of amoxicillin and clavulanate in the treatment of animals:
Incidence more frequent
*Gastrointestinal reactions; headache*
Incidence less frequent
*Allergic reactions, specifically anaphylaxis; oral candidiasis; serum sickness–like reactions; skin rash, hives, or itching; vaginal candidiasis*
Incidence rare
*Chest pain; chills; Clostridium difficile colitis; dysuria or urinary retention; edema; epistaxis; erythema multiforma or Stevens-Johnson syndrome; fatigue; glossitis; hepatic dysfunction, including cholestatic hepatitis; leukopenia or neutropenia; malaise; platelet dysfunction; proteinuria or pyuria; seizures; toxic epidermal necrolysis*
Note: *Clostridium difficile colitis may occur up to several weeks after discontinuation of these medications.***Seizures are more likely to occur in patients receiving high doses of a penicillin and/or patients with severe renal function impairment.***

OVERDOSE
For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-000; a fee may be required for consultation) and/or the drug manufacturer.

VETERINARY DOSING INFORMATION
In cats and dogs, the therapeutic efficacy of amoxicillin and clavulanate is not significantly affected by administration with food.

FOR TREATMENT OF ADVERSE EFFECTS
For anaphylaxis
• Parenteral epinephrine
• Oxygen administration and breathing support.

ORAL DOSAGE FORMS
Note: The dosing and strengths of the dosage forms available are expressed in terms of clavulanic acid (not the potassium salt).

AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP
Usual dose:
**Antibacterial**—
*Cats* and *dogs*: Oral, 11 to 20 mg of amoxicillin and 2.75 to 5 mg of clavulanic acid per kg of body weight every eight to twelve hours.*

Strength(s) usually available:
When reconstituted according to manufacturer’s instructions—
**U.S.:**
Veterinary-labeled product(s)—
50 mg of amoxicillin and 12.5 mg clavulanic acid per mL (Rx) [*Clavamox*].

**Canada:**
Veterinary-labeled product(s)—
50 mg of amoxicillin and 12.5 mg of clavulanic acid per mL (Rx) [*Clavamox*].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a tight container.

Stability: After reconstitution, suspensions retain their potency for ten days if refrigerated.

Auxiliary labeling:
• Refrigerate.
• Shake well.

USP requirements: Preserve in tight containers, at controlled room temperature. Contains the labeled amount of amoxicillin, within –10% to +20%, and an amount of clavulanate potassium equivalent to the
labeled amount of clavulanic acid, within –10% to +25%. Contains one or more suitable buffers, colors, flavors, preservatives, stabilizers, sweeteners, and suspending agents. Meets the requirements for Identification, pH (3.8–6.6, in the suspension constituted as directed in the labeling, the test being performed immediately after constitution), and Water (not more than 7.5%, where the label indicates that after constitution as directed, the suspension contains 25 mg of amoxicillin per mL; not more than 8.5%, where the label indicates that after constitution as directed, the suspension contains 50 mg of amoxicillin per mL). [R-30]–[R-14]

**AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP**

**Usual dose:** See *Amoxicillin and Clavulanate Potassium for Oral Suspension USP*.

**Strength(s) usually available** [R-30]–[R-10]:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. —</td>
<td>Veterinary-labeled product(s)</td>
</tr>
<tr>
<td>50 mg of amoxicillin and 12.5 mg of clavulanic acid (Rx)</td>
<td>Clavamox</td>
</tr>
<tr>
<td>100 mg of amoxicillin and 25 mg of clavulanic acid (Rx)</td>
<td>Clavamox</td>
</tr>
<tr>
<td>200 mg of amoxicillin and 50 mg of clavulanic acid (Rx)</td>
<td>Clavamox</td>
</tr>
<tr>
<td>300 mg of amoxicillin and 75 mg of clavulanic acid (Rx)</td>
<td>Clavamox</td>
</tr>
<tr>
<td>Canada—</td>
<td>Veterinary-labeled product(s)</td>
</tr>
<tr>
<td>50 mg of amoxicillin and 12.5 mg of clavulanic acid (Rx)</td>
<td>Clavamox</td>
</tr>
<tr>
<td>100 mg of amoxicillin and 25 mg of clavulanic acid (Rx)</td>
<td>Clavamox</td>
</tr>
<tr>
<td>200 mg of amoxicillin and 50 mg of clavulanic acid (Rx)</td>
<td>Clavamox</td>
</tr>
<tr>
<td>300 mg of amoxicillin and 75 mg of clavulanic acid (Rx)</td>
<td>Clavamox</td>
</tr>
</tbody>
</table>

**Packaging and storage:** Store below 25 °C (77 °F), unless otherwise specified by manufacturer. Store in a tight container.

**Auxiliary labeling:**
- Do not remove from foil strip until ready to use.
- **USP requirements:** Preserve in tight containers. Label chewable Tablets to include the word “chewable” in juxtaposition to the official name. The labeling indicates that chewable Tablets may be chewed before being swallowed or may be swallowed whole. Tablets intended for veterinary use only are so labeled. Contain the labeled amount of amoxicillin, within –10% to +20%, and an amount of clavulanate potassium equivalent to the labeled amount of clavulanic acid, within –10% to +20%. Meet the requirements for Identification, Disintegration (for Tablets labeled for veterinary use only, 30 minutes, in simulated gastric fluid TS). Dissolution (85% of amoxicillin and 80% of clavulanic acid in 30 minutes [or 45 minutes where the Tablets are labeled as chewable] in water in Apparatus 2 at 75 rpm [Note: Tablets labeled for veterinary use only are exempt from this requirement]). Uniformity of dosage units, and Water (not more than 6.0% where the Tablets are labeled as being chewable: not more than 7.5% where the labeled amount of amoxicillin in each Tablet is 250 mg or less; not more than 10.5% where the labeled amount of amoxicillin in each Tablet is greater than 250 mg). [R-30]–[R-14]

References

32. Panel comment, 4/7/95.
CEPHALOSPORINS Veterinary—Systemic

This monograph includes information on the following: Cefaclor; Cefadroxil; Cefazolin; Cefixime; Cefotaxime; Cefotetan; Cefoxitin; Ceftriaxone; Cefprozil; Cefuroxime. Some commonly used brand names are:

For veterinary-labeled products—

- Cefalu-Drops [Cefadroxil]
- Cefalu-Tabs [Cefadroxil]
- Excenel [Ceftiofur]

For selected human-labeled products—

- Apo-Cefaclor [Cefaclor]
- Ceporacin [Cephalothin]
- Ceporanin [Cephalothin]
- Cefadroxil [Cefadroxil]
- Cefaclor [Cefaclor]
- Cefadroxil [Cefadroxil]
- Cefazolin [Cefazolin]
- Cefdinir [Cefdinir]
- Cefixime [Cefixime]
- Cefmenoxime [Cefmenoxime]
- Cefonicid [Cefonicid]
- Cefonicid [Cefonicid]
- Cefoperazone [Cefoperazone]
- Cefotaxime [Cefotaxime]
- Cefotetan [Cefotetan]
- Cefoxitin [Cefoxitin]
- Cefprozil [Cefprozil]
- Cefuroxime [Cefuroxime]
- Cefuroxime [Cefuroxime]
- Cefuroxime [Cefuroxime]
- Ceftriaxone [Ceftriaxone]
- Cefuroxime [Cefuroxime]

Note: Bracketed information in the INDICATIONS section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

GENERAL CONSIDERATIONS

Cephalosporins are wide-spectrum antibiotics used to treat a variety of infections in animals. They have been grouped into three "generations" based primarily on their spectrum of antibacterial activity. Second-generation cephalosporins have the same efficacy as or perhaps slightly less efficacy than first-generation cephalosporins against gram-positive pathogens; however, this lack of efficacy is primarily against S. aureus and S. intermedius. Second-generation cephalosporins are more effective than first-generation cephalosporins in the treatment of infections caused by gram-negative bacteria such as E. coli, Klebsiella, Enterobacter, and Proteus.

Third-generation cephalosporins include ceftazidime, cefepime, ceftriaxone, and cefoperazone. The first- and second-generation cephalosporins generally have the greatest activity against staphylococci and streptococci. Third-generation cephalosporins are reserved for infections that are resistant to first-generation cephalosporins.

ACCEPTED

Escherichia coli infections (treatment)—Chicks and turkey pouls, day-old: Cefotiofur sodium for injection is indicated in the treatment of infections (colibacillosis) caused by susceptible E. coli[81; 99].

Metritis (treatment)—Cattle: Cefotiofur hydrochloride injection is indicated in the treatment of acute metritis (up to 14 days postpartum), caused by susceptible organisms[81; 99].

Pododermatitis, acute (treatment)—Cattle: Cefotiofur sodium for injection and cefotiofur hydrochloride injection are indicated in the treatment of pododermatitis (colibacillosis) caused by susceptible organisms[81; 99].
including bovine respiratory disease complex (shipping fever), caused by susceptible organisms, including Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, and Haemophilus somnus.[R-11; 12; 81; 99]

Goats: Cefiofur sodium for injection is indicated in the treatment of caprine respiratory disease caused by susceptible organisms, including M. haemolytica and P. multocida.[R-11].

Horses: Cefiofur sodium for injection is indicated in the treatment of respiratory tract infections caused by susceptible organisms, including Streptococcus zooepidemicus.[R-11; 12]

Pigs: Cefiofur hydrochloride injection and cefiofur sodium for injection are indicated in the treatment of respiratory tract infections caused by susceptible organisms, including Actinobacillus pleuropneumoniae, P. multocida, Salmonella choleraesuis, and Streptococcus suis type 2. [R-11; 81; 96; 99]

Sheep: Cefiofur sodium for injection is indicated in the treatment of respiratory tract infections caused by susceptible M. haemolytica and P. multocida.[R-11; 12; 97].

Skin and soft tissue infections (treatment)—Cats and dogs: Cefadroxil and [cephalexin] are indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including P. multocida, S. aureus, some S. epidermidis, S. intermedius,[R-12], and Streptococcus species.[R-1; 79]

Urinary tract infections (treatment)—Dogs: Cefadroxil and cefiofur sodium for injection are indicated in the treatment of urinary tract infections caused by susceptible organisms, including E. coli, P. mirabilis, and S. aureus.[R-1; 3; 11; 12].

[Perioperative infections (prophylaxis)]—Dogs: Cefazolin is used in the prevention of infections associated with surgery, including bone surgery, and caused by susceptible organisms when the risk of infection is high or potentially severely damaging.[R-1; 2; 6; 82; 83]

ACCEPTANCE NOT ESTABLISHED

Infections, bacterial (treatment)—

[Birds]: There are insufficient data to establish the efficacy and safety of cephalaxin and cephalothin in the treatment of bacterial infections in birds, such as cranes, ducks, emu, pigeons, and quail; however, based on pharmacokinetic studies and the apparent wide margin of safety, they have been used in the treatment of susceptible bacterial infections.[R-14].

Cats: There are insufficient data to establish the efficacy and safety of [cefoxatine] and [cephalexin] in the treatment of bacterial infections in cats; however, based on pharmacokinetics and the apparent wide margin of safety, these medications are used to treat a variety of susceptible infections, including certain bone, respiratory, skin, soft tissue, and urinary tract infections.

Dogs: There are insufficient data to establish the efficacy and safety of [cefaclor], [cefadroxil], [ceftiofur], [cephalothin] and [cefpodoxime] for the treatment of bacterial infections in dogs; however, based on pharmacokinetic data,[R-13; 49; 50; 72; 82; 83], knowledge about in vitro efficacy, and the apparent wide margin of safety, these medications are used to treat a variety of susceptible infections, including certain bone, respiratory, skin, soft tissue, and urinary tract infections. Also, there are insufficient data to establish the clinical efficacy and safety of [cefixime] in the treatment of bacterial infections in dogs; however, pharmacokinetics and determination of minimum inhibitory concentrations against common pathogens show that cefixime is likely to be effective in the treatment of bone, bladder, skin, and soft tissue infections.[R-77]. There are insufficient data to establish the clinical efficacy and safety of [cefoxitin] and [cefpodoxime] in the treatment of gram-negative or polymicrobial infections (such as Enterobacteriaceae species and an obligate anaerobe) in dogs; however, pharmacokinetics and a determination of minimum inhibitory concentrations against common pathogens show that cefoxitin and cefotixin are likely to be effective in the treatment of these types of infections.[R-84].

[Foals]: There are insufficient data to establish the efficacy and safety of cefiotaxime and other third-generation cephalosporins in the treatment of neonatal sepsis and secondary bacterial meningitis in foals; however, based on known human central nervous system distribution and clinical response in foals, cefotaxime is used to treat these infections when they are not responsive to other antimicrobials.[R-62; 67].

Horses: There are insufficient data to establish the efficacy and safety of [cefoxitin] and [cephalothin] in horses for the treatment of bacterial infections; however, based on the pharmacokinetics known, pathogen sensitivities, and the apparent wide margin of safety, these medications are used to treat a variety of susceptible infections, including certain bone, joint, respiratory, skin, soft tissue, and urinary tract infections.

Not included in Canadian product labeling or product not commercially available in Canada.

REGULATORY CONSIDERATIONS

U.S. and Canada[2; 7]

Withdrawal times have been established for cefiofur (see the Dosage Forms section). Cefiofur is not for use in horses intended for human consumption.

CHEMISTRY

Source: Most cephalosporins are semisynthetic derivatives of the metabolic products of the fungus Cephalosporium acremonium. [R-1–3]

Chemical group: Beta-lactam antibiotics. [R-2; 7]

Molecular formula:[R-13]

Cefadroxil—C_{16}H_{17}N_{3}O_{6}S. H_{2}O.
Cefaxolin sodium—C_{16}H_{17}N_{3}NaO_{5}S. H_{2}O.
Cefazolin sodium—C_{16}H_{17}N_{3}NaO_{5}S. H_{2}O.
Cefuroxime axetil—C_{16}H_{17}N_{3}O_{5}S. H_{2}O.
Cefuroxime sodium—C_{16}H_{17}N_{3}NaO_{5}S. H_{2}O.
Cefotaxime sodium—C_{16}H_{17}N_{3}O_{5}S. H_{2}O.
Cefotetan disodium—C_{16}H_{17}N_{3}O_{5}S. H_{2}O.
Cephalothin sodium—C_{16}H_{17}N_{3}NaO_{5}S. H_{2}O.
Cephradine—C₁₆H₁₉N₃O₄S₂.
Cephadrine—C₁₆H₁₉N₃O₄S.

**Molecular weight:** [R-13]

Cefaclor—185.82.
Cefadroxil—381.40; 372.39 (hemihydrate); 363.4 (anhydrous) [R-14].
Cefazolin sodium—476.49.
Cefixime—507.50.
Cefotaxime sodium—619.59.
Ceftiofur sodium—545.55.
Cephalothin sodium USP—Freely soluble in water, in saline TS, and in methanol; soluble in alcohol, in chloroform, and in ether.
Cefadroxil USP—Slightly soluble in water; practically insoluble in methanol and in chloroform.
Cefadroxil—381.40; 372.39 (hemihydrate); 363.4 (anhydrous).
Cefaclor USP—Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether.
Cefotetan disodium—White to pale yellow powder.
Cefotetan disodium injection—Solution varies from colorless to yellow depending on the concentration and the diluent used.
Cephradine USP—White to off-white, crystalline powder.
Cephalexin Hydrochloride USP—White to off-white crystalline powder.
Cephalexin—365.41.
Cefoxitin sodium—449.44.
Cefotaxime Sodium USP—Off-white to pale yellow crystalline powder.
Cefixime—507.50.
Cefazolin sodium—476.49.

**Description:** [R-14]

Cefadroxil USP—White to off-white, crystalline powder.
Cephalexin—365.41.
Ceftiofur hydrochloride—560.03.
Ceftiofur sodium—545.55.
Cephalexin—349.41.

**Distribution:** [R-68]

Cefotaxime Sodium USP—Freely soluble in water; practically insoluble in organic solvents.
Cefotetan disodium—Very soluble in water.
Cefoxitin sodium—Solubility is pH dependent (greater than 400 mg per mL at pH > 5.5).
Cephalexin USP—Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether.
Cephalothin Sodium USP—Off-white to pale yellow crystalline powder.
Cefapirin Sodium USP—Sparingly soluble in water; very slightly soluble in organic solvents.

**Mechanism of action/effect:**

Cephalosporins are beta-lactam antibiotics that produce their bactericidal effect by inhibition of cell wall synthesis. The site of action for beta-lactam antibiotics is the penicillin-binding proteins (PBPs) on the inner surface of the bacterial cell membrane that are involved in synthesis of the cell wall. [R-2] In actively growing cells, the cephalosporins bind to the PBPs within the cell wall and lead to interference in production of cell wall peptidoglycans and subsequent lysis of the cell in an iso-osmotic environment. [R-7; 9] Differences in affinity for the types of PBPs by different beta-lactam antibiotics and the bacterial defense mechanisms explain the variations in bactericidal activity among cephalosporins. [R-9]

**Solubility:** [R-14]

Cefadroxil USP—Slightly soluble in water; practically insoluble in methanol and in chloroform.
Cefadroxil USP—Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether.
Cefazolin Sodium USP—Freely soluble in water, in saline TS, and in dextrose solutions; very slightly soluble in alcohol; practically insoluble in chloroform; and in ether.
Cefixime USP—Freely soluble in methanol; soluble in propylene glycol; slightly soluble in alcohol, in acetone, and in glycerin; very slightly soluble in 70% sorbitol and in octanol; practically insoluble in ether, in ethyl acetate, in hexane, and in water.

**pKa:**

- Cefotaxime—3.35 [R-15]
- Cefoxitin—5.0 [R-16; 17]
- Cefadroxil—2.15 and 5.44 [R-16]
- Cephalexin—5.3 and 7.3 [R-16; 17]
- Cephapirin—2.6 and 7.3 [R-17]

**Note:** See also Table 1. Pharmacology/Pharmacokinetics at the end of this monograph.

**PHARMACOLOGY/PHARMACOKINETICS**

**Distribution:** Cephalosporins distribute into most body tissues and fluids. They penetrate into pleural fluid, synovial fluid, pericardial fluid, and urine. Cephalosporins can be found in bile fluid if no biliary obstruction is present. [R-1] The cephalosporins penetrate aqueous humor and prostatic fluid less than other body fluids. Most of the cephalosporins have poor penetration of the blood-brain barrier. [R-2] Cefuroxime is the only second-generation cephalosporin known to adequately penetrate into cerebrospinal fluid in people; also, the third-generation antibiotics cefotaxime and ceftazidim have been shown to penetrate inflamed meninges in people. Ceftriaxone has been shown to penetrate normal meninges in horses. [R-103]

The high level of protein binding by ceftiofur in adult animals causes its distribution to differ from that of other cephalosporins. [R-91]. Also, the primary metabolite of ceftiofur, desfuroylceftiofur, has a reactive sulfhydryl group that forms reversible covalent bonds with plasma and tissue proteins. [R-63]. Free concentrations of ceftiofur and its active metabolites tend to be lower than expected when dosages shown to be effective in the treatment of a disease are administered, possibly because of their unique protein binding abilities. [R-63]. Concentrations of ceftiofur and active metabolites in Pasteurella-infected tissue chambers implanted into cattle tend to be higher than concentrations in uninfected...
For most cephalosporins, elimination is by renal tubular secretion and/or glomerular filtration.

**Elimination:**

**PRECAUTIONS TO CONSIDER**

**SPECIES SENSITIVITY**

**Rabbits and small rodents**—Cephalosporins may disturb the normal intestinal microflora, particularly when administered orally at high doses.

**CROSS-SENSITIVITY**

The incidence of cross-sensitivity in animals is unknown. Caution should be used when cephalosporins are administered to patients with a history of an anaphylactic reaction to other beta-lactam antibiotics because cross-reaction may occur, however, a history of a delayed allergic reaction to penicillin does not contraindicate use of a cephalosporin.

**PREGNANCY/REPRODUCTION**

Pregnancy—Cephalosporins have been shown to cross the placenta in animals. Studies in laboratory animals have not shown the cephalosporins to cause adverse effects in the fetus. Studies with cefoxitin have not shown that the medication is teratogenic or fetotoxic in mice and rats, but a slight decrease in fetal weight has occurred.

**LACTATION**

Cephalosporins are distributed into milk; however, when administered systemically at accepted doses, therapeutic concentrations are not reached in milk. When cefotaxime is administered systemically at recommended dosages, distribution is too low to produce residues greater than established regulatory tolerances.

**DRUG INTERACTIONS AND/OR RELATED PROBLEMS**

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive ( = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Although cephapirin has been associated with an increased human risk of nephrotoxicity when administered with an aminoglycoside, this interaction may not apply to other cephalosporins. In fact, there is some evidence that certain cephalosporins such as cefamandole, cefazolin, and cephalexin provide a protective effect against aminoglycoside-induced nephrotoxicity in rats while others, such as cephalaxin, have no effect.

**HUMAN DRUG INTERACTIONS**

In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monograph *Cephalosporins (Systemic)* in USP DI Volume I; these drug interactions are intended for informational purposes only and may or may not be applicable to the use of cephalosporins in the treatment of animals:

- **Anticoagulants, coumarin- or indandione-derivative, or heparin**
- **Thrombolytic agents**
- **Anticoagulants, coumarin- or indandione-derivative, or heparin**
- **Thrombolytic agents**

**Note:** Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
LABORATORY VALUE ALTERATIONS
The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (\(^*\) = major clinical significance):

With diagnostic test results
Coombs’ test
(positive reactions for the Coombs’ test may be seen in animals receiving cephalosporins; this may be due to changes in the red blood cells, but hemolytic anemia usually is not occurring\(^*\))

With physiology/laboratory test values
Ketones, urine
(values may be increased\(^{R-68}\))

HUMAN LABORATORY VALUE ALTERATIONS\(^{R-46}\)
The following laboratory value alterations have been reported in humans, and are included in the human monograph *Cephalosporins (Systemic)* in USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of cephalosporins in the treatment of animals:

With diagnostic test results
Coombs’ (antiglobulin) tests
(a positive Coombs’ reaction frequently appears in patients who receive large doses of a cephalosporin; hemolysis rarely occurs, but has been reported; test may be positive in neonates whose mothers received cephalosporins before delivery)

Creatinine, serum and urine
(cefotetan, cefoxitin, or cephalothin may falsly elevate test values when the Jaffe’s reaction method is used; serum samples should not be obtained within 2 hours after administration)

Glucose, urine
(some cephalosporins [cefaclor, cefazolin, cefixime, cefotetan, cefoxitin, cephalixin, cephalothin, cephapirin, cephradine] may produce false-positive or falsely elevated test results with copper sulfate tests [Benedict’s, Fehling’s, or Clinitest]; glucose enzymatic tests, such as Clinitest and Tes-Tape, are not affected)

Protein, urine
(cefamandole may produce false-positive tests for proteinuria with acid and denaturation-precipitation tests)

Prothrombin time (PT)
(may be prolonged; cephalosporins may inhibit vitamin K synthesis by suppressing gut flora; also, cephalosporins with the NMTT side chain [cefamandole, cefoperazone, cefotetan] have been associated with an increased incidence of hypoprothrombinemia; patients who are critically ill, malnourished, or have liver function impairment may be at the highest risk of bleeding)

With physiology/laboratory test values
Alanine aminotransferase (ALT [SGPT]), serum, or
Alkaline phosphatase, serum, or
Aspartate aminotransferase (AST [SGOT]), serum, or
Lactate dehydrogenase (LDH), serum
(values may be increased)

Bilirubin, serum, or
Blood urea nitrogen (BUN) or
Creatinine, serum
(concentrations may be increased)

Complete blood count (CBC) or
Platelet count
(transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, eosinophilia, lymphocytosis, and thrombocytosis have been reported on rare occasions)

MEDICAL CONSIDERATIONS/CONTRAINDICATIONS
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (\(^*\) = major clinical significance).

Risk-benefit should be considered when the following medical problems exist:
Bleeding disorders, history of
(some of the second- and third-generation cephalosporins have been associated with an increased risk of bleeding in people\(^{R-63}\) due to a decrease in prothrombin activity, and bleeding is considered a potential human risk with all the cephalosporins; there is evidence of a significant increase in bleeding time after cephalothin administration to beagles\(^{R-28}\) but not outside normal reference ranges; clinical problems have not been reported in animals and the clinical significance is unknown)

Hepatic dysfunction, severe
(because ceftaxime, cephalothin, and cephapirin are hepatically metabolized before renal elimination, severe liver dysfunction can inhibit metabolism\(^{R-2}\))

Renal insufficiency
(nephrotoxicity may occur in patients with renal insufficiency who are receiving the full dosage of cephalosporin; dosage should be adjusted\(^{R-1}\))

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
All species
Hypersensitivity reactions (acute anaphylaxis or angioedema, allergic agranulocytosis\(^{R-31}\), fever\(^{R-11}\), serum sickness, urticaria\(^{R-21}\))

Dogs
Anemia; thrombocytopenia\(^{R-11}\)
Note: Anemia and thrombocytopenia have been seen in dogs given ceftiofur at high doses (three to five times the labeled dose) or for long periods of time (5 to 6 weeks). These side effects appear to be reversible when treatment is discontinued.

Horses
Diarrhea\(^{R-11}\)—with ceftiofur
THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME

All species

Anorexia\(^{[R-10; 32]}\); diarrhea and vomiting\(^{[R-1]}\)—possibly due to local irritation from the oral dosage forms\(^{[R-1]}\); diarrhea caused by altered gut flora\(^{[R-2; 10]}\); local reactions\(^{[R-1; 11]}\) (mild to moderate pain, heat, swelling)—with parenteral dosage forms, especially cephalothin and cepaparin; phlebitis\(^{[R-2]}\)—with intravenous administration

Note: Diarrhea and vomiting can occur with any dosage but are more common with high doses.\(^{[R-31]}\) Administration of the antibiotic with food may decrease the incidence of gastrointestinal effects.\(^{[R-31]}\)

HUMAN SIDE/ADVERSE EFFECTS\(^{[R-46]}\)

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Cephalosporins (Systemic) in USP DI Volume I; these side/adverse effects are intended for information purposes only and may or may not be applicable to the use of cephalosporins in the treatment of animals:

Incidence more frequent

Gastrointestinal reactions; headache; oral candidiasis; vaginal candidiasis

Incidence less frequent or rare

Hypoprothrombinemia—more frequent for cefotetan; pseudomembranous colitis

Incidence rare

Allergic reactions, specifically anaphylaxis, erythema multiforme, or Stevens-Johnson syndrome (blistering, peeling, or loosening of skin and mucous membranes, which may involve the eyes or other organ systems); hearing loss—has occurred rarely in pediatric patients being treated for meningitis, but more frequently with cefuroxime; hemolytic anemia, immune, drug-induced—has occurred with many cephalosporins, but reported more commonly with cefotetan; hypersensitivity reactions—has occurred with many cephalosporins, but reported more commonly with cefazolin; renal dysfunction; serum sickness–like reactions—may be more frequent with cefaclor; seizures—especially with high doses and in patients with renal function impairment; thrombophlebitis

OVERDOSE

For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

VETERINARY DOSING INFORMATION

Except for specific veterinary labeled medications, most doses listed have been derived from pharmacokinetic data, rather than from clinical studies.\(^{[R-74]}\)

FOR ORAL DOSAGE FORMS ONLY

Administration of oral cephalosporins, such as cefadroxil, with food appears to decrease nausea in those animals prone to the side effect\(^{[R-31]}\); however, administration of cefixime with food can decrease by one half the bioavailability of the antibiotic\(^{[R-77]}\).

FOR PARENTERAL DOSAGE FORMS ONLY

Many cephalosporins can be reconstituted with 1% lidocaine to decrease injection pain. See the manufacturer’s package insert\(^{[R-80]}\).

FOR TREATMENT OF ADVERSE EFFECTS

For anaphylaxis

Recommended treatment consists of the following:

- Parenteral epinephrine.
- Oxygen administration and breathing support.
- Parenteral fluid administration as needed.

CEFACLOR

SUMMARY OF DIFFERENCES

Indications: General considerations—Second-generation cephalosporin.

ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

CEFACLOR CAPSULES USP

Usual dose:

Note: [Dogs]—Although the efficacy and safety of cefaclor in dogs have not been established, an oral dose of 4 to 20 mg per kg of body weight every eight hours has been used in the treatment of susceptible bacterial infections in dogs.\(^{[R-2]}\) There is very little canine-specific information about cefaclor; therefore, dose recommendations are based primarily on human pharmacokinetics

Strength(s) usually available:

U.S.—\(^{[R-24]}\)

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [Cefclor].

500 mg (Rx) [Cefclor].

Canada—\(^{[R-16]}\)

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [Apo-Cefaclor; Ceclor].

500 mg (Rx) [Apo-Cefaclor; Ceclor].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Contain the equivalent of the labeled amount of anhydrous cefaclor, within –10% to...
Meet the requirements for Identification, Dissolution (80% in 30 minutes in water in Apparatus 2 at 50 rpm), Uniformity of dosage units, and Water (not more than 8.0%).

**CEFACLOR FOR ORAL SUSPENSION USP**

**Usual dose:** See Cefaclor Capsules USP.

**Strength(s) usually available:** When reconstituted according to manufacturer’s instructions—

- U.S.: [R-24]
  - Veterinary-labeled product(s)—
    - Not commercially available.
  - Human-labeled product(s)—
    - 25 mg per mL (Rx) [Celor; GENERIC].
    - 37.4 mg per mL (Rx) [Celor; GENERIC].
    - 50 mg per mL (Rx) [Celor; GENERIC].
    - 75 mg per mL (Rx) [Celor; GENERIC].

- Canada: [R-16]
  - Veterinary-labeled product(s)—
    - Not commercially available.
  - Human-labeled product(s)—
    - 25 mg per mL (Rx) [Apo-Cefaclor; Celor].
    - 50 mg per mL (Rx) [Apo-Cefaclor; Celor].
    - 75 mg per mL (Rx) [Apo-Cefaclor; Celor].

**Packaging and storage:** Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

**Stability:** After reconstitution, suspensions retain their potency for 14 days if refrigerated.

**Auxiliary labeling:**

- Refrigerate.
- Shake well.

**USP requirements:** Preserve in tight containers. A dry mixture of Cefaclor and one or more suitable buffers, colors, diluents, and flavors. Contains the equivalent of the labeled amount of anhydrous cefaclor, within –10% to +20%. Meets the requirements for Identification, Uniformity of dosage units (solid packaged in single-unit containers), Deliverable volume (solid packaged in multiple-unit containers), pH (2.5–5.0, in the suspension constituted as directed in the labeling), and Water (not more than 2.0%).

(Cefaclor Capsules USP)

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**CEFADROXIL**

**SUMMARY OF DIFFERENCES**

**Indications:**

General considerations—First-generation cephalosporin.

Indicated for treatment of susceptible genitourinary tract infections in dogs and skin and soft tissue infections in cats and dogs.

Drug interactions and/or related problems: Concurrent administration of probenecid may prolong the serum half-life of cefadroxil.[R-3]

**ORAL DOSAGE FORMS**

**CEFADROXIL FOR ORAL SUSPENSION USP**

**Usual dose:**

- Skin and soft tissue infections—Cats: Oral, 22 mg per kg of body weight every twenty-four hours.[R-37; 38]
  - Dogs: Oral, 22 mg per kg of body weight every twelve hours.[R-37; 38]
- Urinary tract infections—Dogs: Oral, 22 mg per kg of body weight every twelve hours.[R-37; 38]

**Strength(s) usually available:** When reconstituted according to manufacturer’s instructions—

- U.S.:
  - Veterinary-labeled product(s)—
    - 50 mg per mL (Rx) [Cefa-Drops].
- Canada:
  - Veterinary-labeled product(s)—
    - 50 mg per mL (Rx) [Cefa-Drops].

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

**Stability:** When reconstituted according to manufacturer’s directions and refrigerated, suspensions retain their potency for 14 days.[R-37]

**USP requirements:** Preserve in tight containers. A dry mixture of Cefadroxil and one or more suitable buffers, colors, diluents, and flavors. Contains the equivalent of the labeled amount of anhydrous cefadroxil, within –10% to +20%. Meets the requirements for Identification, Uniformity of dosage units (solid packaged in single-unit containers), Deliverable volume (solid packaged in multiple-unit containers), pH (4.5–6.0, in the suspension constituted as directed in the labeling), and Water (not more than 2.0%).

(Cefadroxil for Oral Suspension USP)

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**CEFADROXIL TABLETS USP**

**Usual dose:** See Cefadroxil for Oral Suspension USP.

**Strength(s) usually available:**

- U.S.—Veterinary-labeled product(s):
  - 50 mg (Rx) [Cefa-Tabs].
  - 100 mg (Rx) [Cefa-Tabs].
  - 200 mg (Rx) [Cefa-Tabs].
  - 1 gram (Rx) [Cefa-Tabs].
- Canada—Veterinary-labeled product(s):
  - 50 mg (Rx) [Cefa-Tabs].
  - 100 mg (Rx) [Cefa-Tabs].
  - 200 mg (Rx) [Cefa-Tabs].

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container. 

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1Not included in Canadian product labeling or product not commercially available in Canada.
USP requirements: Preserve in tight containers. The Tablets prepared using the hemihydrate form of Cefadroxil are so labeled. Contain the labeled amount of anhydrous cefadroxil, within –10% to +20%. Meet the requirements for Identification, Dissolution (75% in 30 minutes in water in Apparatus 2 at 50 rpm), Uniformity of dosage units, and Water (not more than 8.0%).[R-14]

CEFAZOLIN

SUMMARY OF DIFFERENCES

Indications: General considerations—First-generation cephalosporin.

PARENTERAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S. The dosing and strengths of the dosage forms available are expressed in terms of cefazolin base (not the sodium salt).

CEFAZOLIN INJECTION USP

Usual dose: Although Cefazolin Injection USP is the same antimicrobial as Cefazolin For Injection USP, it is only available frozen in premixed dilute concentrations, making it less practical for veterinary use. For dosing information, see Cefazolin For Injection USP.

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):  500 mg (base) in 50 mL (Rx) [Ancef].

1 gram (base) in 50 mL (Rx) [Ancef].

Canada—

Not commercially available.

Packaging and storage: Store at –10 °C (14 °F) or below, unless otherwise specified by the manufacturer.

Preparation of dosage form: Cefazolin sodium injection should be thawed at room temperature, and all ice crystals should have melted, before administration. Thawing should not be forced by immersion in water baths or by microwave irradiation.

Stability: See manufacturer’s product labeling for stability information.

Incompatibilities:
The admixture of cefazolin sodium injection with other medications is not recommended.
The admixture of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation; they should not be mixed in the same intravenous bag or bottle.

USP requirements: Preserve in Containers for Injections. Maintain in the frozen state. A sterile solution of Cefazolin and Sodium Bicarbonate in a diluent containing one or more suitable tonicity-adjusting agents. It meets the requirements for Labeling under Injections. The label states that it is to be thawed just prior to use, describes conditions for proper storage of the resultant solution, and directs that the solution is not to be refrozen. Contains the labeled amount, within –10% to +15%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH (4.5–7.0), and Particulate matter.[R-14]

CEFAZOLIN FOR INJECTION USP

Usual dose: [Perioperative infections (prophylaxis)]¹—Dogs: Intravenous, 22 mg (base) per kg of body weight every two hours, or 8 mg (base) per kg of body weight every hour, starting at the beginning of surgery and continuing until the end of surgery[R-82].

Note: The above dose is based on pharmacokinetic studies, including studies performed during surgical procedures.

Also for [dogs]¹, based on pharmacokinetics studies, an intramuscular or intravenous dose of 20 to 35 mg (base) per kg of body weight every four to eight hours has been used for the treatment of susceptible bacterial infections[R-2; 18; 80].

Size(s) usually available:

U.S.—[R-19]

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (base) (Rx) [Ancef; Kefzol; casanuc].

1 gram (base) (Rx) [Ancef; Kefzol; casanuc].

5 grams (base) (Rx) [Ancef].

10 grams (base) (Rx) [Ancef; Kefzol; casanuc].

Canada—[R-40]

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

50 mg (base) (Rx) [Kefzol].

500 mg (base) (Rx) [Ancef; Kefzol; casanuc].

1 gram (base) (Rx) [Ancef; Kefzol; casanuc].

10 grams (base) (Rx) [Ancef; Kefzol; casanuc].

Packaging and storage: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: To prepare the 100 mg of cefazolin (base) per mL dilution commonly used in veterinary practice for intramuscular or intravenous administration, 9.6 mL of sterile water for injection should be added to each 1-gram vial[R-19; 95]. See manufacturer’s package insert for other preparation instructions.

Stability: See manufacturer’s product labeling for stability information.

Incompatibilities: The admixture of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation; they should not be mixed in the same intravenous bag or bottle.

USP requirements: Preserve in containers for Sterile Solids. Contains an amount of Cefazolin Sodium equivalent to the labeled amount of
cefazolin, within –10% to +15%. Meets the requirements for Constituted solution, Identification, Specific rotation (–10° to –24°), Bacterial endotoxins, Sterility, pH (4.0–6.0, in a solution containing 100 mg of cefazolin per mL), Uniformity of dosage units, Water (not more than 6.0%), and Particulate matter, and for Labeling under Injections.

CEFIXIME

SUMMARY OF DIFFERENCES
Indications: General considerations—Third-generation cephalosporin. Veterinary Dosing Information: Administration with food decreases the bioavailability by one half.

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

CEFIXIME FOR ORAL SUSPENSION USP
Usual dose:
Note: [Dogs]1—Although the efficacy and safety of cefixime have not been established, an oral dose of 5 mg per kg of body weight every twelve to twenty-four hours has been used in the treatment of cystitis in dogs, based on pharmacokinetic data.1-77
There are also some pharmacokinetic data to suggest that the same dose, administered for two to four weeks, is likely to be effective for treatment of bone, skin, and soft tissue infections in dogs.1-77

Strength(s) usually available: When reconstituted according to manufacturer’s directions—
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
20 mg per mL (Rx) [Suprax].
Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
20 mg per mL (Rx) [Suprax].

Packaging and storage: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Stability: After reconstitution, suspension retains its potency for 14 days at room temperature or if refrigerated.

Auxiliary labeling:
• Shake well.

USP requirements: Preserve in tight containers. A dry mixture of Cefixime and one or more suitable diluents, flavors, preservatives, and suspending agents. Label it to indicate that the cefixime contained therein is in the trihydrate form. Contains the labeled amount of anhydrous cefixime, within –10% to +20%, per mL when constituted as directed in the labeling. Meets the requirements for Identification, Uniformity of dosage units (solid packaged in single-unit containers), Deliverable volume (solid packaged in multiple-unit containers), pH (2.5–4.5, in the suspension constituted as directed in the labeling), and Water (not more than 2.0%).1-14

CEFOTAXIME TABLETS USP
Usual dose: See Cefixime for Oral Suspension USP.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
200 mg (Rx) [Suprax].
400 mg (Rx) [Suprax].
Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
200 mg (Rx) [Suprax].
400 mg (Rx) [Suprax].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

USP requirements: Preserve in tight containers. Label Tablets to indicate that the cefixime contained therein is in the trihydrate form. Contains the labeled amount of anhydrous cefixime, within ±10%. Meet the requirements for Identification, Uniformity of dosage units, and Water (not more than 10.0%).1-14

CEFOTAXIME

SUMMARY OF DIFFERENCES
Indications: General considerations—Third-generation cephalosporin. Pharmacology/pharmacokinetics:
Biotransformation—Significant metabolism occurs with the major pathway yielding a desacetyl derivative. Desacetylcefotaxime is less active against staphylococci but acts synergistically with the parent compound against sensitive gram-negative bacteria.1-1
Distribution—In people, when administered at high doses, cefotaxime enters the cerebrospinal fluid in therapeutic concentrations when meninges are inflamed.1-1
Medical considerations/contraindications: Severe hepatic dysfunction can inhibit metabolism.1-2

PARENTERAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.
The dosing and strengths of the dosage forms available are expressed in terms of cefotaxime free acid (not the sodium salt).

**CEFOTAXIME INJECTION USP**

**Usual dose:**

Note: [Cats]¹—Although the efficacy and safety have not been established, an intramuscular or intravenous dose of 20 to 80 mg (free acid) per kg of body weight every six hours has been used in the treatment of susceptible **bacterial infections** in cats, based on pharmacokinetic data.[R-42].

[ Dogs]³—Although the efficacy and safety have not been established, a subcutaneous dose of 50 mg (free acid) per kg of body weight every twelve hours has been used in the treatment of susceptible **bacterial infections** in dogs, based on pharmacokinetic data. When administered intramuscularly, the dose should be repeated every eight hours[R-43].

[ Foals]³—Although the efficacy and safety have not been established, an intravenous dose of 40 mg (free acid) per kg of body weight every six hours has been used in the treatment of **neonatal sepsis or susceptible bacterial meningitis** in foals[R-62].

**Strength(s) usually available:**

**U.S.**[R-44]

Veterinary-labeled product(s): Not commercially available.

Human-labeled product(s):

- 20 mg (free acid) per mL (Rx) [Claforan].
- 40 mg (free acid) per mL (Rx) [Claforan].

**Canada**—Not commercially available.

**Packaging and storage:** Store at –20 °C (–4 °F) or below, unless otherwise specified by manufacturer.[R-44]

**Preparation of dosage form:**[R-44] Cefotaxime sodium injection should be thawed at room temperature, and all ice crystals should have melted, before administration.

**Stability:** See manufacturer’s product labeling for stability information.

**USP requirements:** Preserve in single-dose containers. Maintain in the frozen state. A sterile solution of Cefotaxime Sodium in Water for Injection. Contains one or more suitable buffers. It meets the requirements for Labeling under Injections. The label states that it is to be thawed just prior to use, describes conditions for proper storage of the resultant solution, and directs that the solution is not to be refrozen. Contains an amount of cefotaxime sodium equivalent to the labeled amount of cefotaxime, within –10% to +15%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, Uniformity of dosage units, Particulate matter, and Chromatographic purity.[R-14]

**CEFOTAXIME FOR INJECTION USP**

**Usual dose:** See **Cefotaxime Sodium Injection USP**.

**Size(s) usually available:**

**U.S.**[R-44]

Veterinary-labeled product(s): Not commercially available.

Human-labeled product(s):

- 500 mg (free acid) (Rx) [Claforan].
- 1 gram (free acid) (Rx) [Claforan].
- 2 grams (free acid) (Rx) [Claforan].
- 10 grams (free acid) (Rx) [Claforan].

**Canada**—Veterinary-labeled product(s): Not commercially available.

Human-labeled product(s):

- 500 mg (free acid) (Rx) [Claforan].
- 1 gram (free acid) (Rx) [Claforan].
- 2 grams (free acid) (Rx) [Claforan].

**Packaging and storage:** Prior to reconstitution, store below 30 °C (86 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Preparation of dosage form:** Dilutions should be prepared according to manufacturer’s instructions.

**Stability:** See manufacturer’s product labeling for stability information.

**Additional information:** A solution containing 1 gram of cefotaxime sodium in 14 mL of sterile water for injection is isotonic.[R-44].

**CEFOTETAN**

**SUMMARY OF DIFFERENCES**

**Indications:** General considerations—Second-generation cephalosporin.

**PARENTERAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of cefotetan base (not the disodium salt).

**CEFOTETAN FOR INJECTION USP**

**Usual dose:**

Note: [Dogs]¹—Although the efficacy and safety have not been established, an intravenous dose of 30 mg (base) per kg of body weight every eight hours or the same dose administered subcutaneously every twelve hours has been used in the treatment of susceptible **bacterial infections** in dogs, based on pharmacokinetic data[R-80; 84].

1Not included in Canadian product labeling or product not commercially available in Canada.
Size(s) usually available:

U.S.—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
1 gram (base) (Rx) [Cefoxitin].
2 grams (base) (Rx) [Cefotan].
10 grams (base) (Rx) [Cefotan].

Canada—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
1 gram (base) (Rx) [Cefoxitin].
2 grams (base) (Rx) [Cefotan].

Packaging and storage: Prior to reconstitution, do not store above 22 °C (72 °F), unless otherwise specified by manufacturer. Protect from light.

Preparation of dosage form: Dilutions should be prepared according to manufacturer’s instructions.

Stability: See manufacturer’s product labeling for stability information.

Incompatibilities: The admixture of beta-lactam antibacterials and aminoglycosides may result in substantial mutual inactivation. They should not be mixed in the same intravenous bag or bottle.

USP requirements: Preserve in containers for Sterile Solids. Contains an amount of Cefotetan Disodium equivalent to the labeled amount of cefotetan, within –10% to +20%. Meets the requirements for Constituted solution, Bacterial endotoxins, Sterility, and Particulate matter, for Uniformity of dosage units, and for Labeling under Injections.

CEFOXITIN INJECTION USP

Usual dose:

Note: [Dogs]1—Although the efficacy and safety have not been established, an intravenous dose of 30 mg (base) per kg of body weight every six hours or the same dose administered subcutaneously every eight hours has been used in the treatment of susceptible bacterial infections in dogs, based on pharmacokinetic data.

[Horses]1—Although the efficacy and safety have not been established, an intravenous dose of 20 mg (base) per kg of body weight every four to six hours has been used in the treatment of susceptible bacterial infections in horses, based on pharmacokinetic data.

Strength(s) usually available:

U.S.—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
20 mg (base) per mL (Rx) [Mefoxin].
40 mg (base) per mL (Rx) [Mefoxin].

Canada—
Not commercially available.

Packaging and storage: Store at –20 °C (–4 °F) or below, unless otherwise specified by manufacturer.

Preparation of dosage form: See manufacturer’s product labeling.

USP requirements: Preserve in Containers for Injections. Maintain in the frozen state. A sterile solution of Cefoxitin Sodium and one or more suitable buffer substances in Water for Injection. Contains Dextrose or Sodium Chloride as a tonicity-adjusting agent. It meets the requirements for Labeling under Injections. The label states that it is to be thawed just prior to use, describes conditions for proper storage of the resultant solution, and directs that the solution is not to be refrozen. Contains an amount of cefoxitin sodium equivalent to the labeled amount of cefoxitin, within –10% to +20%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH (4.5–8.0), and Particulate matter.

CEFOXITIN FOR INJECTION USP

Usual dose:

Size(s) usually available:

U.S.—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
1 gram (base) (Rx) [Mefoxin; GENERIC].
2 grams (base) (Rx) [Mefoxin; GENERIC].
10 grams (base) (Rx) [Mefoxin].

Canada—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
1 gram (base) (Rx) [Mefoxin; GENERIC].
2 grams (base) (Rx) [Mefoxin; GENERIC].
10 grams (base) (Rx) [Mefoxin].

1Not included in Canadian product labeling or product not commercially available in Canada.

CEPHALOSPORINS Veterinary—Systemic

CEFOXITIN INJECTION USP

Usual dose:

Note: [Dogs]1—Although the efficacy and safety have not been established, an intravenous dose of 30 mg (base) per kg of body weight every six hours or the same dose administered subcutaneously every eight hours has been used in the treatment of susceptible bacterial infections in dogs, based on pharmacokinetic data.

[Horses]1—Although the efficacy and safety have not been established, an intravenous dose of 20 mg (base) per kg of body weight every four to six hours has been used in the treatment of susceptible bacterial infections in horses, based on pharmacokinetic data.

Strength(s) usually available:

U.S.—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
20 mg (base) per mL (Rx) [Mefoxin].
40 mg (base) per mL (Rx) [Mefoxin].

Canada—
Not commercially available.

Packaging and storage: Store at –20 °C (–4 °F) or below, unless otherwise specified by manufacturer.

Preparation of dosage form: See manufacturer’s product labeling.

USP requirements: Preserve in Containers for Injections. Maintain in the frozen state. A sterile solution of Cefoxitin Sodium and one or more suitable buffer substances in Water for Injection. Contains Dextrose or Sodium Chloride as a tonicity-adjusting agent. It meets the requirements for Labeling under Injections. The label states that it is to be thawed just prior to use, describes conditions for proper storage of the resultant solution, and directs that the solution is not to be refrozen. Contains an amount of cefoxitin sodium equivalent to the labeled amount of cefoxitin, within –10% to +20%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH (4.5–8.0), and Particulate matter.

CEFOXITIN FOR INJECTION USP

Usual dose:

Size(s) usually available:

U.S.—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
1 gram (base) (Rx) [Mefoxin; GENERIC].
2 grams (base) (Rx) [Mefoxin; GENERIC].
10 grams (base) (Rx) [Mefoxin].

1Not included in Canadian product labeling or product not commercially available in Canada.
Packaging and storage: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: Dilutions should be prepared according to manufacturer’s instructions.

Stability: See manufacturer’s product labeling for stability information.

USP requirements: Preserve in Containers for Sterile Solids. Contains Cefoxitin Sodium equivalent to the labeled amount of cefoxitin, within −10% to +20%. Meets the requirements for Constituted solution, Bacterial endotoxins, Sterility, and Particulate matter, for Identification tests, pH, and Water under Cefoxitin Sodium, for Uniformity of dosage units, and for Labeling under Injections. 

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of cefoxitin free acid (not the sodium salt).

CEFTIOFUR

SUMMARY OF DIFFERENCES

Indications:
General considerations—“New-generation” cephalosporin. Indicated in the treatment of susceptible Escherichia coli infections in chicks and turkey pouls; metritis and pododermatitis in cattle, respiratory tract infections in cattle, goats, horses, pigs, and sheep, and urinary tract infections in dogs.

Pharmacology/pharmacokinetics: Biotransformation—Biotransformation to an active antibacterial metabolite, desfuroylecftiofur, occurs.

Drug interactions and/or related problems: Probenecid has not been shown to alter the excretion of cefoxitin.

Side/adverse effects: Often-reversible anemia and thrombocytopenia can occur in animals given three to five times the recommended dose of cefoxitin.

PARENTERAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that are not included in Canadian product labeling or product not commercially available in Canada.

CEFTIOFUR HYDROCHLORIDE INJECTION

Usual dose:
Metritis—Cattle: Intramuscular or subcutaneous, 2.2 mg per kg of body weight every twenty-four hours for five days.

Pododermatitis—Cattle: Intramuscular or subcutaneous, 1.1 to 2.2 mg per kg of body weight every twenty-four hours.

Respiratory tract infections—
Cattle: Intramuscular or subcutaneous, 1.1 to 2.2 mg per kg of body weight every twenty-four hours. Alternatively, the clinician may choose, based on the severity of disease, pathogen susceptibility, and the clinical response, to administer intramuscularly or subcutaneously, 2.2 mg per kg of body weight every forty-eight hours for two doses.

Pigs: Intramuscular, 3 to 5 mg per kg of body weight every twenty-four hours for three days,

Strength(s) usually available:
U.S.—Veterinary-labeled product(s):
50 mg per mL (Rx) [Excenel RTU].

Note: Be aware that this product differs from Excenel available in Canada.

Canada—Veterinary-labeled product(s):
50 mg per mL (Rx) [Excenel RTU].

Withdrawal times:
U.S.—

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Pigs</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: At labeled doses, discarding of milk during treatment is not required.

Product labeling listing the above withdrawal times states that treatment should not exceed five days for cattle or three days for pigs for these withdrawal times to apply.

This product is not labeled for use in preruminating calves. Trim-out of edible tissue at slaughter may occur within 11 days of injection because of areas of discoloration associated with the injection site.

Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>3</td>
</tr>
<tr>
<td>Pigs</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that it applies to a dose for pigs of 3 mg per kg of body weight every twenty-four hours for three days and a dose for cattle of 1 mg per kg of body weight every twenty-four hours for up to five days.

In pigs, trim-out of edible tissue at slaughter may occur within 11 days of intramuscular injection. In cattle, trim-out of edible tissue at slaughter may occur within 11 days of the last subcutaneous injection or within 28 days of the last intramuscular injection into the neck.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Auxiliary labeling:
- Shake well before using.
- Keep out of reach of children.

USP requirements: Not in USP.

CEFTIOFUR SODIUM FOR INJECTION

Usual dose:
Escherichia coli infections—
Chicks, day-old: Subcutaneous, 0.08 to 0.2 mg (free acid) per chick as a single dose.
Turkey poults, day-old: Subcutaneous, 0.17 to 0.5 mg (free acid) per poul as a single dose. Pododermatitis—Cattle: Intramuscular, 1.1 to 2.2 mg (free acid) per kg of body weight every twenty-four hours.

Respiratory tract infections—
Cattle: Intramuscular, 1.1 to 2.2 mg (free acid) per kg of body weight every twenty-four hours.
Goats: Intramuscular, 1.1 to 2.2 mg (free acid) per kg of body weight every twenty-four hours.
Horses: Intramuscular, 2.2 to 4.4 mg (free acid) per kg of body weight every twenty-four hours.

Note: For treatment of susceptible infections in foals, a dose of 2.2 to 6.6 mg (free acid) per kg of body weight every twelve to twenty-four hours has been used, based on pharmacokinetic data.

Pigs: Intramuscular, 3 to 5 mg (free acid) per kg of body weight every twenty-four hours.

Sheep: Intramuscular, 1.1 to 2.2 mg (free acid) per kg of body weight every twenty-four hours for three days. If a satisfactory response is not seen, the dose may be repeated on the fourth and fifth days.

Urinary tract infections—Dogs: Subcutaneous, 2.2 mg (free acid) per kg of body weight every twenty-four hours.

Note: Also for dogs, for treatment of [bacterial infections other than urinary tract infections] a dose of 2.2 to 4.4 mg (free acid) per kg of body weight every twenty-four hours has been used, based on pharmacokinetic data.

Strength(s) usually available: When reconstituted according to manufacturer's instructions—
U.S.: Veterinary-labeled product(s)—50 mg per mL (Rx) [Naxcel].
Canada: Veterinary-labeled product(s)—50 mg per mL (Rx) [Excenel].

Withdrawal times:
U.S.—

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<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
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<tr>
<td>Cattle</td>
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<tr>
<td>Goats, pigs, sheep</td>
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</table>

Note: At labeled doses, discarding of milk during treatment is not required.

Product labeling listing the above withdrawal times states that treatment should not exceed five days for cattle or three days for lambs or pigs for these withdrawal times to apply.

Packaging and storage:
Store unreconstituted product at controlled room temperature, 20 to 25 °C (68 to 77 °F), unless otherwise specified by manufacturer.

Store reconstituted product either in a refrigerator at 2 to 8 °C (36 to 46 °F) for up to seven days or at controlled room temperature, 20 to 25 °C (68 to 77 °F), for up to twelve hours, unless otherwise specified by manufacturer.

Protect from light.

Preparation of dosage form: To prepare dilution for intramuscular use, 20 or 80 mL of sterile water for injection should be added to the 1-gram or 4-gram vial, respectively.

Stability:
After reconstitution, solutions retain their potency for 7 days when refrigerated at 2 to 8 °C (36 to 46 °F) or 12 hours at room temperature, 15 to 30 °C (59 to 86 °F).

After reconstitution, solutions may be frozen for up to eight weeks. Frozen cefotiofur sodium may be thawed at room temperature or under warm to hot running water. Solutions should not be refrozen.

Variations in color do not affect potency.

USP requirements: Not in USP.

CEPHALEXIN

SUMMARY OF DIFFERENCES
Indications: General considerations—First-generation cephalosporin.

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

CEPHALEXIN CAPSULES USP

Usual dose:
Note: [Birds]—Although the efficacy and safety have not been established, an oral dose of 35 to 50 mg per kg of body weight every two to six hours has been used in the treatment of susceptible bacterial infections in birds, based on pharmacokinetic studies.

In general, larger birds maintain measurable serum concentrations of cephalalexin longer than do smaller birds; adequate concentrations may be achieved in larger birds with a six-hour dosing interval.

[Domestic mammals]—Although the efficacy and safety have not been established, an oral dose of 10 to 30 mg per kg of body weight every six to twelve hours has been used in the treatment of susceptible bacterial infections in dogs, based on pharmacokinetic data.
For *pyoderma* in dogs, a dose of 25 mg per kg of body weight every twelve hours for three weeks has been used, based on clinical efficacy studies. Recurrent pyodermas may require at least five weeks of therapy and deep pyodermas, nine weeks.

**Strength(s) usually available:**

**U.S.**
- Veterinary-labeled product(s):
  - Not commercially available.
- Human-labeled product(s):
  - 250 mg (Rx) [Keflex; GENERIC].
  - 500 mg (Rx) [Keflex; GENERIC].

**Canada**
- Veterinary-labeled product(s):
  - Not commercially available.
- Human-labeled product(s):
  - 250 mg (Rx) [Novo-Lexin].
  - 500 mg (Rx) [Novo-Lexin].

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

**USP requirements:** Preserve in tight containers. Contain the equivalent of the labeled amount of anhydrous cephalexin, within –10% to +20%. Meet the requirements for Identification, Uniformity of dosage units (solid packaged in single-unit containers), Deliverable volume (solid packaged in multiple-unit containers), pH (3.0–6.0, in the suspension constituted as directed in the labeling), and Water (not more than 2.0%).

CEPHALEXIN TABLETS USP

**Usual dose:** See Cephalexin Capsules USP.

**Strength(s) usually available:**

**U.S.**
- Veterinary-labeled product(s):
  - Not commercially available.
- Human-labeled product(s):
  - 250 mg (Rx) [Apo-Cephalex; Keflex; Novo-Lexin; Nu-Cephalex; PMS-Cephalexin].
  - 500 mg (Rx) [Apo-Cephalex; Keflex; Novo-Lexin; Nu-Cephalex; PMS-Cephalexin].

**Canada**
- Veterinary-labeled product(s):
  - Not commercially available.
- Human-labeled product(s):
  - 250 mg (Rx) [Keflex; Novo-Lexin; PMS-Cephalexin].
  - 500 mg (Rx) [Keflex; Novo-Lexin; PMS-Cephalexin].

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

**USP requirements:** Preserve in tight containers. They are prepared from Cephalexin or Cephalexin Hydrochloride. The label states whether the Tablets contain Cephalexin or Cephalexin Hydrochloride. Contain the equivalent of the labeled amount of anhydrous cephalexin, within –10% to +20%. Meet the requirements for Identification, Dissolution (80% in 30 minutes in water in Apparatus 1 [use 40-mesh cloth]) at 100 rpm, Uniformity of dosage units, and Water (not more than 9.0% where Tablets contain cephalexin; not more than 8.0% where Tablets contain cephalexin hydrochloride).

CEPHALEXIN HYDROCHLORIDE TABLETS USP

**Usual dose:** See Cephalexin Capsules USP.

**Strength(s) usually available:**

**U.S.**
- Veterinary-labeled product(s):
  - Not commercially available.
- Human-labeled product(s):
  - 500 mg (Rx) [Keftab].

**Canada**
- Not commercially available.

**Packaging and storage:** Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.
**USP requirements:** Preserve in tight containers. They are prepared from Cephalixin or Cephalexin Hydrochloride. The label states whether the Tablets contain Cephalexin or Cephalexin Hydrochloride. Contain the equivalent of the labeled amount of anhydrous cephalexin, within –10% to +20%. Meet the requirements for Identification, Dissolution (80% in 30 minutes in water in Apparatus 1 [use 40-mesh cloth] at 100 rpm for cephalexin and 75% in 45 minutes in water in Apparatus 1 [use 10-mesh cloth] at 150 rpm for cephalexin hydrochloride). Uniformity of dosage units, and Water (not more than 9.0% where Tablets contain cephalexin; not more than 8.0% where Tablets contain cephalexin hydrochloride). [R-14]

1Not included in Canadian product labeling or product not commercially available in Canada.

**CEPHALOTHIN**

**SUMMARY OF DIFFERENCES**

Indications: General considerations—First-generation cephalosporin.

Drug interactions and/or related problems: Concurrent administration with probenecid may prolong the serum half-life of cephalothin. [R-10]

Medical considerations/contraindications: Severe hepatic dysfunction may inhibit metabolism. [R-2]

Side/adverse effects: Local irritation may occur. [R-1]

**PARENTERAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of cephalexin base (not the sodium salt).

**CEPHALOTHIN FOR INJECTION USP**

**Usual dose:**

Note: [Birds]—Although the efficacy and safety have not been established, an intramuscular dose of 100 mg (base) per kg of body weight every two to six hours has been used in the treatment of susceptible bacterial infections in birds, based on pharmacokinetic studies.[R-14]

In general, larger birds maintain measurable serum concentrations of cephalothin longer than do smaller birds; adequate concentrations may be achieved in larger birds with a six-hour dosing interval.[R-14], [Dogs]—Although the efficacy and safety have not been established, an intramuscular or intravenous dose of 10 to 30 mg (base) per kg of body weight every four to eight hours has been used in the treatment of susceptible bacterial infections in dogs, based on pharmacokinetic data.[R-38]

[Horses]—Although the efficacy and safety have not been established, an intramuscular or intravenous dose of 10 to 25 mg (base) per kg of body weight every four hours has been used in the treatment of susceptible bacterial infections in horses, based on pharmacokinetic data.[R-9, 19].

**Size(s) usually available:**

U.S.—[R-22; 51]

Veterinary-labeled product(s):

Not commercially available.

**Stability:**[R-22]

After reconstitution, solutions retain their potency for 96 hours if refrigerated. Solutions for intramuscular use retain their potency for 12 hours at room temperature.

A precipitate may form in the solution. Upon being warmed to room temperature and shaken, the precipitate will dissolve.

Concentrated solutions will darken in color, especially at room temperature. However, slight discoloration does not affect potency.

If frozen immediately after reconstitution with sterile water for injection, 5% dextrose injection, or 0.9% sodium chloride injection, solutions retain their potency in the original container up to 12 weeks at –20 °C (–4 °F). Once thawed, solutions should not be refrozen.

**Incompatibilities:**

The admixture of other medications with cephalothin sodium injection is not recommended.

The admixture of beta-lactam antibiotics (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation; they should not be mixed in the same intravenous bag or bottle.

**USP requirements:** Preserve in Containers for Sterile Solids. Contains an amount of Cephalothin Sodium equivalent to the labeled amount of cephalexin, within –10% to +15%. May contain Sodium Bicarbonate. Meets the requirements for Constituted solution, Specific rotation (+124° to +134°, calculated on the dried and sodium bicarbonate-free basis), Content of sodium bicarbonate (if present), Bacterial endotoxins, Sterility (6.0–8.5, in the solution constituted as directed in the labeling), Uniformity of dosage units, and Particulate matter, for Identification test A and Loss on drying under Cephalothin Sodium, and for Labeling under Injections.[R-14]

1Not included in Canadian product labeling or product not commercially available in Canada.

**CEPHAPIRIN**

**SUMMARY OF DIFFERENCES**

Indications: General considerations—First-generation cephalosporin.

Pharmacology/pharmacokinetics: Human biotransformation—Hepatic metabolism to the desacetyl form occurs.[R-2]

Drug interactions and/or related problems: Concurrent administration with probenecid may prolong the serum half-life of cephalothin. [R-10]
Medical considerations/contraindications: In people, severe hepatic dysfunction can inhibit metabolism. Side/adverse effects: Local reactions may occur.

PARENTERAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.
The dosing and strengths of the dosage forms available are expressed in terms of cepharpin base (not the sodium salt).

CEPHAPIRIN FOR INJECTION USP
Usual dose:
Note: [Dogs]—Although the efficacy and safety have not been established, an intramuscular or intravenous dose of 10 to 30 mg (base) per kg of body weight every four to eight hours has been used in the treatment of susceptible bacterial infections in dogs, based on pharmacokinetic data.

[Horses]—Although the efficacy and safety have not been established, an intramuscular or intravenous dose of 20 to 30 mg per kg of body weight every four to eight hours has been used in the treatment of susceptible bacterial infections in horses, based on pharmacokinetic data.

Size(s) usually available:
U.S.—[R-54]
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
500 mg (base) (Rx) [Cefadyl].
1 gram (base) (Rx) [Cefadyl].
2 grams (base) (Rx) [Cefadyl].
4 grams (base) (Rx) [Cefadyl].
20 grams (base) (Rx) [Cefadyl].
Canada—
Not commercially available.

Packaging and storage: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: Dilutions should be prepared according to manufacturer’s instructions.

Stability: See manufacturer’s product labeling for stability information.

Incompatibilities: The admixture of beta-lactam antibiotics (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation; they should not be mixed in the same intravenous bag or bottle.

USP requirements: Preserve in Containers for Sterile Solids. Contains an amount of Cephapirin Sodium equivalent to the labeled amount of cepharpin, within –10% to +15%. Meets the requirements for Constituted solution, Bacterial endotoxins, Sterility, and Particulate matter, for Identification, Crystallinity, pH, and Water under Cephapirin Sodium, and for Uniformity of dosage units and Labeling under Injections.

Note: [R-14] Not included in Canadian product labeling or product not commercially available in Canada.

CEPHRADINE
SUMMARY OF DIFFERENCES
Indications: General considerations—First-generation cephalosporin.

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

CEPHRADINE CAPSULES USP
Usual dose:
Note: [Dogs]—Although the efficacy and safety have not been established, an oral dose of 10 to 25 mg per kg of body weight every six to twelve hours has been used in the treatment of susceptible bacterial infections in dogs, based on pharmacokinetic data.

[Horses]—Although the efficacy and safety have not been established, an oral dose of 25 mg per kg of body weight every six to eight hours has been used in the treatment of susceptible bacterial infections in foals, based on pharmacokinetic data.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [Velosef; generic].
500 mg (Rx) [Velosef; generic].
Canada—
Not commercially available.

Packaging and storage: Store below 30 °C (86 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. The quantity of cephradine stated in the labeling is in terms of anhydrous cephradine. Contain the labeled amount of cephradine, within –10% to +20%, calculated as the sum of cephradine and cephalixin. Meet the requirements for Identification, Dissolution (75% in 45 minutes in 0.12 N hydrochloric acid in Apparatus 1 at 100 rpm), Uniformity of dosage units, and Loss on drying (not more than 7.0%).

CEPHRADINE FOR ORAL SUSPENSION USP
Usual dose: See Cephradine Capsules USP.

Strength(s) usually available: When reconstituted according to manufacturer’s instructions—
U.S.:
Veterinary-labeled product(s)—
Not commercially available.
Human-labeled product(s)—
25 mg per mL (Rx) [Velosef; GENERIC].
50 mg per mL (Rx) [Velosef; GENERIC].

Canada:
Not commercially available.

Packaging and storage: Prior to reconstitution, store below 40° C (104° F), preferably between 15 and 30° C (59 and 86° F), unless otherwise specified by manufacturer. Store in a tight container.

Stability:
After reconstitution, suspensions retain their potency for 7 days at room temperature or for 14 days if refrigerated.

Auxiliary labeling:
- Refrigerate.
- Shake well.

Table 1. Pharmacology/Pharmacokinetics*.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein binding (%)</th>
<th>Half-life of elimination (hr)</th>
<th>VolD Steady state (L/kg)</th>
<th>Clearance (mL/min/kg)</th>
<th>Route; Dose (mg/kg)</th>
<th>Tmax (min)</th>
<th>Cmax (mcg/mL)</th>
<th>Bioavailability (%)</th>
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<td>Cats (R-3)</td>
<td>Low (20)</td>
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<td></td>
<td>Oral; 22</td>
<td>60–120</td>
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<td></td>
<td>Oral; 22</td>
<td>60–120</td>
<td>18.6</td>
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<td>Horses</td>
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<td>25</td>
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<td>Dogs (R-2)</td>
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USP requirements: Preserve in tight containers. A dry mixture of Cephadrine and one or more suitable buffers, colors, diluents, and flavors. Contains the labeled amount of cephadrine, within –10% to +25%, calculated as the sum of cephadrine and cephalexin. Meets the requirements for Identification, Uniformity of dosage units (solid packaged in single-unit containers), Deliverable volume (solid packaged in multiple-unit containers), pH (3.5–6.0, in the suspension constituted as directed in the labeling), and Water (not more than 1.5%). [R-14]

Not included in Canadian product labeling or product not commercially available in Canada.

Developed: 08/02/95
Interim revision: 07/08/98; 11/5/99; 09/30/02; 04/04/03
## Table 1 (Contd.)

<table>
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<tr>
<th>Drug</th>
<th>Protein Binding (%)</th>
<th>Half-life of Elimination (hr)</th>
<th>VolD Steady state (L/kg)</th>
<th>Clearance (mL/min/kg)</th>
<th>Route; Dose (mg/kg)</th>
<th>Tmax (min)</th>
<th>Cmax (mcg/mL)</th>
<th>Bioavailability (%)</th>
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<td>SC: 30</td>
<td>30–60</td>
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<td>Cats[R-42]</td>
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<td>0.18</td>
<td>2.8</td>
<td>IV: 10</td>
<td>IM: 10</td>
<td>42</td>
<td>93–98</td>
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<td>Cefotetan</td>
<td>Calves[R-78]</td>
<td>High (90)</td>
<td>3.5–4</td>
<td>0.34</td>
<td>Orak: 5</td>
<td>240</td>
<td>3.4</td>
<td>Fed: 20–28</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>Dogs[R-77; 87–89]</td>
<td>High (82–92)</td>
<td>7 to 8</td>
<td>0.22</td>
<td>IM: 5</td>
<td>360</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>Gees[R-15]</td>
<td>0.4</td>
<td>0.3–04</td>
<td>0.78</td>
<td>2.9</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotetan</td>
<td>Sheep[R-20; 60]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Generation</td>
<td>Cefclofur†</td>
<td>Calves[R-61]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Generation</td>
<td>Cows[R-70]</td>
<td>7.1</td>
<td>2</td>
<td>0.2</td>
<td>0.5</td>
<td>IV: 2</td>
<td>IM: 2</td>
<td>60</td>
</tr>
<tr>
<td>New Generation</td>
<td>Cows, lactating</td>
<td>3.6</td>
<td>0.39</td>
<td>1.27</td>
<td>IV: 2</td>
<td>IM: 0.22</td>
<td>45</td>
<td>1.7</td>
</tr>
<tr>
<td>New Generation</td>
<td>Dogs[R-72]</td>
<td>5 to 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Generation</td>
<td>Pigs[R-75]</td>
<td>12–13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Generation</td>
<td>Sheep[R-97]</td>
<td>5–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Abbrevations: IM = Intramuscular, IV = Intravenous, SQ = Subcutaneous, VolD = Volume of distribution, Tmax = Time to peak concentration, Cmax = Peak serum concentration.

† Assays for serum concentrations of cefclofur listed include cefclofur and its active desfuroylceftiofur metabolite.

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CEPHAPIRIN Veterinary—Intramammary-Local

Some commonly used brand names for veterinary-labeled products are: Cefa-Dri; Cefa-Lak; ToDay; and ToMorrow.

Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

**CATEGORY:**
Antibacterial (intramammary-local).

**INDICATIONS**

**GENERAL CONSIDERATIONS**

Cephapirin is a first-generation cephalosporin that has a wide spectrum of activity against gram-positive and gram-negative organisms. \([R-5]\) Cephapirin is more resistant to beta-lactamases than are the penicillins \([R-6]\) and so is effective against staphylococci, with the exception of methicillin-resistant staphylococci \([R-5]\)

**ACCEPTED**

 Mastitis (treatment)—Cattle: Cephapirin is indicated in the treatment of mastitis caused by susceptible bacteria, such as *Staphylococcus aureus* \([R-1; 4–7]\) and *Streptococcus agalactiae* \([R-1–4]\). Cephalosporins are the primary treatment of choice for acute staphylococcal mastitis \([R-9]\); however, cows with acute or peracute mastitis are often given other medications, such as systemic antibiotics and/or supportive therapy, concurrently with intramammary therapy \([R-10]\).

**REGULATORY CONSIDERATIONS**

**CHEMISTRY**

**Source:** Cephalosporins are semi-synthetic derivatives of metabolic products of the fungus *Cephalosporium acremonium*. \([R-6; 11]\)

**Chemical group:** Beta-lactam antibiotics. \([R-5]\)

**Chemical name:**

Cephapirin benzathine—5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[(acetyloxy)methyl]-8-oxo-7-[(4-pyridinylthio)acetyl]amino], (6R-trans), cmpd. with N,N’-bis(phenylmethyl)-1,2-ethanediamine (2:1) \([R-12]\)

Cephapirin sodium—5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[(acetyloxy)methyl]-8-oxo-7-[(4-pyridinylthio)acetyl]amino]-monosodium salt, (6R-trans) \([R-12]\)

**Molecular formula:**

Cephapirin benzathine—\((C_{17}H_{17}N_{2}O_{3}S_{2}N) \cdot C_{16}H_{30}N_{2}\) \([R-12]\)

Cephapirin sodium—\(C_{17}H_{17}N_{2}NaO_{3}S_{2}\) \([R-12]\)

**Molecular weight:**

Cephapirin benzathine—1087.27 \([R-12]\)

Cephapirin sodium—445.45 \([R-12]\)

**Description:**

Cephapirin Benzathine USP—White, crystalline powder \([R-21]\).

Cephapirin Sodium USP—White to off-white crystalline powder, odorless or having a slight odor \([R-21]\).

**pkA:** Cephapirin sodium—2.15 and 7.3 \([R-13]\)

**Solubility:**

Cephapirin Benzathine USP—Practically insoluble in water, in ether, and in toluene; freely soluble in alcohol; soluble in 0.1 N hydrochloric acid \([R-21]\).

Cephapirin Sodium USP—Very soluble in water; insoluble in most organic solvents \([R-21]\).

**PHARMACOLOGY/PHARMACOKINETICS**

**Mechanism of action/effect:** Cephapirin produces its bactericidal effect by inhibiting cell wall synthesis. Its action is only effective in actively growing cells.

**Distribution:** Medications infused into a teat are considered to be fairly evenly distributed in the treated quarter of the healthy mammary gland; however, in an udder affected by moderate to severe mastitis, the presence of edema, blockage of milk ducts, and reduced blood circulation can cause uneven distribution of medication \([R-14]\).

**PRECAUTIONS TO CONSIDER**

**PATIENT MONITORING**

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; *a* = major clinical significance):

**Bacterial pathogens in milk**

(milk samples should be tested 3 weeks after treatment is discontinued; mastitis is not considered bacteriologically cured until samples show an absence of the mastitis-causing organisms)

**Clinical signs**

(although resolution of clinical signs of mastitis is not an indication that a bacteriologic cure has been achieved \([R-15]\), monitoring of the clinical condition of the mammary gland, teat, and milk produced can aid in diagnosis of a recurrence of mastitis or initial diagnosis of mastitis in another cow in the herd)

**Somatic cell count**

(somatic cell counts performed on milk to monitor the dairy herd are used primarily to maintain milk quality but are also used to assess the approximate overall effectiveness of mastitis control programs, which may include antibiotic treatment of cows \([R-10]\))

**SIDE/ADVERSE EFFECTS**

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

**THOSE INDICATING NEED FOR MEDICAL ATTENTION**

**Incidence unknown**

**Cows**

**Allergic reactions** \([R-1; 21]\)—local or systemic; *drug fever* \([R-19]\)

**OVERDOSE**

For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals

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CLIENT CONSULTATION

Treatment of mastitis in dairy cattle is best achieved by a comprehensive mastitis control program in which herd management is the primary focus. The program should include routine milk testing, good maintenance of milking equipment, and constant evaluation of milking procedures and teat health as well as strategic treatment of clinical cases of mastitis.\[R-16\]

VETERINARY DOSING INFORMATION

Antibiotic therapy in the dry cow is more effective than treatment during lactation for mastitis caused by *Staphylococcus aureus*.\[R-15; 16; 20\]

Choice of antibiotic for treatment of mastitis should be based on knowledge of identity and sensitivity of pathogens causing mastitis in the cow and the dairy herd.

Before intramammary administration of cephapirin, the following actions should be taken:\[R-1–4\]

- The udder should be milked out completely and the teats washed with warm water and a disinfectant. Care should be taken to avoid washing excess dirt down from the udder onto the teat ends. The area should be dried thoroughly. An effective germicidal teat dip should be applied for one minute and then each teat wiped with a separate cotton ball soaked with an antiseptic such as 70% alcohol.
- Persons performing the treatment should wash and dry their hands before each treatment.
- The tip of the syringe should be inserted into the teat end as little as possible and the contents of the syringe should be injected into each streak canal while the teat is held firmly. The medication should then be gently massaged up the teat canal into the udder.

Following treatment, an effective teat dip is recommended on all teats.

INTRAMAMMARY DOSAGE FORMS

CEPHAPIRIN BENZATHINE INTRAMAMMARY INFUSION USP

Usual dose: Mastitis—Cows, nonlactating: Intramammary. 300 mg administered into each quarter of the udder at the time of drying-off.\[R-1; 2\]

Strength(s) usually available:

U.S.—\[R-1; 2; 22\]

Veterinary-labeled product(s):

300 mg per 10 mL (OTC) [Cefa-Dri; ToMorrow].

Canada—\[R-17; 22\]

Veterinary-labeled product(s):

300 mg per 10 mL (Rx) [Cefa-Dri].

Withdrawal times:

U.S.—\[R-1; 2; 22\]

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows, nonlactating</td>
<td>42</td>
<td>72</td>
</tr>
</tbody>
</table>

Note: Cephapirin benzathine intramammary infusion should not be used any later than thirty days prior to calving.

Canada—\[R-17; 22\]

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows, nonlactating</td>
<td>42</td>
<td>84</td>
</tr>
</tbody>
</table>

Note: Cephapirin benzathine intramammary infusion should not be used any later than thirty days prior to calving.

Package and storage: Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

USP requirements: Preserve in well-closed unit-dose disposable syringes at controlled room temperature. A suspension of Cephapirin Benzathine in a suitable vegetable oil vehicle. Contains a suitable dispersing agent. Label Intramammary Infusion to indicate that it is for veterinary use only. Contains an amount of cephapirin benzathine equivalent to the labeled amount of cephapirin, within -10% to +20%. Meets the requirements for Identification and Water (not more than 1.0%).\[R-21\].

CEPHAPIRIN SODIUM INTRAMAMMARY INFUSION USP

Usual dose: Mastitis—Cows, lactating: Intramammary. 200 mg into each affected quarter of the udder every twelve hours for two treatments.\[R-3; 4\]

Strength(s) usually available:

U.S.—\[R-3; 4; 22\]

Veterinary-labeled product(s):

200 mg per 10 mL (OTC) [Cefa-Lak; ToDay].

Canada—\[R-18; 22\]

Veterinary-labeled product(s):

200 mg per 10 mL (Rx) [Cefa-Lak].

Withdrawal times:

U.S. and Canada—\[R-3; 4; 18; 22\]

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows, lactating</td>
<td>4</td>
<td>96</td>
</tr>
</tbody>
</table>

Package and storage: Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

USP requirements: Preserve in well-closed unit-dose disposable syringes at controlled room temperature. A suspension of Cephapirin Sodium in a suitable vegetable oil vehicle. Contains a suitable dispersing agent. Label Intramammary Infusion to indicate that it is for veterinary use only. Contains an amount of cephapirin sodium equivalent to the labeled amount of cephapirin, within -10% to +20%. Meets the requirements for Identification and Water (not more than 1.0%).\[R-21\].
REFERENCES

CHLORAMPHENICOL Veterinary—Systemic

Some commonly used brand names are:

For veterinary-labeled products—Ampheic Film-Coated Tablets; Azramycin S125; Azramycin S250; Chlor 100; Chlor 250; Chlor 500; Chlor 1000; Chlor Palm 125; Chlor Palm 250; Duricid; Karomycin Palmitate 125; Karomycin Palmitate 250; and Vicetin.

For human-labeled products—Chloromycetin and Novochlorocap.

Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:
Antibacterial (systemic).

INDICATIONS

Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

ACCEPTED

Chloramphenicol is a broad-spectrum antibiotic shown to have specific activity against a wide variety of organisms that are the causative agents of several disease conditions in domestic animals. Such organisms include Staphylococcus aureus, Streptococcus pyogenes, Brucella bronchiseptica, Escherichia coli, Proteus vulgaris, Aerobacter aerogenes, Corynebacterium renale, Salmonella species, Shigella species, Neisseria catarrhalis, anaerobic bacteria, and many rickettsiae. The species treated with chloramphenicol include dogs, [cats]¹, and [horses]².

¹Not included in Canadian product labeling or product not commercially available in Canada.

REGULATORY CONSIDERATIONS

U.S.—

Food and Drug Administration regulations ban chloramphenicol from use in animals that are used for food production.

There are no safe residue levels, and no withdrawal times have been established.

Chloramphenicol Tablets USP are labeled for veterinary use only.

Canada—

Chloramphenicol is prohibited from use in food-producing animals by the Canadian Health Protection Branch.

Chloramphenicol Tablets USP are labeled for veterinary use only.

CHEMISTRY

Source:

Originally derived from Streptomyces venezuelae.¹⁰

Chemical name:

Chloramphenicol—Acetamide, 2,2-dichloro-N-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]-, [R-(-R,R⁺)].¹²
Chloramphenicol palmitate—Hexadecanoic acid, 2-[2,2-dichloroacetyl]-amino]-3-hydroxy-3-(4-nitrophenyl)propyl ester, [R-(-R,R⁺)].¹²
Chloramphenicol sodium succinate—Butanedioic acid, mono[2-[2,2-dichloroacetyl]amino]-3-hydroxy-3-(4-nitrophenyl)propyl ester monosodium salt, [R-(-R,R⁺)].¹²

Molecular formula:

Chloramphenicol—C₁₁H₁₂Cl₂N₂O₅.¹²
Chloramphenicol palmitate—C₂₇H₄₂Cl₂N₂O₆.¹²
Chloramphenicol sodium succinate—C₁₄H₁₅Cl₂N₂NaO₆.¹²

Molecular weight:

Chloramphenicol—323.33.¹²
Chloramphenicol palmitate—561.54.¹²
Chloramphenicol sodium succinate—445.18.¹²

Description:¹²

Chloramphenicol USP—Fine, white, to grayish white or yellowish white, needle-like crystals or elongated plates. Its solutions are practically neutral to litmus. Is reasonably stable in neutral or moderately acid solutions. Its alcohol solution is dextrorotatory and its ethyl acetate solution is levorotatory.

Chloramphenicol Palmitate USP—Fine, white, unctuous, crystalline powder, having a faint odor.

Chloramphenicol Sodium Succinate USP—Light yellow powder.

Solubility:¹²

Chloramphenicol USP—Slightly soluble in water; freely soluble in alcohol, in propylene glycol, in acetone, and in ethyl acetate. Chloramphenicol Palmitate USP—Insoluble in water; freely soluble in acetone and in chloroform; soluble in ether; sparingly soluble in alcohol; very slightly soluble in solvent hexane.

Chloramphenicol Sodium Succinate USP—Freely soluble in water and in alcohol.

PHARMACOLOGY/PHARMACOKINETICS

Note: See also Table 1. Pharmacokinetic Parameters at the end of this monograph.

Mechanism of action/effect:

Chloramphenicol is bacteriostatic. However, it may be bactericidal in high concentrations or when used against highly susceptible organisms.

Chloramphenicol, which is lipid soluble, diffuses through the bacterial cell membrane and reversibly binds to the 50 S subunit of the bacterial ribosomes where transfer of amino acids to growing peptide chains is prevented (perhaps by suppression of peptidyl transferase activity), thus inhibiting peptide bond formation and subsequent protein synthesis.

Absorption:

Chloramphenicol is rapidly absorbed from the gastrointestinal tract after oral administration in many simple-stomach animals. Cats—Chloramphenicol palmitate is not absorbed well after oral administration to fasted cats.¹²

Distribution:

Chloramphenicol diffuses readily into all body tissues, but at different concentrations. Highest concentrations are found in the liver and kidneys of dogs.

The lungs, spleen, heart, and skeletal muscles contain concentrations similar to that in the blood. Chloramphenicol reaches significant concentrations in the aqueous and vitreous humors of the eye. Within 3 to 4 hours after administration, the concentration in the cerebrospinal fluid reaches, on the average, 50% of the concentration in the serum. The percentage increases if there is inflammation of the meninges.
Chloramphenicol diffuses readily into milk and pleural and ascitic fluids and crosses the placenta, attaining concentrations of about 75% of that in maternal blood.

**Biotransformation:** Chloramphenicol is rather rapidly metabolized, mainly in the liver, by conjugation with glucuronic acid.

**Elimination:** Approximately 55% of a single daily dose can be recovered from the urine of a treated dog. A small fraction of this is in the form of unchanged chloramphenicol. The unchanged chloramphenicol is excreted by glomerular filtration (5 to 10%), whereas 80% is excreted via tubular secretion as inactive metabolite.

**PRECAUTIONS TO CONSIDER**

**SPECIES SENSITIVITY**

**Cats**—Chloramphenicol should not be used in the cat for more than 14 days because it can cause dose-related blood dyscrasias. The reported increased susceptibility of cats to development of blood dyscrasias relative to dogs or horses may be attributable to chloramphenicol’s significantly longer elimination half-life in the cat.

**PEDIATRICS**

*All species*

In the fetus and neonate, the immature liver cannot conjugate chloramphenicol, and toxic concentrations of active drug accumulate.

*Dog and cats*

Sudden death has been reported in puppies and kittens receiving intravenous chloramphenicol.

**DRUG INTERACTIONS AND/OR RELATED PROBLEMS**

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (« = major clinical significance):

Note: Combinations containing any of the following medications, especially:

- Digitalis glycosides
- Erythromycin
- Primidone
- Phenobarbital or Pentobarbital

**SIDE/ADVERSE EFFECTS**

Note: Although aplastic anemia has occurred in human patients as a result of chloramphenicol administration, it has not been documented in animals. A dose-related reversible bone marrow suppression may occur, sometimes manifesting as pancytopenia or agranulocytosis.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

**THOSE INDICATING NEED FOR MEDICAL ATTENTION**

*All species*

- However; bone marrow suppression; depression; diarrhea and vomiting

Note: Intermediate metabolites are thought to be responsible for the reversible bone marrow suppression seen in domestic animals. The effect is dose-dependent, often occurring with long-term therapy.

**HUMAN SIDE/ADVERSE EFFECTS**

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Chloramphenicol (Systemic) in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may not be applicable to the use of chloramphenicol in the treatment of animals:

Note: The hematologic toxicity of chloramphenicol can manifest itself in 1 of 2 ways—either as a reversible bone marrow depression or an idiosyncratic aplastic anemia. Bone marrow depression is dose-related and most commonly seen when serum concentrations of chloramphenicol exceed 25 mcg/mL. Bone marrow changes are usually reversible when chloramphenicol is discontinued. Aplastic anemia is an idiosyncratic reaction that occurs in 1 of every 25,000 to 40,000 courses of treatment. It is not related to dose or duration of therapy. Most cases have been associated with oral chloramphenicol, and the onset of aplasia may not occur until weeks or months after treatment with chloramphenicol has been discontinued.

Incidence less frequent

**Blood dyscrasias; gastrointestinal reaction**

Incidences rare

- Gray syndrome—in neonates only: hypersensitivity reactions; neurotoxic reactions; optic neuritis; peripheral neuritis
Note: Gray syndrome (or “gray baby syndrome”) almost always occurs in newborn infants treated with inappropriately high doses of chloramphenicol. Typically, the infant has been started on chloramphenicol within the first 48 hours of life; symptoms first appear after 3 to 4 days of continued treatment with high doses of chloramphenicol; and serum concentrations are high, often between 40 and 200 mcg/mL. If detected early and chloramphenicol is discontinued, the infant may have a complete recovery. On rare occasion, older patients, including adults with severe liver disease, have also had a gray syndrome–type reaction.

Symptoms of possible fatal, irreversible bone marrow depression

Pale skin; sore throat and fever; unusual bleeding or bruising; unusual tiredness or weakness

Note: Pale skin, sore throat and fever, unusual bleeding or bruising, unusual tiredness or weakness may be symptoms of irreversible bone marrow depression leading to aplastic anemia, and the need for immediate medical attention if they occur weeks or months after medication is discontinued.

OVERDOSE

For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

CLIENT CONSULTATION

Because of the risk of idiosyncratic aplastic anemia that occurs in people after exposure to chloramphenicol, extreme care during administration to animals should be exercised. Animals do not appear prone to develop the idiosyncratic aplastic anemia that can occur in people weeks or months after cessation of drug therapy. In humans, the reported incidence of idiosyncratic aplastic anemia following chloramphenicol exposure ranges from 1/25,000 to 1/40,000. Aplastic anemia in humans may occur following oral, intramuscular, intravenous, ophthalmic, and/or topical administration. Due to these risks, chloramphenicol is banned in food-producing animals in the United States and people should avoid other types of exposure as well.

When administering chloramphenicol to animals, people should avoid direct contact with the medication (for example, avoid opening the capsules).

VETERINARY DOSING INFORMATION

Most susceptible infectious disease organisms will respond to chloramphenicol therapy in 3 to 5 days when the recommended dosage regimen is followed.

If no response to chloramphenicol therapy is obtained in 3 to 5 days, use should be discontinued and the diagnosis reviewed.

Cats—Chloramphenicol should not be used in the cat for more than 14 days because it can cause dose-related blood dyscrasias.

Chloramphenicol palmitate is not absorbed well after oral administration to fasted cats.

ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of chloramphenicol base.

CHLORAMPHENICOL CAPSULES USP

Usual dose: Antibacterial—

Dogs: Oral, 45 to 60 mg per kg of body weight every eight hours.

[Cats]: Oral, 13 to 20 mg per kg of body weight every twelve hours.

Note: The oral dose for cats is based on the best information available, which may, however, underestimate the dose needed in some cases. Doses of 25 to 50 mg per kg of body weight every twelve hours have been recommended, and may be necessary for some infections, but could increase the risk of side effects.

[Horses]: Oral, 45 to 60 mg per kg of body weight every eight hours.

Strength(s) usually available:

Usa—

Veterinary-labeled product(s):

50 mg (Rx) [Duricol].

100 mg (Rx) [Duricol].

250 mg (Rx) [Duricol].

500 mg (Rx) [Duricol].

Human-labeled product(s):

250 mg (Rx) [sensac].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [Novochlorcap].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Contain the labeled amount, within –10 to +20%. Meet the requirements for Identification, Dissolution (85% in 30 minutes in 0.01 N hydrochloric acid in Apparatus 1 at 100 rpm), and Uniformity of dosage units.

CHLORAMPHENICOL PALMITATE ORAL SUSPENSION USP

Usual dose: [Antibacterial]—

Dogs: Oral, 45 to 60 mg per kg of body weight every eight hours.

Cats: Oral, 13 to 20 mg per kg of body weight every twelve hours.

Note: The oral dose for cats is based on the best information available, which may, however, underestimate the dose needed in some cases. Doses of 25 to 50 mg every twelve hours have been recommended, and may be necessary for some infections, but could increase the risk of side effects.

Strength(s) usually available:

Usa—

Veterinary-labeled product(s):

Not commercially available.

Canada—

Veterinary-labeled product(s):

25 mg (base) per mL (Rx) [Azramycine S125; Chlor Palm 125; Karomycin Palmitate 125].

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50 mg (base) per mL (Rx) [Azramycin S250; Chlor Palm 250; Karomycin Palmitate 250].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container. Protect from freezing.

USP requirements: Preserve in tight, light-resistant containers. Contains an amount of chloramphenicol palmitate equivalent to the labeled amount of chloramphenicol, within –10 to +20%. Contains one or more suitable buffers, colors, flavors, preservatives, and suspending agents. Meets the requirements for Identification, Uniformity of dosage units (suspension packaged in single-unit containers), Deliverable volume (suspension packaged in multiple-unit containers), pH (4.5–7.0), and Limit of polymorph A^{1[R-10]}.  

CHLORAMPHENICOL TABLETS USP

Usual dose: Antibacterial—

Dogs: Oral, 45 to 60 mg per kg of body weight every eight hours.

[Cats]: Oral, 13 to 20 mg per kg of body weight every twelve hours. Note: The oral dose for cats is based on the best information available, which may, however, underestimate the dose needed in some cases. Doses of 25 to 50 mg per kg of body weight every twelve hours have been recommended, and may be necessary for some infections, but could increase the risk of side effects.

[Horses]: Oral, 45 to 60 mg per kg of body weight every eight hours.

Strength(s) usually available^{R-11}:

U.S.—

Veterinary-labeled product(s):
100 mg (Rx) [Viceton].
250 mg (Rx) [Amphicol Film-Coated Tablets; Viceton].
500 mg (Rx) [Amphicol Film-Coated Tablets; Viceton].
1000 mg (Rx) [Amphicol Film-Coated Tablets; Viceton].

Canada—

Veterinary-labeled product(s):
100 mg (Rx) [Chlor 100].
250 mg (Rx) [Chlor 250].
500 mg (Rx) [Chlor 500].
1000 mg (Rx) [Chlor 1000].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Label Tablets to indicate that they are for veterinary use only and are not to be used in animals raised for food production. Contain the labeled amount, within –10 to +20%. Meet the requirements for Identification, Disintegration (60 minutes), and Uniformity of dosage units.

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S. The dosing and strengths of the dosage forms available are expressed in terms of chloramphenicol base.

CHLORAMPHENICOL SODIUM SUCCINATE FOR INJECTION USP

Usual dose: [Antibacterial]^{1—}

Cats: Intramuscular, intravenous, or subcutaneous, 12 to 30 mg (base) per kg of body weight every twelve hours.

Dogs and horses: Intramuscular, intravenous, or subcutaneous, 45 to 60 mg (base) per kg of body weight every six to eight hours.

Strength(s) usually available^{R-8; 12}:

U.S.—

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
1 gram (base) per vial (Rx) [Chloromycetin; generic].

Canada—

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
1 gram (base) (Rx) [Chloromycetin].

Packaging and storage: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: To prepare a 10% (100-mg-per-mL) solution, add 10 mL of an aqueous diluent such as sterile water for injection or 5% dextrose injection to each 1-gram vial^{R-8}.

USP requirements: Preserve in Containers for Sterile Solids. Contains an amount of chloramphenicol sodium succinate equivalent to the labeled amount of chloramphenicol, within –10 to +15%. Meets the requirements for Bacterial endotoxins, Sterility, Particulate matter, and Limit of free chloramphenicol (not more than 2.0%), and for Identification, Specific rotation, pH, and Water under Chloramphenicol Sodium Succinate^{R-10}.

1Not included in Canadian product labeling or product not commercially available in Canada.

Revised: 07/28/94
Interim revision: 03/30/95; 04/24/96; 05/07/97; 05/27/98; 10/15/99; 09/30/02; 04/04/03

Table 1. Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Species</th>
<th>Elimination half-life (hours)</th>
<th>First order elimination rate constant (min⁻¹)</th>
<th>Volp (L/kg)</th>
<th>Total body clearance (mL/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cats</td>
<td>5.1</td>
<td>0.0023</td>
<td>2.36</td>
<td>5.5</td>
</tr>
<tr>
<td>Dogs</td>
<td>1.20 ± 0.10</td>
<td>0.0098 ± 0.001</td>
<td>0.85 ± 0.06</td>
<td>8.57 ± 0.83</td>
</tr>
<tr>
<td>Horses</td>
<td>0.63 ± 0.04</td>
<td>0.0188 ± 0.001</td>
<td>1.41 ± 0.08</td>
<td>26.14 ± 1.28</td>
</tr>
</tbody>
</table>

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REFERENCES
ERYTHROMYCIN Veterinary—Intramammary-Local

Some commonly used brand names for veterinary-labeled products are: Erythro-36; Erythro-Dry Cow; Gallimycin-36; and Gallimycin-Dry Cow. Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:
Antibacterial (intramammary-local).

INDICATIONS

GENERAL CONSIDERATIONS
Erythromycin is an antibiotic that is active primarily against gram-positive bacteria, such as Staphylococcus and Streptococcus species, including many that are, by means of beta-lactamase production, resistant to penicillins. Resistant strains of streptococci have been reported,[R-1] particularly in populations recently treated with erythromycin.[R-2] Cross-resistance to the other macrolide antibiotics can also occur.[R-2]

ACCEPTED
Mastitis (treatment)—Cattle: Erythromycin is indicated in the treatment of mastitis caused by susceptible Staphylococcus aureus,[R-4] Streptococcus agalactiae, Streptococcus dysgalactiae, and Streptococcus uberis.[R-3; 14] It may be most effective against Streptococcus agalactiae,[R-5; 17] and Streptococcus dysgalactiae.[R-4] Intramammary therapy alone is indicated only in the treatment of subacute or subclinical mastitis manifested by mild changes in the milk or udder. Cows with acute or peracute mastitis, which has been defined as the presence of gross changes in the milk or udder or systemic signs, should be administered other medications also, which may include systemic antibiotics and/or supportive therapy.[R-6]

REGULATORY CONSIDERATIONS
U.S. and Canada—[R-8]
Withdrawal times have been established. See the Dosage Forms section.

CHEMISTRY
Source: Produced from a strain of Streptomyces erythraeus.

Chemical group: Macrolide group of antibiotics.[R-2]

Chemical name: Erythromycin.[R-7]

Molecular formula: C37H67NO13.[R-7]

Molecular weight: 733.93.[R-7]

Description: Erythromycin USP—White or slightly yellow, crystalline powder. Is odorless or practically odorless.[R-8]

pKa: Erythromycin base—8.8.[R-9; 10]

Solubility: Erythromycin USP—Slightly soluble in water; soluble in alcohol, in chloroform, and in ether.[R-8]

PHARMACOLOGY/PHARMACOKINETICS

Mechanism of action/effect: Bacteriostatic; however, high concentrations may be bactericidal.[R-2; 11] Erythromycin is thought to enter the cell and reversibly bind to the 50S ribosomal subunit, inhibiting translocation of peptides and therefore inhibiting protein synthesis.[R-11] Erythromycin is effective only against rapidly dividing bacteria. Bacterial resistance occurs by alteration of the ribosome receptor site and/or by not allowing erythromycin to enter the cell.

Distribution: Medications infused into a teat are thought to be fairly evenly distributed in that quarter of the healthy mammary gland; however, in an udder affected by moderate to severe mastitis, the presence of edema, blockage of milk ducts, and reduced blood circulation can cause uneven distribution.[R-12]

PRECAUTIONS TO CONSIDER

PREGNANCY/REPRODUCTION
Pregnancy—Erythromycin crosses the placenta; however, there was no evidence of teratogenicity or other adverse effects when pregnant rats were fed erythromycin base.[R-13]

PATIENT MONITORING
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; * = major clinical significance):

Bacteriologic pathogens in milk
(milk samples should be tested 3 weeks after treatment is discontinued; mastitis is not considered bacteriologically cured until samples show an absence of the mastitis-causing organisms)

Clinical signs of mastitis
(although a resolution of clinical signs of mastitis is not an indication that a bacteriologic cure has been achieved, monitoring of the clinical condition of the mammary gland, teat, and milk produced can aid in diagnosis of a recurrence of mastitis or initial diagnosis of mastitis in another cow in the herd)

Somatic cell count
(somatic cell counts performed on milk to monitor the dairy herd are used primarily to maintain milk quality, but they are also used to assess the approximate overall effectiveness of mastitis control programs, which may include antibiotic treatment of cows)

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown

Cows

Allergic reaction—local or systemic

OVERDOSE
For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.
CLIENT CONSULTATION
Treatment of mastitis in dairy cattle is best achieved by a comprehensive mastitis control program in which herd management is the primary focus. The program should include good maintenance of milking equipment and constant evaluation of milking procedures and teat health as well as strategic treatment of clinical cases of mastitis.

VETERINARY DOSING INFORMATION
The choice of antibiotic for the treatment of mastitis should be based on knowledge of the identity and sensitivity of the pathogens causing mastitis in the cow and the dairy herd.

Before administration of intramammary erythromycin, the following actions should be taken:

- The udder should be milked out completely and the teats and udder washed with warm water and a disinfectant. Care should be taken to avoid washing excess dirt down from the udder onto the teat ends. The area should be dried thoroughly and each teat wiped with a separate cotton ball soaked with an antiseptic such as 70% isopropyl alcohol.
- Persons performing the treatment should wash and dry their hands before each treatment.
- The tip of the syringe should be inserted into the teat end as little as possible and the contents of the syringe should be injected into each streak canal while the teat is held firmly. The medication should then be gently massaged up the teat canal into the udder.

A teat dip is recommended on all teats following treatment.

INTRAMAMMARY DOSAGE FORMS

ERYTHROMYCIN INTRAMAMMARY INFUSION USP

Usual dose: Mastitis—

Cows, lactating: Intramammary, 300 mg administered into each affected quarter every twelve hours for three treatments. [R-14; 17]

Cows, nonlactating: Intramammary, 600 mg administered into each quarter at the time of drying-off. [R-3; 17]

Strength(s) usually available:

U.S.—[R-3; 14; 16]

Veterinary-labeled product(s):

50 mg per mL (OTC) [Gallimycin-36 (lactating cows); Gallimycin-Dry Cow (dry cows only)].

Canada—[R-16; 17]

Veterinary-labeled product(s):

50 mg per mL (OTC) [Erythro-36 (dry or lactating cows); Erythro-Dry Cow (dry cows only); Gallimycin-36 (dry or lactating cows)].

Withdrawal times:

U.S.—[R-3; 14; 16]

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows</td>
<td></td>
</tr>
<tr>
<td>Meat (day)</td>
<td>14</td>
</tr>
<tr>
<td>Milk (hours)</td>
<td>36</td>
</tr>
</tbody>
</table>

Note: Also, for nonlactating cows, treated animals should not be slaughtered for food within 96 hours post-calving. Calves born to treated cows should not be slaughtered for food until they are 10 days of age. [R-3]

Canada—[R-16; 17]

Withdrawal time

<table>
<thead>
<tr>
<th>Species</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows, lactating</td>
<td>36</td>
</tr>
</tbody>
</table>

Packaging and storage: Store at 15 to 30 °C (59 to 86 °F). Protect from freezing.

USP requirements: Preserve in single-dose disposable syringes that are well-closed containers. A solution of Erythromycin in a suitable vegetable oil vehicle. Contains one or more suitable preservatives. Label it to state that it is for veterinary use only. Contains the labeled amount, within ±10% to ±20%. Meets the requirements for Identification, Minimum fill, and Water (not more than 1.0%). [R-8]

Developed: 07/25/95
Interim revision: 04/24/96; 05/07/97; 06/16/98; 10/15/99; 9/30/02; 03/28/03

REFERENCES
3. Gallimycin-Dry Cow package insert (Bimeda—US), Rec 2/17/03.
14. Gallimycin-16 package insert (Bimeda—US), Rec 2/17/03.
NOTE: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

GENERAL CONSIDERATIONS
Florfenicol is a broad-spectrum, primarily bacteriostatic, antibiotic with a range of activity similar to that of chloramphenicol, including many gram-negative and gram-positive organisms[R-1]; however, florfenicol does not carry the risk of inducing human aplastic anemia that is associated with chloramphenicol[R-13]. Florfenicol has been demonstrated to be active in vitro and in vivo against Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, and Haemophilus somnus[R-1; 21]. In vitro studies have demonstrated florfenicol activity against Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Salmonella typhi, and Shigella dysenteriae[R-2; 15; 16] but with at least a 2- to 10-fold higher minimum inhibitory concentration than that for the Mannheimia, Pasteurella, and Haemophilus species listed above[R-15; 16]. It also has activity against some chloramphenicol-resistant strains of bacteria[R-17], possibly because it is less affected by the major enzyme produced in plasmid-mediated bacterial resistance against chloramphenicol and thiamphenicol[R-2; 26]. Although the activity of florfenicol against obligate anaerobes is not addressed in the literature, it is likely to be quite effective[R-28].

ACCEPTED
Pneumonia, bacterial (treatment and control)[3]—Cattle: Florfenicol injection is indicated in the treatment of bacterial pneumonia and associated respiratory infections (bovine respiratory disease) in cattle caused by susceptible M. haemolytica, P. multocida, and H. somnus[R-1; 11]. Florfenicol injection is also indicated in the control of bacterial pneumonia and associated respiratory disease in cattle at high risk of developing bovine respiratory disease associated with susceptible M. haemolytica, P. multocida, and H. somnus[R-1; 12; 32].

Pododermatitis (treatment)—Cattle: Florfenicol injection is indicated in the treatment of infectious pododermatitis (interdigital phlegmon) associated with susceptible Fusobacterium necrophorum and Bacteroides melaninogenum[R-1; 13; 10].

[Furunculosis (treatment)]—Salmon: Florfenicol premix is indicated in the treatment of furunculosis caused by susceptible strains of Aeromonas salmonicida in salmon[R-11].

[Keratoconjunctivitis (treatment)]—Cattle: Florfenicol injection is indicated in Canadian product labeling in the treatment of infectious bovine keratoconjunctivitis caused by Moraxella bovis[R-2; 33; 14].

REGULATORY CONSIDERATIONS
U.S.—
Withdrawal times have been established for florfenicol in cattle; however, it is not labeled for use in lactating dairy cattle or in veal calves[R-1] (see the Dosage Forms section).

Canada—
Withdrawal times have been established for florfenicol in cattle and salmon; however, it is not labeled for use in lactating dairy cattle[R-1] (see the Dosage Forms section).

CHEMISTRY
Source: A fluorinated derivative of thiamphenicol[R-12].

Chemical name: Acetamide, 2,2-dichloro-N-[1-(flouromethyl)-2-hydroxy-2-[4-(methylsulfonyl)phenyl]ethyl]-[1R,4R,5S]-

Molecular formula: C12H14Cl2FNO4S

Molecular weight: 358.21

Solubility: Soluble in water[R-12; 13]. Lipid soluble[R-13].

PHARMACOLOGY/PHARMACOKINETICS
Mechanism of action/effect: Florfenicol is a bacteriostatic antibiotic that inhibits protein synthesis by binding to ribosomal subunits of susceptible bacteria, leading to the inhibition of peptidyl transferase[R-1; 11; 26] and thereby preventing the transfer of amino acids to growing peptide chains and subsequent protein formation. The bacterial receptor that is the site of action for florfenicol is considered to be the same as that for chloramphenicol and thiamphenicol[R-13; 26]. In the treatment of bovine respiratory disease, florfenicol may be considered bactericidal against some Mannheimia (Pasteurella) haemolytica and Pasteurella multocida when it is administered to achieve minimum inhibitory concentrations (MICs)[R-14]; the minimum bactericidal concentrations (MBCs) are very close to the MICs.

Florfenicol has a fluorine atom instead of the hydroxyl group located at C-3 in the structure of chloramphenicol and thiamphenicol[R-13]. This may allow florfenicol to be less susceptible to deactivation by bacteria with plasmid-transmissible resistance that involves acetylation of the C-3 hydroxyl group in chloramphenicol and thiamphenicol, and prevents their interaction with bacterial ribosomes[R-13; 26].

Other actions/effects: Florfenicol, like thiamphenicol, lacks the nitro group located on the chloramphenicol aromatic ring that has been associated with chloramphenicol-induced, non–dose-related, irreversible aplastic anemia in people[R-13; 24; 25]. However, chloramphenicol and thiamphenicol also cause a dose-dependent, reversible bone marrow suppression in some animals and people[R-13] due to mitochondrial injury[R-24]. It is theoretically possible that florfenicol could cause some dose-dependent, reversible bone marrow suppression, but it has not been clinically reported[R-13].

Absorption: Bioavailability—
Intramuscular administration:
Calfes, 3 to 6 months of age—78.5% (range 59.3 to 106%), with a dose of 20 mg per kg of body weight (mg/kg)[R-1; 2; 8].

Cattle, lactating—38 ± 14%, with a dose of 20 mg/kg[R-9].

1Not included in Canadian product labeling or product not commercially available in Canada.
**Horses**—81%, with a dose of 22 mg/kg\[^{[R-19]}\].

**Oral administration:**

Calves—2 to 5 weeks of age—89%, at a dose of either 11 or 22 mg/kg; however, the absorption was widely variable\[^{[R-6; 7]}\]. Oral absorption may decrease when florfenicol is administered with milk replacers\[^{[R-6; 7]}\]; one study reported bioavailability that ranged from 44 to 86% among calves when florfenicol was administered 5 minutes after feeding\[^{[R-7]}\].

**Horses**—83.3%, with a dose of 22 mg/kg\[^{[R-19]}\].

**Salmon**, Atlantic—96.5%, with a dose of 10 mg/kg when water temperature is 10.8 ± 1.5 °C\[^{[R-22]}\].

Note: After intramammary administration of a 20 mg/kg dose to lactating dairy cows, the systemic bioavailability was found to be 54 ± 18%\[^{[R-9]}\].

**Distribution:**

**Cattle**—2 to 5 weeks of age—After multiple oral dosing (11 mg/kg every twelve hours for seven doses), florfenicol was well distributed into many tissues, reaching concentrations of 4 to 8 mcg per gram (mcg/gram) in lungs, heart, pancreas, skeletal muscle, spleen, and synovia\[^{[R-6]}\]. These concentrations were at least as high as serum concentrations\[^{[R-6]}\]. Relatively high concentrations were found in bile, kidney, small intestine, and urine\[^{[R-6]}\]. Concentrations in the brain (1 to 2 mcg/gram), cerebrospinal fluid (2 to 3 mcg/mL), and aqueous humor (2 to 3 mcg/mL) have been found to be one quarter to one half the serum concentration in healthy calves\[^{[R-6]}\].

**Salmon**, Atlantic—Florfenicol is distributed to all organs and tissues with a dose of 10 mg/kg when the water temperature is 8.5 to 11.5 °C\[^{[R-23]}\]. Concentrations in muscle and blood are similar to serum concentrations, while fat and the central nervous system (CNS) have lower concentrations. Only 25% of serum drug and metabolite concentrations are found in the brain\[^{[R-23]}\].

**Volume of distribution (V\(\text{ld}\))**—Intravenous administration:

Calves—2 weeks to 6 months of age—

- **Area**: 0.88 liter per kg (L/kg)\[^{[R-22]}\]; 0.91 L/kg\[^{[R-6]}\].
- **Steady state**: 0.77 L/kg\[^{[R-1; 2; 8]}\], 0.87 L/kg\[^{[R-6]}\].

**Cattle**—

- **Lactating**: Steady state—0.35 L/kg\[^{[R-9]}\].
- **Nonlactating**:
  - Area—0.61 L/kg (range, 0.57 to 0.68 L/kg)\[^{[R-5]}\].
  - Steady state—0.62 L/kg (range, 0.57 to 0.68 L/kg)\[^{[R-5]}\].

Note: Although the data above imply that lactation causes a decrease in the volume of distribution of florfenicol, other data from these studies, including half-life of elimination and clearance, correlate well between the two trials, one conducted in lactating and one in nonlactating cattle. The apparent difference here between lactating and nonlactating cattle may be due to calculation methods or dosing\[^{[R-27]}\].

**Goats**, lactating—Steady state: 0.98 ± 0.09 L/kg\[^{[R-18]}\].

**Horses**—Steady state: 0.72 ± 0.17 L/kg\[^{[R-19]}\].

**Salmon**, Atlantic—Steady state: 1.12 L/kg at a water temperature of 10.8 ± 1.5 °C\[^{[R-22]}\].

**Protein binding:**

Calves—3 to 6 months of age—

- **Low** (12.7%), with serum concentration of 0.5 mcg/mL\[^{[R-2]}\].
- **Low** (13.2%), with serum concentration of 3 mcg/mL\[^{[R-1; 2]}\].
- **Low** (18.3%), with serum concentration of 16 mcg/mL\[^{[R-1; 2]}\].

**Cattle**—Considered independent of drug concentration:

Low (17.5%), with serum concentration of 5 mcg/mL\[^{[R-5]}\].

Low (18.6%), with serum concentration of 50 mcg/mL\[^{[R-5]}\].

**Biotransformation:**

**Cattle**—Approximately 64% of a 20 mg/kg dose of intramuscular florfenicol administered two times, 48 hours apart, is excreted as parent drug in the urine\[^{[R-13]}\]. Urinary metabolites include florfenicol amine, florfenicol alcohol, florfenicol oxamic acid, and monochloroflorfenico\(^{[R-13]}\). Florfenicol and its metabolites, such as monochloroflorfenicol and florfenicol oxamic acid, also are eliminated in the feces\[^{[R-13]}\]. Florfenicol amine is the longest-lived major metabolite in the liver, and, therefore, it was used as the marker residue for withdrawal calculations\[^{[R-13]}\].

**Salmon** Atlantic—Florfenicol is rapidly metabolized at water temperatures of 8.5 to 11.5 °C and the major metabolite is florfenicol amine\[^{[R-23]}\].

**Half-life:**

**Distribution**—Intravenous administration: Calves, less than 8 weeks of age—0.13 hour (range, 0.075 to 0.27 hour)\[^{[R-6; 7]}\]; 0.098 hour (range, 0.081 to 0.17 hour)\[^{[R-7]}\].

**Elimination**—

Intravenous administration:

Calves, less than 8 weeks of age—2.86 hours (range, 2.3 to 3.39 hours)\[^{[R-7]}\]; 3.71 hours (range, 3.5 to 4.11 hours)\[^{[R-6]}\].

Calves, 3 to 6 months of age—2.6 hours (range, 2.4 to 3 hours)\[^{[R-2; 8]}\].

**Cows**—

- Lactating: 2.9 hours\[^{[R-9]}\].
- Nonlactating: 3.2 hours\[^{[R-5]}\].

**Goats**, lactating—2.3 ± 0.2 hours\[^{[R-18]}\].

**Horses**—1.8 ± 0.9 hours\[^{[R-19]}\].

**Salmon**, Atlantic—12.2 hours at a water temperature of 10.8 ± 1.5 °C\[^{[R-22]}\].

**Intramuscular administration** (terminal half-life): Calves, 3 to 6 months of age—18.3 hours (range, 8.3 to 44 hours)\[^{[R-1; 2]}\].

**Concentrations:**

**Peak serum concentration**—

**Intramuscular administration:**

Calves, 3 to 6 months of age—3 mcg per mL (range, 1.43 to 5.6 mcg/mL), with a dose of 20 mg/kg\[^{[R-1; 2; 8]}\].

**Cows**, lactating—2.3 mcg/mL, with a dose of 20 mg/kg\[^{[R-9]}\].

**Horses**—4 ± 1.2 mcg/mL, with a dose of 22 mg/kg\[^{[R-19]}\].

**Oral administration:**

**Calves** less than 8 weeks of age—11.32 ± 4.04 mcg/mL, with a dose of 22 mg/kg\[^{[R-7]}\].

**Horses**—13.8 ± 4.8 mcg/mL, with a dose of 22 mg/kg\[^{[R-19]}\].

**Salmon**, Atlantic—4 mcg/mL, with a dose of 20 mg/kg\[^{[R-19]}\].

**Horses**—1.3 ± 0.5 hours, with a dose of 22 mg/kg\[^{[R-19]}\].
Oral administration:

Calves, less than 8 weeks of age—2.5 ± 0.72 hours, with a dose of 22 mg/kg.

Horses—1.1 ± 0.5 hours, with a dose of 22 mg/kg.

Salmon, Atlantic—10.3 hours, with a dose of 10 mg/kg when water temperature is 10.8 ± 1.5 °C.

Other peak concentrations—In milk:

Intramuscular administration—

Cows, lactating: 5.4 mcg/mL at 3 hours, with a 20 mg/kg dose.

Goats, lactating: 13.2 ± 1.9 mcg/mL at 1 hour, with a 25 mg/kg dose.

Duration of action:

Calves, 3 to 6 months of age—The serum concentration of florfenicol was maintained above the MIC of V. anguillarum, A. salmonicida, and V. salmonicida for 36 to 40 hours after a single oral florfenicol dose of 10 mg/kg in water temperatures of 10.8 ± 1.5 °C.

Elimination:

Calves, less than 8 weeks of age—Approximately 50% of a 22 mg/kg intravenous dose is eliminated unchanged in the urine within 30 hours.

Cattle—Approximately 64% of a 20 mg/kg intramuscular dose administered two times, 48 hours apart, is excreted as parent drug in the urine.

Horses—Approximately 13% of a 22 mg/kg intravenous dose, 7% of the same dose given intramuscularly, and 6% when given orally, is excreted unchanged in the urine in the first 30 hours.

Rats—Approximately 60 to 70% of a 20 mg/kg oral dose administered once a day for 7 days is eliminated in the urine. Approximately 20 to 30% is eliminated in the feces in the first 24 hours after a 20 mg/kg oral dose.

Total clearance—Intravenous administration:

Calves—

Less than 8 weeks of age: 2.9 mL per minute per kg (range, 2.44 to 4 mL/min/kg).

3 to 6 months of age: 3.75 mL/min/kg (range, 3.17 to 4.31 mL/min/kg).

Cows—

Lactating: 2.7 ± 0.6 mL/min/kg.

Nonlactating: 2.45 mL/min/kg (range, 2.25 to 2.67 mL/min/kg).

Goats, lactating: 8.1 ± 2.6 mL/min/kg.

Horses: 6.7 ± 1.7 mL/min/kg.

Salmon, Atlantic—1.4 mL/min/kg when water temperature is 10.8 ± 1.5 °C.

PRECAUTIONS TO CONSIDER

PREGNANCY/REPRODUCTION

The effects of florfenicol on reproductive performance and pregnancy have not been determined.

Administration to breeding cattle is not recommended by product labeling.

LACTATION

The effect of florfenicol on lactation has not been determined.

Goats: Florfenicol concentrations in milk equal serum concentrations when serum concentrations are nearly constant.

MEDICAL CONSIDERATIONS/CONTRAINDICATIONS

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive:

« Previous allergy or toxic reaction to florfenicol

SIDE/ADVERSE EFFECTS

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION

Note: There is no documentation of dose-dependent, reversible bone-marrow suppression caused by florfenicol use in animals; however, the protection against human aplastic anemia, due to the difference in structure of florfenicol from chloramphenicol, does not necessarily protect against suppression of mitochondrial protein synthesis in bone marrow and subsequent reversible anemia.

This phenomenon is not considered a side/adverse effect with normal clinical use, but an awareness of this possibility may be useful if long-term therapy with this medication is considered.

Incidence unknown

Horses, ponies

Diarrhea, mild—in one study, occurred in all three horses and three ponies administered a single dose of 22 mg per kg of body weight by either the oral or parenteral route.

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOthersome

Incidence unknown

Cattle

Decreased food consumption—usually transient; decreased water consumption—usually transient; diarrhea—usually transient; local tissue reactions—more severe if administered at injection sites other than the neck.

Note: In a controlled study over 43 days, florfenicol administration had no long-term effect on body weight, rate of weight gain, or feed consumption, although a transient decrease in food and water consumption occurred at the start of therapy.

OVERDOSE

For more information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.
CLINICAL EFFECTS OF OVERDOSE
The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Acute—
Calves, with intramuscular administration of 200 mg per kg of body weight (mg/kg) repeated in forty-eight hours (10 times the label dose) Anorexia, marked; decreased body weight; decreased rumen activity; decreased water consumption; ketosis, slight—secondary to anorexia; serum enzymes, including alanine aminotransferase [SGPT], aminoacyltransferase [GGT], aspartate aminotransferase [SGOT], and lactase dehydrogenase [LDH], mildly increased; soft feces.

Chronic—
Dogs, 4- to 6-months old, with oral administration of 12 mg/kg a day for thirteen weeks.

Hepatotoxicity
Note: Oral dosing of 100 mg/kg for thirteen weeks resulted in CNS vacuolation, hematopoietic toxicity, renal tubule dilation, and testicular atrophy.

TREATMENT OF OVERDOSE
There is no specific treatment for florfenicol overdose. Therapy should be supportive.

VETERINARY DOSING INFORMATION
Minimum inhibitory concentrations (MICs) of florfenicol were determined for pathogens involved in natural bovine respiratory complex in the U.S., Canada, and Europe between 1990 and 1993:

Note: MIC can vary according to pathogen strain; therefore, cattle in different geographic locations may harbor organisms with different MICs.

Safety considerations—Precautions for personnel administering florfenicol injection include the recommendation to avoid direct contact with eyes, skin, and clothing. In case of accidental eye exposure, flush with water for 15 minutes; for skin exposure, wash with soap and water. Remove exposed clothing and consult a physician if irritation persists. Accidental injection may cause local irritation and a physician should be consulted immediately.

FOR TREATMENT OF ADVERSE EFFECTS
Recommended treatment consists of the following:

For anaphylaxis
- Parenteral epinephrine and cardiovascular support.
- Oxygen administration and respiratory support.

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

FLORFENICOL FOR MEDICATED FEED
Usual dose: [Furunculosis]—Salmon: Oral, 10 mg per kg of body weight a day, administered in the only ration, according to manufacturer labeling.

Strength(s) usually available:
U.S.—Veterinary-labeled product(s):
Not commercially available.
Canada—Veterinary-labeled product(s):
500 grams per kg of premix (Rx) [Aquaflor].

Withdrawal times:
Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon</td>
<td>12 (days)</td>
</tr>
</tbody>
</table>

Note: Not labeled for use in fish maintained at water temperatures less than 5 °C.

Packaging and storage: Store between 2 and 30 °C (36 and 86 °F), unless otherwise specified by the manufacturer. Keep separate from other feeds. Store in a dry place.

Stability: Premix should be used within 12 months of opening pouch. Medicated feed should be used within 6 months of the manufacture date.

Caution: Product labeling recommends that handlers avoid inhalation of dust and contact with skin and eyes. Protective clothing should be worn when handling the medication and hands should be washed after administration.

USP requirements: Not in USP.

PARENTERAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

FLORFENICOL INJECTION
Usual dose:
- Pneumonia (bovine respiratory disease) (treatment); or Pododermatitis—Cattle:
  - Intramuscular, 20 mg per kg of body weight to be repeated in forty-eight hours.
  - Subcutaneous, 40 mg per kg of body weight as a single dose.
Note: Canadian product labeling lists the same dose as above, a single subcutaneous dose of 40 mg per kg of body weight or two intramuscular doses of 20 mg per kg of body weight, administered forty-eight hours apart, in the treatment of [keratoconjunctivitis] in cattle^{[R-1]}. pneumonia (bovine respiratory disease) (control)\textsuperscript{1}—Cattle; Subcutaneous, 40 mg per kg of body weight as a single dose\textsuperscript{[R-1; 32]}

Note: No more than 10 mL should be injected at each site\textsuperscript{[R-1]}. Injections should be given in the neck to avoid local reaction and trim loss of edible tissues at slaughter\textsuperscript{[R-1]}. According to the product labeling, if clinical improvement is not noted within twenty-four hours, the diagnosis should be reevaluated\textsuperscript{[R-1]}. Strength(s) usually available\textsuperscript{[R-15]};

U.S.—

Veterinary-labeled product(s): 300 mg per mL (Rx) [\textit{Nuflor}\textsuperscript{[R-11]}].

Canada—

Veterinary-labeled product(s): 300 mg per mL (Rx) [\textit{Nuflor}\textsuperscript{[R-11]}].

Withdrawal times:

U.S.\textsuperscript{[R-11]}—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat) (days)</th>
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<tr>
<td>Cattle</td>
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<tr>
<td>Intramuscular injection</td>
<td>28</td>
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<tr>
<td>Subcutaneous injection</td>
<td>38</td>
</tr>
</tbody>
</table>

Canada\textsuperset{[R-11]}—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat) (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td></td>
</tr>
<tr>
<td>Intramuscular injection</td>
<td>36</td>
</tr>
<tr>
<td>Subcutaneous injection</td>
<td>55</td>
</tr>
</tbody>
</table>

Note: This product is not labeled for use in dairy cattle 20 months of age or older, veal calves, calves under 1 month of age, or calves being fed an all-milk diet\textsuperscript{[R-11]} as withdrawal times have not been studied. If florfenicol is injected at sites other than the neck, local reaction may result in trim loss of edible tissue at slaughter\textsuperscript{[R-1]}. Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Protect from freezing.

Caution: Florfenicol injection can be irritating to eyes and skin; therefore, avoid direct contact with skin, eyes, and clothes\textsuperscript{[R-11]}. Accidental injection may cause local irritation\textsuperscript{[R-11]}. Additional information: The light yellow to straw color of the solution does not affect potency\textsuperscript{[R-11]}. USP requirements: Not in USP\textsuperscript{[R-11]}. \textsuperscript{1}Not included in Canadian product labeling or product not commercially available in Canada.
27. Panel comment, Rec 8/25/97.
29. Manufacturer comment, Rec 12/2/97.
FLUOROQUINOLONES Veterinary—Systemic

This monograph includes information on the following: Ciprofloxacin, Difloxacin, Enrofloxacin, Marbofloxacin, and Orbifloxacin. Some commonly used brand names for veterinary-labeled products are:

- Baytril 3.2% Concentrate [Enrofloxacin]
- Baytril Injectable Solution [Enrofloxacin]
- Baytril 100 Injectable Solution 2.27% [Enrofloxacin]
- Baytril Injectable Solution [Difloxacin]
- Orbx Tablets [Orbifloxacin]
- Zeniquin Tablets [Marbofloxacin]

Some commonly used brand names for human-labeled products are: Cipro [Ciprofloxacin] and Cipro I.V. [Ciprofloxacin].

Note: For a listing of dosage forms and brand names by country and availability, see the Dosage Forms section(s).

CATEGORY:
Antibacterial (systemic).

INDICATIONS
Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

GENERAL CONSIDERATIONS
The fluoroquinolone antimicrobials are rapidly bactericidal against a variety of clinically important organisms, are well tolerated by animals, and can be administered by a variety of routes. The members of this group that are currently labeled for use in animals have the same quinolone structure, each with modifications that account for pharmacokinetic variations in the medications but do not significantly change the antibacterial spectrum of activity.

Fluoroquinolones exhibit good activity against most gram-negative bacteria, including Escherichia coli, Enterobacter species, Klebsiella species, Pasteurella species, Proteus species, and Salmonella species. Pseudomonas aeruginosa is variably susceptible, usually having a higher minimum inhibitory concentration (MIC) than other susceptible organisms.

Some gram-positive bacteria are susceptible to fluoroquinolones. Staphylococcus aureus and Staphylococcus intermedius are usually susceptible. However, the MIC values for staphylococci typically are higher than for gram-negative bacteria and staphylococcal resistance to fluoroquinolones has been a problem in human patients.

Chlamydia, mycobacteria, mycoplasma, and ureaplasma can also be moderately to very susceptible to fluoroquinolones.

Local factors that affect activity are cations at the site of infection and low pH: however, fluoroquinolones are active in abscesses in spite of often unfavorable environmental conditions.

Bacterial resistance to fluoroquinolones most commonly occurs by alteration of the target, DNA-gyrase (topoisomerase II), via mutation (gyr-A). Less common, but perhaps more importantly for gram-positive bacteria, mutation occurs at the topoisomerase-IV target (parC). Other mechanisms of resistance occur when bacteria decrease the ability of the drug to enter the cell or increase active transport out of the cell. Resistance is usually chromosomally developed and, therefore, remains after antimicrobial therapy ends. While there is evidence for plasmid-mediated resistance, its clinical significance in veterinary medicine has not been shown. Cross-resistance of enrofloxacin with other fluoroquinolones can occur. Changes in levels of resistance to fluoroquinolones over time by Campylobacter and Salmonella species are being monitored because of their possible impact on human health.

ACCEPTED
Colibacillosis (treatment)—Chickens and turkeys: Enrofloxacin oral solution is indicated in the control of mortality associated with Escherichia coli infection in chickens and turkeys.

Fowl cholera (treatment)—Turkeys: Enrofloxacin oral solution is indicated in the control of mortality associated with Pasteurella multocida infection in turkeys.

Infections, bacterial (treatment), including:
- Cystitis, urinary, bacterial (treatment):
- Respiratory infections, bacterial (treatment): or
- Skin and soft tissue infections (treatment):

Cats: Enrofloxacin [injection] and tablets are indicated in the treatment of susceptible bacterial infections in cats. Clinical efficacy has been established specifically in the treatment of skin and soft tissue infections.

Dogs: Difloxacin tablets, enrofloxacin injection and tablets are indicated in the treatment of susceptible bacterial infections in dogs. Clinical efficacy has also been established for enrofloxacin injection in the treatment of respiratory tract infections in dogs.

There is evidence to suggest that enrofloxacin is as effective as chloramphenicol or tetracycline in the treatment of Rocky Mountain spotted fever in dogs.

Pneumonia (treatment)—Cattle: Enrofloxacin injection is indicated in the treatment of bovine respiratory disease caused by susceptible organisms, including Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, and Haemophilus somnus.

ACCEPTANCE NOT ESTABLISHED
Infections, bacterial (treatment)—

- [Bustards, camels, ducks, emus, llamas, oryx, red pacu, African grey parrots, and pythons]: In the U.S., for use only in animals not to be used for food production—Although the safety and efficacy of enrofloxacin have not been established, dose recommendations for use in the treatment of susceptible bacterial infections have been made, based on pharmacokinetic data, for bustards, camels, ducks, emus, llamas, oryx, red pacu.
African grey parrots\textsuperscript{[R-19; 40]}, and pythons\textsuperscript{[R-48]}. Further clinical studies are necessary. See also the Regulatory Considerations section.

[Horses]: For use only in animals not to be used for food production—Although the safety and efficacy of enrofloxacin and orbifloxacin in the treatment of susceptible bacterial infections in horses have not been established, pharmacokinetic evidence and case reports are available to suggest that they may be safe and effective\textsuperscript{[R-25–27; 79–80; 116]}. Due to reports of articular cartilage damage in foals from administration of enrofloxacin, neither enrofloxacin nor orbifloxacin should be administered to horses less than 3 years of age, except as a last resort for severe infections not treatable with other medications\textsuperscript{[R-25; 26; 85]}. Although there have been reports of unpublished studies showing articular damage from enrofloxacin administration to adult horses, subsequent studies have shown no effect on cartilage in adults when used continuously for up to 21 days\textsuperscript{[R-86]}.

[Pigs, potbellied and miniature]: In the U.S., for use only in animals not to be used in food production—Although the safety and efficacy of enrofloxacin in the treatment of susceptible bacterial infections in pigs have not been established, there is some pharmacokinetic evidence to suggest that this therapy may be effective\textsuperscript{[R-29]}. See also the Regulatory Considerations section.

[Sheep, pet and research]: In the U.S., for use only in animals not to be used in food production—Although the safety and efficacy of enrofloxacin in the treatment of susceptible bacterial infections in sheep have not been established, there is some pharmacokinetic evidence to suggest that this therapy may be effective\textsuperscript{[R-28]}. See also the Regulatory Considerations section.

[Bartonella infections (treatment)]\textsuperscript{[1]}; or [Herborbartonella felis infections (treatment)]\textsuperscript{[1]}—Cats: Although the safety and efficacy have not been established, enrofloxacin has been used in an attempt to eradicate Bartonella bacteremia in cats\textsuperscript{[R-72; 73]}. Controlled therapeutic trials investigating the efficacy of enrofloxacin in clearing Bartonella from cats show a positive response in some animals, but tests used to document that an infection has been cleared remain unreliable, making the results difficult to interpret\textsuperscript{[R-72]}. It should not be assumed that a Bartonella infection is cleared by a course of enrofloxacin. Long-term monitoring is necessary\textsuperscript{[R-72; 73]}. Although the safety has not been clearly established, a controlled, randomized study demonstrated the efficacy of enrofloxacin in the treatment of Herborbartonella felis infection, by showing it more quickly resolved clinical signs, raised hematocrit, and decreased organism counts than in control animals. In this study, some cats treated with a high dose of enrofloxacin or with doxycycline were apparently cleared of the organism\textsuperscript{[R-83; 148]}.

[Brucellosis (treatment)]\textsuperscript{[1]}—Dogs: Historically, the treatment of dogs infected with Brucella canis has been controversial. Due to the zoonotic potential and the difficulty in clearing the infection, some have advocated euthanasia of infected animals. Studies using a combination of tetracycline and dihydrostreptomycin did demonstrate that infected animals, following neutering, could be cured of the infection\textsuperscript{[R-119]}. However, dihydrostreptomycin is no longer available in the US. The Centers for Disease Control recommend a combination of doxycycline and rifampin for the treatment of brucellosis in human patients\textsuperscript{[R-140]}. In a clinical trial, rifampin plus ciprofloxacin, a metabolite of enrofloxacin, was shown to be as effective as the standard rifampin and doxycycline regimen in the treatment of human brucellosis\textsuperscript{[R-117]}. It is not known whether the fluoroquinolones have any efficacy in the treatment of canine brucellosis.

[Chlamydial infections (treatment)]\textsuperscript{[1]}—Cats: There are no studies to document the effectiveness of the veterinary fluoroquinolones, diloxacin, enrofloxacin, marbofloxacin, and orbifloxacin, in the treatment of chlamydial infections in cats. Clinical trials of related human-labeled fluoroquinolones in the treatment of genital, respiratory, or ocular chlamydial infections in human patients have shown efficacy; however, concern exists that the organisms are not eradicated and recrudescence is common.

[Endophthalmitis, bacterial (treatment)]\textsuperscript{[1]}—Cats and dogs: There are no specific studies to document the effectiveness of the veterinary fluoroquinolones, diloxacin, enrofloxacin, marbofloxacin and orbifloxacin, in the treatment of bacterial endophthalmitis due to susceptible organisms. However, these bactericidal drugs have been shown to produce aqueous and vitreous humor concentrations within the therapeutic range for many pathogens\textsuperscript{[R-1; 102]}. Also, related human-labeled fluoroquinolones, including ciprofloxacin (a metabolite of enrofloxacin), have been reported as efficacious in several small studies and case reports in human patients\textsuperscript{[R-120–125]}.

[Meningitis, bacterial (treatment)]\textsuperscript{[1]}—Cats and dogs: There are no studies to document the effectiveness of the veterinary fluoroquinolones, diloxacin, enrofloxacin, marbofloxacin, and orbifloxacin, in the treatment of bacterial meningitis due to susceptible organisms. However, these bactericidal drugs have been shown to obtain central nervous system concentrations within the therapeutic range for many pathogens\textsuperscript{[R-1; 102]}. Also, related human-labeled fluoroquinolones, including ciprofloxacin (a metabolite of enrofloxacin), have been reported as efficacious in several small studies and case reports in human patients\textsuperscript{[R-120–125]}. Although the potential for fluoroquinolones to induce seizures has been suggested as a reason to avoid these drugs in the treatment of meningitis, the above mentioned human studies, as well as disease models in animals, have failed to indicate an increased incidence of seizures in fluoroquinolone-treated subjects. Careful monitoring for seizures is nevertheless advised if fluoroquinolones are used in such infections.

[Mycobacterial infections (treatment)]\textsuperscript{[1]}—Cats: Although the safety and efficacy have not been established, enrofloxacin and ciprofloxacin have been used in the treatment of mycobacterial infections in cats, based on case reports of successful treatment of cutaneous lesions of opportunistic mycobacteria\textsuperscript{[R-75; 76; 142]}. There is some evidence to suggest that fluoroquinolones are effective in the treatment of tubercular mycobacteriosis, an often serious but also often asymptomatic or insidious disease in cats. Cats are also prone to infection with Mycobacterium lepraemurium, which is a nontubercular form of mycobacteria. Safety and efficacy of fluoroquinolones have not yet been proven in the treatment of M. lepraemurium, but successful treatment of the cutaneous form of mycobacterial infection with enrofloxacin indicates possible efficacy in the treatment of nontubercular forms\textsuperscript{[R-142]}.

[Mycoplasmal infections (treatment)]\textsuperscript{[1]}—Although the efficacy has not been established, fluoroquinolones have been used to treat infections caused by Mycoplasma species in animals. Activity of these antibiotics against Mycoplasma can be variable but enrofloxacin and danofloxacin have been shown to be consistently more active in vitro (minimum inhibitory concentrations [MIC] of 0.05 to 1.0 mcg/mL) against veterinary isolates than flumequine\textsuperscript{[R-143]}.
REGULATORY CONSIDERATIONS

U.S.— Federal law prohibits the extralabel use of fluoroquinolones in food-producing animals (21 CFR 530.41). The prohibition is based on a finding by the Food and Drug Administration that the extralabel use of these antibiotics in food-producing animals presents a risk to the public health because such use could increase the level of drug-resistant zoonotic pathogens at the time of slaughterRI.106]. Some researchers are concerned that such use can lead to the transfer of pathogens resistant to fluoroquinolones from animals to human beings.

Difloxacin, enrofloxacin, marbofloxacin, and orbifloxacin are restricted to use by or on the order of a licensed veterinarianRI; 2; 94; 96–98]. Ciprofloxacin is not labeled for veterinary use.

Canada— Difloxacin, enrofloxacin, marbofloxacin, and orbifloxacin are restricted to use by or on the order of a licensed veterinarian. They are not labeled for use in food-producing animals. Ciprofloxacin is not labeled for veterinary use.

CHEMISTRY

Chemical group: Quinoline carboxylic acid derivativesRI.1].

Chemical name:

Ciprofloxacin—3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)RI.7].

Difloxacin hydrochloride—3-Quinolinecarboxylic acid, 6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo, mono hydrochlorideRI.7].

Enrofloxacin—3-Quinolinecarboxylic acid, 1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxoRI.7].

Marbofloxacin—9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[3,2,1-ij][4,1,2]benzoxadiazine-6-carboxylic acidRI.7].

Orbifloxacin—1-Cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-5,6,8-tri fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acidRI.7].

Molecular formula:

Ciprofloxacin—C19H22FN3O3 [R-7]

Difloxacin hydrochloride—C21H19F2N3O3 [R-7]

Enrofloxacin—C19H21FN3O3 [R-7]

Marbofloxacin—C17H19FN4O4 [R-7; 97]

Orbifloxacin—C19H20F3N3O3 [R-7; 98].

Molecular weight:

Ciprofloxacin—331.34RI.78]

Difloxacin hydrochloride—435.85RI.7]

Enrofloxacin—359.39RI.7]

Marbofloxacin—362.36RI.7; 97]

Orbifloxacin—395.38RI.7; 98].

Description:

Ciprofloxacin Hydrochloride USP—Faintly yellowish to light yellow crystalsRI.105]).

Difloxacin hydrochloride—White to light yellow powder.

Enrofloxacin—Pale yellow crystals with a melting point of 219 to 221 °C.

Orbifloxacin—White to pale yellow crystalline powderRI.82].

pKa:

Ciprofloxacin—Carboxylic acid group, 6.1; tertiary amine, 7.8RI.95].

Difloxacin—Carboxylic acid group, 4.33; methyl substituted nitrogen group, 9.05RI.96].

Enrofloxacin—Carboxylic acid group, 6.0; tertiary amine, 8.8RI.95].

Orbifloxacin—5.95 and 9.01RI.98].

Solubility:

Ciprofloxacin hydrochloride—Sparingly soluble in water; slightly soluble in acetic acid and in methanol; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, in acetonitrile, in ethyl acetate, in hexane, and in methylene chlorideRI.105].

Difloxacin—Poorly water soluble at neutral pH, more soluble under acidic conditions, and highly water soluble under basic conditionsRI.96].

Enrofloxacin—Slightly soluble in water at pH 7.

Marbofloxacin—Soluble in water; less soluble under alkaline conditionsRI.97].

Orbifloxacin—Slightly soluble in water; more soluble in both acidic and alkaline conditionsRI.98].

PHARMACOLOGY/PHARMACOKINETICS

Note: See also Table 1 and Table 2 at the end of this monograph.

Mechanism of action/effect: BactericidalRI.2; 95–100]. The fluoroquinolones inhibit bacterial DNA gyrase or topoisomerase IV (a type II topoisomerase), thereby preventing DNA supercoiling and replicationRI.1; 2; 86]. Cell respiration and division end, and other processes are interrupted, including membrane integrityRI.11]. Mammalian cell topoisomerase II is not affected by fluoroquinolones until drug concentrations are at least 100 times higher than concentrations recommended to inhibit the bacteriaRI.95].

Fluoroquinolones enter cells via porins and accumulate rapidly in susceptible bacteriaRI.99]. Some bacteria are able to pump the antibiotic agent back out of the cell by an energy-dependent efflux transport systemRI.99].
Absorption: Oral absorption of fluoroquinolones is high for most animals [R-1; 10; 97; 98]. It is not affected by administration with food, although absorption may be delayed [R-99]. Divalent and trivalent cations can affect absorption (see the Drug Interactions section in this monograph) [R-96]. In cats, dogs, and pigs, oral absorption of fluoroquinolones approaches 100%, but in ruminants, it is generally less [R-95]. The horse may be unique regarding oral absorption patterns in that while enrofloxacin is well absorbed, ciprofloxacin is poorly absorbed [R-144]. Other fluoroquinolones have not been studied as to oral bioavailability in horses.

Absorption from parenteral administration of fluoroquinolones is rapid and often nearly complete [R-9; 11; 22; 28; 29; 32; 41; 45]. In some animals, there is delayed absorption from intramuscular or subcutaneous administration, producing longer half-lives from these routes compared to intravenous absorption [R-95].

Enrofloxacin—
Oral—Rapidly absorbed in monogastric species and pruruminant calves [R-1; 10]. Absorption in adult ruminants is variable and has ranged from 10 to 50% [R-86].

Distribution: Fluoroquinolones achieve concentrations that are at least as high as plasma in a wide range of tissues, with the exception of the central nervous system and the eye [R-1; 26; 95–98]. This is true in many species, including cats, cattle, chickens, dogs, horses, and rabbits [R-1; 5; 19; 18; 26; 31; 12]. Differences in volume of distribution among the fluoroquinolones however, account for a range of maximum plasma concentrations among the drugs. Drugs with the lowest volume of distribution are reflected in the dose administered; to achieve the same peak serum concentration, drugs with a high volume of distribution require a higher dose [R-95].

Fluoroquinolones are rapidly accumulated in macrophages and neutrophils. Unlike other antibiotics that concentrate in subcellular sites within phagocytic cells, the quinolones are distributed into the cytosol where they can reach intracellular pathogens [R-20]. This concentration in leukocytes may explain the higher fluoroquinolone concentrations in infected tissue compared to healthy tissue [R-95].

Because of renal elimination, urine concentration of fluoroquinolones occurs in many species. Enrofloxacin concentration in canine prostate tissue matches that in the serum and concentration in urine reaches about 100 times that in the serum [R-18; 19]. The orbifloxacin concentration in canine prostate tissue exceeds that in serum and concentration in urine reaches about 50 times that in serum [R-82]. Even ciprofloxacin, for which less than 5% of the dose is excreted into the urine in the dog, concentrations in the urine are 10 times plasma concentration after a single dose of 10 mg per kg of body weight (mg/kg) [R-96]. After multiple oral doses in horses, urine concentrations are higher than serum concentrations [R-27].

Marbolloxacin—Dogs: Tissue concentrations of marbolloxacin were determined in healthy male beagle dogs at 2, 18, and 24 hours after a single oral dose (2.75 or 5.5 mg/kg). Based on the terminal elimination half-life and the dosing interval, steady-state levels are reached after the third dose and are expected to be approximately 25% greater than those achieved after a single dose.

Protein binding:
Ciprofloxacin—Dogs: 44 ± 3% [R-12].
Difloxacin—Dogs: 46 to 52% [R-97].
Enrofloxacin—
Camels: Concentration dependent—
1.7% at 1.8 mcg of enrofloxacin per mL of serum (mcg/mL) [R-45],
5% at 0.6 mcg/mL [R-45],
24.2% at 0.33 mcg/mL [R-45].
Cattle, lactating: 36 to 45% [R-11].
Chickens: 24 ± 2% [R-10].
21 ± 0.1 [R-12].
Dogs: 72% at 1 mcg/mL [R-86].
Horses: 22 ± 2% [R-12].
Pigs: 27 ± 3% [R-12].
Rabbits: Up to 30 days of age—40 to 50% [R-14; 15].
Adult—53 ± 1% [R-12].
Does, pregnant—35 ± 5% [R-63].
Marbolloxacin [R-97]—
Cats: 7.3%.
Dogs: 9.1%.
Orbifloxacin—Dogs: 7.7 to 14.5% [R-82].

Biotransformation:
Difloxacin—In the dog, difloxacin is metabolized to an ester glucuronide and the desmethyl derivative [R-96].
Enrofloxacin—Enrofloxacin is de-ethylated to form ciprofloxacin, an antimicrobially active metabolite in many species [R-11; 13; 18; 22; 24; 28; 29; 31; 39; 42; 46; 71; 72]. Therefore, microbiologic assays in pharmacokinetic studies are likely to measure the activity of both enrofloxacin and ciprofloxacin combined. Because minimum inhibitory concentrations for some pathogens are lower for ciprofloxacin than for enrofloxacin [R-13], therapeutic concentrations of ciprofloxacin can be reached with dosing calculated to achieve effective enrofloxacin concentrations [R-16; 25; 28]. Ciprofloxacin can be considered an important contributor to the activity of enrofloxacin [R-16; 28]. Evaluations of enrofloxacin activity based on serum or tissue concentrations should consider the contributions of both enrofloxacin and ciprofloxacin. It is also possible that other as yet undiscovered metabolites have antimicrobial activity [R-16].

Cats: After oral administration, the half-time for conversion of enrofloxacin to ciprofloxacin is about 13 minutes [R-22]. Ciprofloxacin serum concentration is about 20% of the enrofloxacin concentration in the serum at any one time; about 10% at maximum serum concentrations [R-22; 72; 86].

Cattle, lactating: The serum concentration of ciprofloxacin is 35% that of enrofloxacin during the elimination phase, after an intravenous dose of 5 mg/kg [R-11].

Chickens: Enrofloxacin is extensively metabolized to ciprofloxacin [R-31].
Dogs: Overall, 40% of the oral or intravenous enrofloxacin dose administered is metabolized to ciprofloxacin\(^\text{[R-23]}\). Ciprofloxacin makes up about 20% of the total serum concentration of enrofloxacin and ciprofloxacin after enrofloxacin administration; ciprofloxacin makes up about 35% of the total body concentration when calculated based on the area under the concentration-time curve (AUC)\(^\text{[R-16; 18; 86]}\).

Ducks: Less than 10% of the administered enrofloxacin dose is converted to ciprofloxacin after a 10 mg/kg dose\(^\text{[R-42]}\).

Horses: The concentration of ciprofloxacin in the serum reaches 20 to 35% of the enrofloxacin concentration in adult horses\(^\text{[R-24]}\). In foals, the amount of ciprofloxacin measured is negligible\(^\text{[R-85]}\).

Llamas: Approximately 36% of enrofloxacin administered is converted to ciprofloxacin in llamas\(^\text{[R-46]}\).

Macaws, long-tailed: Ciprofloxacin makes up about 22% of the total amount of active drug measured in the serum after intramuscular administration of 5 mg/kg of enrofloxacin\(^\text{[R-71]}\).

Parrots, African grey: Ciprofloxacin concentration in the serum reaches 3 to 78% of the enrofloxacin dose administered\(^\text{[R-39]}\). The ratio of ciprofloxacin to enrofloxacin in the serum increases with multiple dosing over 10 days\(^\text{[R-19]}\).

Pigs: The concentration of ciprofloxacin in the plasma comprises less than 10% of the amount of enrofloxacin present in the plasma\(^\text{[R-29]}\).

Sheep: In one study, the concentration of ciprofloxacin in the plasma reached 35 and 55% of the serum enrofloxacin concentrations, with intravenous and intramuscular administration, respectively, of a 2.5 mg/kg dose\(^\text{[R-28]}\). Another study found the concentration of ciprofloxacin in the plasma to be 10 to 20% of the serum drug concentration\(^\text{[R-86]}\).

Marbofloxacin—Dogs: 10 to 15% of the dose is metabolized in the liver\(^\text{[R-97]}\).

Serum concentrations:

**Chickens**—
Mean plasma concentrations at 6, 12, and 24 to 168 hours after beginning oral administration of enrofloxacin at a dose of 25 parts per million (ppm) in the drinking water were 0.241, 0.317, and 0.381 mcg/mL, respectively\(^\text{[R-1]}\). Mean plasma concentrations at 6, 12, and 24 to 168 hours after beginning oral administration of enrofloxacin at a dose of 50 ppm in the drinking water were 0.464, 0.653, and 0.712 mcg/mL, respectively\(^\text{[R-1]}\).

**Turkeys**—
Mean plasma concentrations at 6 hours and 24 to 168 hours after beginning oral administration of enrofloxacin at a dose of 25 ppm in the drinking water were 0.204 and 0.240 mcg/mL, respectively\(^\text{[R-1]}\). Mean plasma concentrations at 6 hours and 24 to 168 hours after beginning oral administration of enrofloxacin at a dose of 50 ppm in the drinking water were 0.352 and 0.458 mcg/mL, respectively\(^\text{[R-1]}\).

Elimination:

Difloxacin—Dogs: Primarily through glucuronidation and subsequent biliary secretion. The glucuronide metabolite may be hydrolyzed back to the parent compound and reabsorbed in the gastrointestinal tract. After intravenous administration, 80% of the dose is eliminated in the feces while renal clearance accounts for less than 5% of difloxacin elimination\(^\text{[R-96]}\).

Enrofloxacin—Renal. Primarily by glomerular filtration and tubular secretion\(^\text{[R-10]}\).

Marbofloxacin—
Cats: Primarily renal. 70% of an oral dose is excreted into the urine as parent drug and metabolites\(^\text{[R-97]}\).

Dogs: 40% of an oral or subcutaneous dose is excreted as parent drug into the urine. Elimination of parent drug into the feces is also a significant route of elimination\(^\text{[R-97; 118]}\).

Orbifloxacin—
Cats: Of the orbifloxacin eliminated in urine after subcutaneous administration, 96% is unchanged parent drug and 4% is N-hydroxy orbifloxacin, an active metabolite with somewhat higher MICs for pathogens sensitive to orbifloxacin\(^\text{[R-111]}\).

Dogs: 40% of an oral dose is excreted as parent drug into the urine\(^\text{[R-97]}\). Of the orbifloxacin eliminated in the urine after a subcutaneous dose, 87% is parent compound and 13% is glucuronide metabolite\(^\text{[R-111]}\).

**PRECAUTIONS TO CONSIDER**

**BACTERIAL RESISTANCE**

Concerns about the risk of increasing resistance of human pathogens to fluoroquinolones as well as the ability of infections in animals to resist treatment should be considered by health practitioners when prescribing these medications. There have been warnings by infectious disease experts that widespread use of fluoroquinolones may lead to increased resistance, and transfer of resistance to humans has been suggested for *Campylobacter* species and *Salmonella typhimurium* type DT-104. Increased resistance in *Campylobacter jejuni* infecting people was reported after 1995, the same period in which fluoroquinolones were first approved for use in poultry. There has also been discussion about the appearance of resistant strains of *Salmonella typhimurium* during the time fluoroquinolones have been used in livestock. However, some resistant strains have been traced to farms that were not administering fluoroquinolones, leading to the suggestion that the resistance may have arisen spontaneously\(^\text{[R-91]}\).

As scientists continue to uncover evidence pertaining to the potential for transfer of fluoroquinolone-resistant pathogens from animals to man, fluoroquinolones have had limited approval for use in food-producing animals and extra-label use in these animals is prohibited in the United States\(^\text{[R-95; 106]}\).

**SPECIES SENSITIVITY**

Cats: Because of the risk of retinal degeneration that has been associated with enrofloxacin administration at high doses (20 mg per kg of body weight [mg/kg] a day)\(^\text{[R-1]}\), it has been recommended that administration of high doses of all fluoroquinolones be avoided in cats whenever possible. However, it may be that not all fluoroquinolones have the same potential to cause retinal damage. Limited studies show that marbofloxacin caused no retinal changes visible with funduscopic or histologic examination when administered to 8-month-old cats at 10 times the recommended dosage for 2 weeks\(^\text{[R-97]}\), whereas enrofloxacin has been shown to cause ocular lesions at 4 times the recommended dosage\(^\text{[R-1]}\). A study with orbifloxacin showed that no
retinal changes were visible with fundoscopic or histologic examination when administered to cats at levels which exceeded the highest recommended dose of 7.5 mg/kg [R-146].

CARCINOGENICITY
Enrofloxacin—No evidence of carcinogenicity was found in studies of laboratory animal models [R-3].

PREGNANCY/REPRODUCTION
The attributes of fluoroquinolones make them likely to cross the placenta in many species; however, adverse effects have not yet been reported when fluoroquinolones have been administered to pregnant animals [R-95]. Adequate and well-controlled studies of the effects of fluoroquinolones in pregnant human beings have not been done; however, administration during human pregnancy is generally not recommended, based on reports of arthropathy in immature animals [R-107].

Ciprofloxacin—Ciprofloxacin crosses the human placenta [R-107]. Intravenous doses of ciprofloxacin of up to 20 mg per kg of body weight (mg/kg) in pregnant rats and mice have not shown evidence of maternal toxicity, embryotoxicity, or teratogenic effects [R-107].

Diltiazem, marbofloxacin, and orbifloxacin—Safety in breeding or pregnant animals has not been determined [R-96–98].

Enrofloxacin—

Cats, cattle, turkeys: Effect on reproduction or pregnancy has not been established [R-1–3].

Chickens: No adverse effects were noted in measured reproductive parameters when male and female chickens were given an enrofloxacin dose of 150 parts per million in the drinking water for 7 days. This regimen was repeated at five different ages between 1 day and 206 days of age with no reproductive effect noted [R-3]. The parameters measured included egg production, egg weight, hatchability, chick viability, and reproductive histology of treated birds and their hatchedd chicks [R-4].

Dogs: No adverse effects were noted in measured reproductive parameters, including libido, successful pregnancy, and number of pups per litter, when male dogs were administered 5 to 15 mg/kg a day for 10 days beginning at 90, 45, or 14 days before breeding [R-1: 9].

No adverse effects were noted in female dogs administered 15 mg/kg a day for 10 days in the last 30 days before breeding, between the 10th and 30th days of gestation, between the 40th and 60th days of gestation, or during the first 28 days of lactation [R-1; 5: 6].

Rabbits: Enrofloxacin is transferred across the placenta in rabbits [R-61]; adverse effects on pups have not been reported. Ciprofloxacin also crosses the placenta but at a much slower pace (6% of the rate of enrofloxacin) [R-63].

LACTATION
Because of the risk of producing arthropathies in immature animals, it has been recommended that significant levels of fluoroquinolones in the milk of nursing animals be avoided [R-95; 107]. Fluoroquinolones can be distributed into milk, sometimes at a higher concentration than in plasma, [R-11–14; 14] but it is not known under what conditions significant amounts might be absorbed by nursing animals [R-86].

Mastitis—It has not been shown that fluoroquinolones are effective in treating mastitis [R-95], perhaps because of factors in milk that inhibit activity [R-11].

Cattle: Federal law prohibits the extra-label use of fluoroquinolones in food-producing animals (see the Regulatory Considerations section). The following information is included in case of accidental dosing. Enrofloxacin appears rapidly in milk after parenteral administration, reaching a peak concentration at 30 to 60 minutes after intravenous injection, followed by a gradual decline in milk concentration similar to that occurring in serum concentration [R-11; 14]. Approximately 0.2% of a 5 mg per kg of body weight dose of enrofloxacin is measured in milk in the first 24 hours; therapeutic antimicrobial concentrations can be reached [R-11].

The ciprofloxacin metabolite of enrofloxacin also appears rapidly in milk, but this occurs 4 to 8 hours after parenteral administration. It concentrates to a higher peak than enrofloxacin itself [R-11; 14].

Horses: Following an oral dose of 5 mg/kg to lactating mares, concentration of ciprofloxacin and enrofloxacin in milk ranged from 0.25 to 0.78 mcg per mL. At this concentration, a nursing foal would ingest a dose of less than 0.1 mg per kg of body weight a day. producing plasma concentrations in the foal below detection limits [R-86].

Rabbits: Therapeutic concentrations of enrofloxacin are reached in milk following a dose of 7.5 mg per kg of body weight [R-14].

PEDIATRICS
See also the Side/Adverse Effects section for information on risk of arthropathies in immature animals.

Enrofloxacin—

Calves: Until at least 1 week of age, the elimination of enrofloxacin is slower in calves than in adult cattle [R-13]. Adjustment of dosage, including increased dosing interval, may be necessary [R-13].

Foals: Elimination of enrofloxacin in foals (half-life = 18 hrs) is slower than in adult horses and oral absorption in foals is approximately 42% [R-86; 88]. Administering enrofloxacin to a dose of 10 mg per kg a day caused every one of five healthy foals to have lesions on articular cartilage [R-85].

Rabbits: Elimination of enrofloxacin is significantly less in neonates until at least 16 days of age compared with that in adult rabbits [R-14]. The ease of penetration of enrofloxacin into milk should be considered when treating lactating does that continue to nurse [R-15]. Enrofloxacin pharmacokinetics in 30-day-old rabbits are similar to those in adult rabbits [R-15].

DRUG INTERACTIONS AND/OR RELATED PROBLEMS
The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Digoxin: A small study investigating specifically the effect of enrofloxacin administration on digoxin clearance and serum concentrations in dogs showed no effect with concomitant administration [R-59].

Antacids, aluminum-, calcium-, or magnesium-containing or Laxatives, magnesium-containing or Multivitamins or Sucralfate or
Zinc
(compounds containing divalent or trivalent cations, such as aluminum, calcium, iron, magnesium, or zinc, administered concurrently with a fluoroquinolone, may reduce the absorption of the fluoroquinolone[1: 96–98])
Theophylline[61] or
Hepatically metabolized drugs, other[1]
(in dogs, the clearance of theophylline was reduced by 43% with the concurrent administration of enrofloxacin [5 mg per kg of body weight every 24 hours]; peak serum concentration of theophylline was significantly increased; the pharmacokinetics of enrofloxacin were unaffected[62])
(the concurrent administration of a fluoroquinolone with other drugs metabolized by hepatic enzymes may affect the pharmacokinetics of one or both drugs[1]; enrofloxacin has been shown to inhibit liver microsomal mixed-function oxidases in broiler chicks, including aniline hydroxylase and aminopyrine N-demethylase[60]; cytochrome P450 activity was not significantly affected in chickens[60]; in mice, there is indirect evidence that cytochrome P450 enzymes may be affected by enrofloxacin administration[62]; the effect of these enzyme inhibitions on specific drugs has not yet been demonstrated)

HUMAN DRUG INTERACTIONS AND/OR RELATED PROBLEMS[107]
In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monograph Fluoroquinolones (Systemic) in USP DI Volume I; these drug interactions are intended for informational purposes only and may or may not be applicable to the use of fluoroquinolones in animals:
Note: There are no difloxacin, enrofloxacin, marbofloxacin, or orbifloxacin products labeled for use in humans.
Anticonvulsants, hydantoin, especially:
Phenytoin
(concurrent administration of ciprofloxacin with phenytoin has resulted in a 34 to 80% decrease in the plasma concentration of phenytoin; caution should be used when administering quinolones, especially ciprofloxacin, to patients stabilized on phenytoin; careful monitoring of phenytoin dosage after discontinuation of quinolones is highly recommended)
Antidiabetic agents, sulfonylurea, especially:
Glyburide or Insulin
(concurrent use of ciprofloxacin with glyburide or other antidiabetic agents has, on rare occasions, resulted in hypoglycemia; also, hyperglycemia and hypoglycemia have been reported in patients taking quinolone antibiotics and antidiabetic agents concurrently; since the mechanism is not understood, similar effects with other sulfonylurea antidiabetic agents may be expected when these medications are used with fluoroquinolones; careful monitoring of blood glucose concentrations is recommended when these medications are used concurrently)
Anti-inflammatory drugs, nonsteroidal (NSAIDs)
(quinolone antibiotics may increase the risks of CNS stimulation and convulsions)
Cyclosporine
(concurrent use with ciprofloxacin has been reported to elevate serum creatinine and serum cyclosporine concentrations; other studies have not found ciprofloxacin to alter the pharmacokinetics of cyclosporine; cyclosporine concentrations should be monitored when used concurrently with fluoroquinolones, and dosage adjustments may be required)
Probenecid
(concurrent use of probenecid decreases the renal tubular secretion of fluoroquinolones, resulting in decreased urinary excretion of the fluoroquinolone, prolonged elimination half-life, and increased risk of toxicity; this interaction is more significant with fluoroquinolones excreted largely unchanged in the urine, and of less clinical significance with fluoroquinolones that have larger nonrenal elimination, such as ciprofloxacin)
Warfarin
(concurrent use of warfarin with ciprofloxacin has been reported to increase the anticoagulant effect of warfarin, increasing the chance of bleeding; other studies have not found fluoroquinolones to alter the prothrombin time [PT] significantly; however, it is recommended that the PT of patients receiving warfarin and fluoroquinolones concurrently be monitored carefully)

HUMAN LABORATORY VALUE ALTERATIONS[107]
The following laboratory value alterations have been reported in humans, and are included in the human monograph Fluoroquinolones (Systemic) in USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of fluoroquinolones in the treatment of animals:
Note: There are no difloxacin, enrofloxacin, marbofloxacin, or orbifloxacin products labeled for use in human beings.
With physiology/laboratory test values
Alanine aminotransferase (ALT [SGPT]) and Alkaline phosphatase and Amylase and Aspartate aminotransferase (AST [SGOT]) and Lactate dehydrogenase (LDH)
(sero values may be increased)

MEDICAL CONSIDERATIONS/CONTRAINdicATIONS
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist:
Hypersensitivity to quinolones[1: 96–98]
(animals with a history of hypersensitivity to quinolones are at risk for developing reactions to them[1: 97, 98])
Immature animals in some species[1]
(quinolone administration during rapid growth has been associated with arthropathies and cartilage erosions in weight-bearing joints in immature cats, dogs, and horses[1: 4, 5, 25, 26, 85, 96–98]; in dogs, enrofloxacin has been shown to cause abnormal carriage of the carpal joint and hindlimb weakness, as well as
Risk-benefit should be considered when the following medical problems exist:

Central nervous system (CNS) disorders
Seizures, history of (fluoroquinolones have been associated with CNS stimulation that may lead to seizures in a few rare cases and should be used with caution;
the clinical significance of a report of increased seizure incidence with enrofloxacin administration to dogs with phenobarbital-controlled seizures is not known)

Hepatic disease, severe
Renal failure
(fluoroquinolones are primarily eliminated by a combination of renal clearance and hepatic metabolism, sometimes with significant biliary secretion; the predominance of one route over another depends on the quinolone and the animal species; there is little research information on changes in elimination in various disease states in animals; the induction of moderate renal impairment in dogs [glomerular filtration rate decreased 37% and serum creatinine values increased 85% from normal controls] had only a minor effect on the clearance of marbofloxacin)

PATIENT MONITORING
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

Culture and sensitivity in vitro and Minimum inhibitory concentration (MIC)
(in vitro cultures and MIC tests should be done on samples collected prior to fluoroquinolone administration to determine pathogen susceptibility)

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
Multiple species

Arthropathy—in immature animals, especially dogs and foals
Note: The risk of arthropathy increases with increasing dose but has been reported to occur at recommended dosages in young dogs.

Difloxacin—Articular cartilage lesions were seen in 15- to 16-week-old puppies administered difloxacin at 5, 25, or 35 mg per kg of body weight (mg/kg) a day for 90 days. Cartilage lesions and lameness were observed in puppies administered 50 and 125 mg/kg a day.

Enrofloxacin—Cartilage damage has been observed in 10- to 28-week-old puppies with an oral enrofloxacin dose of 5 to 25 mg/kg a day for 30 days and 5- to 7-month-old kittens with an oral dose of 25 mg/kg a day for 30 days; changes include splitting of the articular cartilage surface and, in some cases, necrosis of the hyaline cartilage. Arthropathy has been reported in growing horses.

In unpublished manufacturer data, a dose of 5 mg/kg administered to foals once a day was reported to cause cartilage lesions and signs of arthropathy after 6 days; however, studies have shown no effect on cartilage in adults when used continuously for up to 21 days. In 23-day-old calves, a dose of 25 mg/kg a day for 15 days had no measurable effect on articular cartilage in the stifle joint at 2 and 9 days after the end of treatment.

Marbofloxacin—Lameness and articular cartilage lesions were reported in large breed, 3- to 4-month-old dogs administered 11 mg/kg a day for 14 days.

Orbifloxacin—Microscopic cartilage lesions typical of fluoroquinolone arthropathy have also been reported with orbifloxacin administration; in one of eight, 8- to 10-week-old puppies given 12.5 mg/kg a day and all 8 puppies given 25 mg/kg a day. Cats appear to be resistant to this effect, showing no cartilage lesions after one month of a 25 mg/kg-a-day dose.

Cats

Retinal degeneration (acute blindness, mydriasis)—reported with enrofloxacin at doses higher than 5 mg per kg of body weight (mg/kg) a day

Note: Administering enrofloxacin to cats at a dose of 20 mg/kg can cause retinal degeneration, often manifested as temporary or permanent blindness with mydriasis. Mild to severe fundic lesions are observed on ophthalmologic exam of affected cats, including changes in the color of the fundus and central or generalized retinal degeneration. There are also abnormal electroretinogram results and diffuse light microscopic changes in the retinas. Retinal degeneration has not been reported in cats in association with other fluoroquinolones; however, caution is recommended when considering high dose therapy of any fluoroquinolone in cats.

Ataxia; seizures—with enrofloxacin

Note: Although ataxia and seizures were not observed during preapproval clinical field trials, they have been noted as part of voluntary postapproval adverse drug experience reporting.

Parrots, African grey

Appetite, decreased; polydipsia and polyuria—with a dose of 30 mg/kg every 12 hours for 10 days or in drinking water with 1.5 to 3 mg/mL of water; may resolve within 2 or 3 days of treatment cessation.

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME
Incidence more frequent

Cats

Vomiting—with enrofloxacin, occasional vomiting was observed in up to 75% of 7- to 10-month-old cats administered a 5 to 15 mg/kg dose for 30 days; however, 25% of untreated cats also vomited occasionally.

Incidence less frequent

Cats

Diarrhea—reported with marbofloxacin (2.1% of cats in one report)

Dogs

Decreased activity—reported with marbofloxacin (4.4% of dogs in one report); decreased appetite—reported with marbofloxacin (5.4%); vomiting—reported with marbofloxacin (2.9%)
Incidence rare

Cats

**Vomiting**—with marbofloxacin (<1%)[^R-97]

Dogs

**Vomiting**—with enrofloxacin (0.7% of dogs)[^R-1]

Incidence unknown

Cattle[^R-2; 4], horses[^R-24], and rabbits[^R-68; 69]

**Local tissue reaction, transient**—in cattle, can cause trim loss of edible tissue at slaughter[^R-2]

**Dogs**

**Anorexia; decreased appetite; diarrhea; vomiting**—with difloxacin

Note: No adverse effects were reported in association with a clinical study using recommended dosages of difloxacin in dogs. **Anorexia, decreased appetite, diarrhea, and vomiting** have been reported in clinical cases[^R-96] but the incidence is unknown.

**HUMAN SIDE/ADVERSE EFFECTS[^R-107]**

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans and are included in the human monograph *Fluoroquinolones (Systemic)* in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of fluoroquinolones in the treatment of animals:

Note: The following human side/adverse effects are those pertaining to ciprofloxacin or fluoroquinolones in general. Difloxacin, enrofloxacin, marbofloxacin, and orbifloxacin are not available as products labeled for human use.

Note: The relative insolubility of ciprofloxacin at an alkaline pH has resulted in *crystalluria*, usually when the urinary pH exceeds 7. *Seizures* have been reported very rarely with ciprofloxacin therapy; however, the patients who did have seizures either had a previous seizure history, were alcoholic, or were taking ciprofloxacin concurrently with theophylline.

Incidence more frequent

**Central nervous system (CNS) toxicity; gastrointestinal reactions; vaginitis**

Incidence less frequent or rare

**Arthralgia; back pain; cardiovascular reactions such as palpitation, vasodilation, or tachycardia; central nervous system (CNS) stimulation; change in sense of taste; dreams, abnormal; dysuria; headache; hematuria; hepatotoxicity; hypersensitivity reactions; interstitial nephritis; moniliasis, oral; moniliasis, vaginal; myalgia; phlebitis—for intravenous ciprofloxacin; photosensitivity; phototoxicity; pseudomembranous colitis; Stevens-Johnson Syndrome** (blistering, itching, loosening, peeling, or redness of skin; diarrhea): **tendinitis or tendon rupture; vision, abnormal**

Note: **Achilles tendinitis and tendon rupture** have been reported in patients receiving fluoroquinolones. The ruptures occurred 2 to 42 days after the start of therapy. Concomitant use of corticosteroids with fluoroquinolones may increase the risk of tendon disorders or ruptures. These injuries may require surgical repair or result in prolonged disability. It is recommended that fluoroquinolone treatment be discontinued at the first sign of tendon pain or inflammation, and that patients refrain from exercising until the diagnosis of tendinitis has been excluded.

Some patients note a reduced incidence of nausea and taste perversions if the dose is administered in the evening. **Photosensitivity** reactions generally appear within a few days of the start of fluoroquinolone treatment but can occur up to 3 weeks after its discontinuation. The reactions usually subside within 1 month of discontinuation. Indicating possible photocytotoxicity, pseudomembranous colitis, or tendinitis or tendon rupture and the need for medical attention if they occur after medication is discontinued:

**Abdominal or stomach cramps and pain, severe; abdominal tenderness; blisters; diarrhea, watery and severe, which may also be bloody; fever; pain in calves, radiating to heels; sensation of skin burning; skin rash, itching, or redness; swelling of calves or lower legs**

**OVERDOSE**

For more information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

Reported lethal doses of enrofloxacin—

**Cats:** 125 mg per kg of body weight (mg/kg) a day for 5 days[^R-1].

**Dogs:** Oral—125 mg/kg a day for up to 11 days[^R-1; 5].

**Mice:** Oral—LD<sub>50</sub> for female mice is 4335 mg/kg and for male mice is 5000 mg/kg[^R-4].

**Rabbits:** Oral—LD<sub>50</sub> for male and female rabbits is 500 to 800 mg/kg[^R-4].

**Rats:** Oral—LD<sub>50</sub> for male and female rats is more than 5000 mg/kg[^R-2; 3; 4]. A dose of 500 parts per million (40 mg/kg) has no observable effect[^R-4].

**Turkey poults:** 1-day-old: Oral—626 parts of enrofloxacin per million parts of drinking water administered for 21 days caused the death of 11 out of 40 birds in the first 10 days[^R-3; 4]. Surviving birds showed signs of listlessness and decreased body weight gain[^R-1; 11].

**CLINICAL EFFECTS OF OVERDOSE**

The following effects have been selected on the basis of their potential clinical significance—not necessarily inclusive:

**For difloxacin**

Dogs, with doses of 5, 15, or 25 mg/kg a day for 30 consecutive days[^R-96]

**Decreased appetite; diarrhea; erythema/edema on the facial area, transient; weight loss**

**For enrofloxacin**

Calves, feeder, with a dose of 15 or 25 mg/kg a day for 10 to 15 days or a dose of 50 mg/kg a day for 3 days[^R-2]

Note: Federal law prohibits the extra-label use of fluoroquinolones in food-producing animals (see the *Regulatory Considerations* section). The following information is included in case of accidental dosing.

**Depression; decreased appetite; incoordination; muscle fasciculations**

**Cats, with a dose of 20 mg/kg a day for 21 days[^R-1]**

**Depression: retinal degenerative effects; salivation; vomiting**

**Cats, with a dose ≥ 50 mg/kg a day for 6 days[^R-1]**

**Convulsions; depression; incoordination; loss of appetite; retinal degenerative effects; vomiting**

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**TREATMENT OF OVERDOSE**

Although there is no specific information available on treatment of fluoroquinolone overdose in animals, treatment of human overdose includes induction of vomiting or use of gastric lavage, observation, and supportive care, including hydration and dialysis.

**CLIENT CONSULTATION**

Care should be exercised to avoid contact of medication with the eyes or skin while handling solutions.

**VETERINARY DOSING INFORMATION**

Fluoroquinolone antibiotics have concentration-dependent bactericidal activity or AUIC. Serum and tissue concentrations must be high enough for a long enough period of time to be effective against the target pathogen. Fortunately, minimum inhibitory concentrations (MIC) for fluoroquinolones are relatively low. Depending on many variables, such as the organism treated and the presence of neutrophils, fluoroquinolones can also produce a post-antibiotic effect, suppressing bacterial growth after local drug concentrations have fallen. Cats: Because of the risk of retinal damage associated with high dosages of enrofloxacin, it is recommended that caution be used when considering administering fluoroquinolone at dosages higher than those recommended for cats.

Flexible Labeling—Because there is a wide minimum inhibitory range among bacteria susceptible to fluoroquinolones, it was possible to create a “flexible” product label that includes a dosage range allowing for doses at the low end to be used to treat pathogens susceptible at a lower MIC and higher doses for less susceptible organisms. The upper end of the dosage range is determined by safety factors.

Product labeling for veterinary fluoroquinolone products include MIC data for bacterial pathogens for specific indications in which efficacy was confirmed, and a dosage range. It is recommended that the dose be chosen based on clinical experience, the type and severity of infection, and susceptibility of the pathogen.

The effective treatment of canine infections caused by *Pseudomonas aeruginosa* and *Staphylococcus species* may require the high end of the dosage range.

**Breakpoints determined for ciprofloxacin**

<table>
<thead>
<tr>
<th>Breakpoint (mcg/mL)</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>≤ 1.0</td>
<td>Susceptible</td>
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<tr>
<td>2.0</td>
<td>Intermediate</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

Note: Be aware that ciprofloxacin may not be appropriate for use as a representative of veterinary fluoroquinolones in susceptibility testing. Use of specific antibiotic MIC ranges has been recommended.

**Breakpoints determined for difloxacin**

<table>
<thead>
<tr>
<th>Breakpoint (mcg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 21</td>
<td>Susceptible</td>
</tr>
<tr>
<td>18–20</td>
<td>Intermediate</td>
</tr>
<tr>
<td>≤ 17</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

Note: The disk content is 10 mcg.

**Breakpoints recommended for marbofloxacin**

<table>
<thead>
<tr>
<th>Breakpoint (mcg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 17</td>
<td>Susceptible</td>
</tr>
<tr>
<td>14–16</td>
<td>Intermediate</td>
</tr>
<tr>
<td>≤ 13</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

Note: The disk content is 5 mcg.
Zone diameter (millimeters) | MIC (mcg/mL) | Interpretation
--- | --- | ---
≥ 23 | ≤ 1 | Susceptible
18–22 | 2–4 | Intermediate
≤ 17 | ≥ 8 | Resistant

Note: The disk content is 10 mcg.

CIPROFLOXACIN

SUMMARY OF DIFFERENCES
Regulatory considerations: Ciprofloxacin is not labeled for use in animals.

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

CIPROFLOXACIN FOR ORAL SUSPENSION
Usual dose: Note: [Dogs]1—Although the safety and efficacy have not been established, an oral dose of 10 to 20 mg per kg of body weight every twenty-four hours has been recommended in the treatment of susceptible bacterial infections, based on pharmacokinetic data1[R-95; 118; 134]. For empiric treatment of infections in dogs caused by probable Pseudomonas aeruginosa or Staphylococcus infections, the higher end of the dosage range may be preferable, pending susceptibility results.

[Horses]1—Due to poor bioavailability1[R-144], oral ciprofloxacin should not be used in horses.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg per 5 mL (5%) (Rx) [Cipro].
500 mg per 5 mL (5%) (Rx) [Cipro].

Canada—
Not commercially available.


Preparation of dosage form: To prepare the oral suspension, the small bottle containing the microcapsules should be emptied into the large bottle containing the diluent. Water should not be added to the suspension. The large bottle should be closed and shaken vigorously for about 15 seconds.

Stability: The suspension is stable for 14 days when stored in a refrigerator or at room temperature (below 30 °C [86 °F]).

USP requirements: Not in USP[R-105].

CIPROFLOXACIN TABLETS
Usual dose: See Ciprofloxacin for Oral Suspension.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
100 mg (base) (Rx) [Cipro].
250 mg (base) (Rx) [Cipro].
500 mg (base) (Rx) [Cipro].
750 mg (base) (Rx) [Cipro].

Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
100 mg (base) (Rx) [Cipro].
250 mg (base) (Rx) [Cipro].
500 mg (base) (Rx) [Cipro].
750 mg (base) (Rx) [Cipro].

Packaging and storage: Store below 30 °C (86 °F), in a well-closed container, unless otherwise specified by manufacturer.

USP requirements: Preserve in well-closed containers. Contain an amount of ciprofloxacin hydrochloride equivalent to the labeled amount of ciprofloxacin, within ± 10%. Meet the requirements for Identification, Dissolution (80% in 30 minutes in 0.01 N hydrochloric acid in Apparatus 2 at 50 rpm), and Uniformity of dosage units1[R-105].

1Not included in Canadian product labeling or product not commercially available in Canada.

PARENTERAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

CIPROFLOXACIN INJECTION USP
Usual dose: Note: [Dogs]1—Although the safety and efficacy have not been established, an intravenous dose of 10 to 15 mg per kg of body weight, administered slowly every twenty-four hours has been recommended in the treatment of susceptible bacterial infections[R-81].

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
200 mg per 20 mL (Rx) [Cipro I.V. (in sterile water for injection; requires dilution prior to administration)].
400 mg per 40 mL (Rx) [Cipro I.V. (in sterile water for injection; requires dilution prior to administration)].

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400 mg per 200 mL (Rx) [Cipro I.V. (in 5% dextrose injection; premixed)].
1200 mg per 120 mL (Rx) [Cipro I.V. (in sterile water for injection; requires dilution prior to administration)].

**Packaging and storage:** Store in a cool place (between 8 and 15 °C).

**Preparation of dosage form:** To prepare a solution for intravenous injection, the concentrate in sterile water for injection should be withdrawn aseptically from the vial and diluted to a final concentration of 1 to 2 mg per mL with a suitable intravenous solution (see manufacturer’s package insert). Solutions that come from the manufacturer in 5% dextrose injection should not be diluted prior to intravenous infusion. The resulting solution should be infused over a period of at least 60 minutes by direct infusion or through a Y-type intravenous set. It is recommended that administration of any other solutions be discontinued during infusion of ciprofloxacin.

**Stability:** When diluted with appropriate intravenous fluids (see manufacturer’s package insert) to concentrations from 0.5 to 2 mg per mL, solutions retain their potency for up to 14 days when refrigerated or stored at room temperature.

**Incompatibilities:** Ciprofloxacin is incompatible with aminophylline, amoxicillin, cefepime, clindamycin, dexamethasone, floxacillin, furosemide, heparin, and phenytoin.

If ciprofloxacin is to be given concurrently with another medication, each medication should be administered separately according to the recommended dosage and route of administration for each medication.

**USP requirements:** Preserve in single-dose containers, preferably of Type I glass, in a cool place or at controlled room temperature. Avoid freezing and exposure to light. A sterile solution of Ciprofloxacin in Sterile Water for Injection, in 5% Dextrose Injection, or in 0.9% Sodium Chloride Injection prepared with the aid of Lactic Acid. The label indicates whether the vehicle is Sterile Water for Injection, 5% Dextrose Injection, or 0.9% Sodium Chloride Injection. Label the Injection that has Sterile Water for Injection as the vehicle to indicate that it is a concentrated form that must be diluted to appropriate strength (1 to 2 mg per mL) with 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration, and that the resulting solution is stable for up to 14 days when stored in a cool place or at controlled room temperature. Contains the labeled amount, within ± 10%. Meets the requirements for Color (where it is labeled as being in a concentrated form), Identification, Pyrogen, Sterility, pH (3.5–4.6, except that where the Injection is labeled as being a concentrated form, its pH is between 3.3 and 3.9), Particulate matter, Limit of ciprofloxacin ethylenediamine analog (not more than 0.5%), Lactic acid content (0.288–0.352 mg per mg of ciprofloxacin claimed on label, except that where the Injection is labeled as being a concentrated form, it contains between 0.335 and 0.409 mg per mg of ciprofloxacin claimed on the label), Dextrose content (if present), and Sodium chloride content (if present), and for Volume in Container under Injections.[R-105]

1Not included in Canadian product labeling or product not commercially available in Canada.

**DIFLOXACIN**

**ORAL DOSAGE FORMS**

**DIFLOXACIN HYDROCHLORIDE TABLETS**

**Usual dose:** Bacterial infections—Dogs: Oral, 5 to 10 mg per kg of body weight every twenty-four hours.[R-96; 99]

Note: The 5 mg per kg dose was found to be clinically effective in the treatment of susceptible skin, soft tissue, and urinary tract infections.[R-99]

For empiric treatment of probable *Pseudomonas aeruginosa* or *Staphylococcus* infections in dogs, the higher end of the dosage range may be preferable, pending susceptibility results.

**Strength(s) usually available:**

**U.S.[R-96]**—

Veterinary-labeled product(s):

- 11.4 mg (Rx) [Dicural Tablets].
- 45.4 mg (Rx) [Dicural Tablets].
- 136 mg (Rx) [Dicural Tablets].

**Canada[R-99]**—

Veterinary-labeled product(s):

- 11.4 mg (Rx) [Dicural Tablets].
- 45.4 mg (Rx) [Dicural Tablets].
- 136 mg (Rx) [Dicural Tablets].

**Packaging and storage:** Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer.

**USP requirements:** Not in USP[R-105].

**ENROFLOXACIN**

**SUMMARY OF DIFFERENCES**

Pharmacology/pharmacokinetics: Biotransformation—Enrofloxacin is de-ethylated to form ciprofloxacin; therapeutic concentrations of ciprofloxacin can be reached with dosing calculated to achieve effective enrofloxacin concentrations.

Side/adverse effects: Cats—Retinal degeneration (acute blindness, mydriasis) has been reported with enrofloxacin at doses higher than 5 mg per kg of body weight a day.
ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

ENROFLOXACIN ORAL SOLUTION
Usual dose:
_Escherichia coli_ infection — _Chickens_ and _turkeys:_ Oral, 25 to 50 parts enrofloxacin per million parts water (ppm), administered as the only source of drinking water for three to seven days.
_Fowl cholera_ — _Turkeys:_ Oral, 25 to 50 parts enrofloxacin per million parts water (ppm), administered as the only source of drinking water for three to seven days.
Note: Medication should be initiated as soon after diagnosis as possible. The effects of environment and other factors on water consumption should be considered.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
32.3 mg per mL (Rx) [Bagtril 3.23% Concentrate Solution].
Canada—
Veterinary-labeled product(s):
Not commercially available.

Withdrawal times:
U.S. — Withdrawal time

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens, turkeys</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: This product is not labeled for use in laying hens producing eggs for human consumption.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store container in an upright position.

Preparation of dosage form: Product labeling recommends that stock solutions be prepared fresh daily. Once stock solution or medicated water is prepared, protect it from freezing or direct sunlight. This product should not be used in automatic water proportioners if the water hardness is greater than 196 parts per million (ppm). Galvanized metal watering systems or containers should not be used to carry or store this product and chlorinators should not be operated while administering this medication.

Additional information: Product labeling recommends that poultry litter from treated flocks spread on agricultural land be incorporated into the soil whenever possible. It also recommends a 10- to 14-day interval between flocks, top dressing with clean litter, and an increased frequency of removal of caked litter from each house. Poultry litter from treated flocks should not be used in cattle feed.

Caution: Those who administer medication should avoid contact with their eyes and skin. If contact occurs, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following exposure. In human beings, there is a risk of user sensitization within a few hours of significant exposure to quinolones.

USP requirements: Not in USP.

ENROFLOXACIN TABLETS
Usual dose: Bacterial infections —
_Cats:_ Oral, 5 mg per kg of body weight a day. The dose may be administered as a single daily dose or divided into two equal doses administered every twelve hours.

Note: The above dose recommendation is based on risk of retinal damage in cats administered doses higher than 5 mg/kg.

_Dogs:_ Oral, 5 to 20 mg per kg of body weight a day. The dose may be administered as a single daily dose or divided into two equal doses administered every twelve hours.

Note: For empiric treatment of probable _Pseudomonas aeruginosa_ or _Staphylococcus_ infections in dogs, the higher end of the dosage range may be preferable, pending susceptibility results.

Note: [Bustards] — Although the safety and efficacy have not been established, an oral dose of 10 mg per kg of body weight every twelve hours has been suggested for the treatment of susceptible bacterial infections, based on pharmacokinetic data.

_Cats_— Although the efficacy has not been established, if enrofloxacin is used in the treatment of _Bartonella henselae_ infection or _hemobartonellosis_ in cats, the USP Veterinary Medicine Committee currently recommends the administration of 5 mg per kg of body weight a day. Limited research studies on the treatment of these infections have sometimes led to recommendations for higher dosages; however, there is concern about the occurrence of retinal degeneration when a dose of 20 mg/kg is administered to cats and the lack of information on relative risk of retinal damage at dosages between 5 and 20 mg/kg a day.

The following information is provided in the event other therapies have failed:

_An oral dose of 5 to 8 mg per kg of body weight every twelve hours (10 to 16 mg per kg a day) for four to six weeks has been recommended in the treatment of _Bartonella henselae_ infection, based on efficacy trials._

_An oral dose of 5 to 10 mg per kg of body weight every twenty-four hours for two weeks has been recommended in the treatment of _hemobartonellosis_. Cats apparently completely cleared of infection were treated with the high end of this dosage range; however, the low end is the labeled dose._

_Dogs_— Although the efficacy has not been established, an oral dose of 5 mg per kg of body weight every twenty-four hours for fifteen days has been used in the treatment of _Ehrlichia_ in dogs, based on a comparative, randomized therapeutic trial.

An oral dose of 3 mg per kg of body weight every twelve hours for seven days has been used in the treatment of _Rocky Mountain spotted fever_ in dogs, based on a controlled therapeutic trial using disease models.

_Ducks, pet or research_ — In the U.S., for use only in animals not to be used for food production: Although the safety and efficacy have not been established, an oral dose of 10 mg per kg of body weight a day has been suggested for the treatment of susceptible bacterial infections in Muscovy ducks, based on pharmacokinetic data.

_Foals_ — Although the safety and efficacy have not been established, an oral dose of 2.5 mg per kg of body weight once a day for eight days has been recommended in the treatment of susceptible bacterial infections.
infections in foals. Because of the potential for arthropathy in immature animals, use is recommended in foals only when other antimicrobials are inappropriate.  

**[Horses]**—In the U.S., for use only in animals not to be used for food production—Although the safety and efficacy have not been established, an oral dose of 7.5 to 10 mg per kg of body weight every twenty-four hours has been recommended. Tablets have been crushed and suspended in water for administration or ground into a powder and mixed in sugar syrup.

**[Pacu, red]**—Although the safety and efficacy have not been established, administration of enrofloxacin by immersion of fish in a bath of a 2.5 mg per liter solution of enrofloxacin for five hours, every twenty-four to forty-eight hours, has been suggested for the treatment of susceptible bacterial infections in red pacu fish, based on pharmacokinetic data.

**[Parrots. African grey]**—Although the safety and efficacy have not been established, an oral dose of 7.5 to 30 mg per kg of body weight every twelve hours has been suggested in the treatment of susceptible bacterial infections in African grey parrots, based on pharmacokinetic data.

The risk of side effects increases with higher doses; polyuria and polydipsia have been reported at the 30 mg per kg of body weight dose.

**[Rabbits. pet or research]**—In the U.S., for use only in animals not to be used for food production: Although the safety and efficacy have not been established, an oral dose of 5 mg per kg of body weight every twelve hours for fourteen days has been recommended in the treatment of pasteurellosis in rabbits, based on clinical efficacy studies.

**Strengths usually available:**

U.S.—

Veterinary-labeled product(s):

- 22.7 mg (Rx) [Baytril Tablets (film-coated)]
- 68 mg (Rx) [Baytril Tablets (film-coated)]
- 136 mg (Rx) [Baytril Tablets]

Canada—

Veterinary-labeled product(s):

- 15 mg (Rx) [Baytril Tablets]
- 50 mg (Rx) [Baytril Tablets]
- 150 mg (Rx) [Baytril Tablets]

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

**USP requirements:** Not in USP.

1Not included in Canadian product labeling or product not commercially available in Canada.

**PARENTERAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**ENROFLOXACIN INJECTION**

**Usual dose:**

**Bacterial infections**—

**Dogs:**

- Intramuscular—2.5 mg per kg of body weight.

**Intravenous**—5 mg per kg of body weight a day. The drug may be administered as a single daily dose or divided into two equal doses administered every twelve hours. To avoid adverse effects, the drug should be diluted in a 2X volume of saline and infused over 15 to 20 minutes.

Note: For empiric treatment of probable *Pseudomonas aeruginosa* or *Staphylococcus* infections, the higher end of the dosage range may be preferable, pending susceptibility results.

**[Cats]**—

- Intramuscular—2.5 mg per kg of body weight. For dogs, U.S. product labeling recommends that this be an initial single dose, to be followed by a dosage regimen using enrofloxacin tablets; this was based on studies establishing the efficacy of 2.5 mg per kg of body weight every twelve hours.

Intravenous—5 mg per kg of body weight a day. The dose may be administered as a single daily dose or divided into two equal doses administered every twelve hours. To avoid adverse effects, the drug should be diluted in a 2X volume of saline and infused over 15 to 20 minutes.

Note: The above dosage recommendations are based on risk of retinal damage in cats administered doses higher than 5 mg/kg a day.

**Bacterial pneumonia**—**Cattle:** Subcutaneous, 7.5 to 12.5 mg per kg of body weight as a single dose or 2.5 to 5 mg per kg of body weight every twenty-four hours for three to five days.

Note: Up to at least 1 week of age, calves eliminate enrofloxacin and the active metabolite ciprofloxacin more slowly than do adult cattle.

**[Emus, pet or research]**—Although the safety and efficacy have not been established, an intramuscular or subcutaneous dose of 2.5 mg per kg of body weight every twelve hours has been suggested for the treatment of susceptible bacterial infections in emus, based on pharmacokinetic data.

**[Ducks, pet or research]**—In the U.S., for use only in animals not to be used for food production: Although the safety and efficacy have not been established, a parenteral dose of 10 mg per kg of body weight every twenty-four hours has been suggested for the treatment of susceptible bacterial infections, based on pharmacokinetic data.

**[Cameleons]**—Although the safety and efficacy have not been established, an intramuscular or subcutaneous dose of 2.5 mg per kg of body weight every twelve hours has been suggested for the treatment of susceptible bacterial infections in camels, based on pharmacokinetic data.

**[Ducks, pet or research]**—In the U.S., for use only in animals not to be used for food production: Although the safety and efficacy have not been established, a parenteral dose of 10 mg per kg of body weight every twenty-four hours has been suggested for the treatment of susceptible bacterial infections, based on pharmacokinetic data.

**[Horses]**—In the U.S., for use only in animals not to be used for food production: Although the safety and efficacy have not been established, an intravenous dose of 5 mg per kg of body weight every twenty-four hours has been used in the treatment of susceptible bacterial infections.
bacterial infections in horses.\(^{[R-93]}\) If a dose higher than 5 mg per kg of body weight is administered, slow injection by indwelling catheter is recommended to avoid adverse effects; dilution in 500 mL of sterile saline solution may also be necessary.\(^{[R-116]}\)

[Llamas, pet or research]—In the U.S., for use only in animals not to be used for food production: Although the safety and efficacy have not been established, an intramuscular or subcutaneous dose of 5 mg per kg of body weight every twelve hours has been suggested for the treatment of susceptible bacterial infections in llamas, based on pharmacokinetic data.\(^{[R-41]}\)

[Oryx]—Although the safety and efficacy have not been established, a parenteral dose of 1.6 mg per kg of body weight every six to eight hours has been suggested for the treatment of susceptible bacterial infections in oryx, based on pharmacokinetic data.\(^{[R-45]}\)

[Pacu, red]—Although the safety and efficacy have not been established, an intramuscular dose of 5 mg per kg of body weight every forty-eight hours has been suggested for the treatment of susceptible bacterial infections in the red pacu, based on pharmacokinetic data.\(^{[R-44]}\)

[Parrots, African grey]—Although the safety and efficacy have not been established, an intramuscular dose of 7.5 to 30 mg per kg of body weight every twelve hours has been suggested in the treatment of susceptible bacterial infections in African grey parrots, based on pharmacokinetic data.\(^{[R-39]}\). The risk of side effects increases with higher doses; polyuria and polydipsia have been reported with the 30 mg per kg of body weight dose.\(^{[R-39]}\)

[Pigs, potbellied and miniature]—In the U.S., for use only in animals not to be used in food production: Although the safety and efficacy have not been established, an oral dose of 10 mg per kg of body weight every 24 hours has been recommended for pigs in the treatment of susceptible bacterial infections, based on pharmacokinetic data.\(^{[R-25]}\). See also the Withdrawal times section.

[Pythons]—Although the safety and efficacy have not been established, an intramuscular dose of 10 mg per kg of body weight as a loading dose followed by 5 mg per kg of body weight every forty-eight hours has been suggested for the treatment of susceptible bacterial infections in pythons.\(^{[R-48]}\). For the treatment of Pseudomonas species infections, 10 mg per kg of body weight every forty-eight hours has been suggested, based on pharmacokinetic data.\(^{[R-48]}\)

[Rabbits, pet or research]—In the U.S., for use only in animals not to be used in food production: Although the safety and efficacy have not been established, a subcutaneous dose of 5 mg per kg of body weight every twelve hours for fourteen days has been recommended in the control of pasteurellosis in rabbits.\(^{[R-33; 67-69]}\)

[Sheep, pet or research]—In the U.S., for use only in animals not to be used in food production—Although the safety and efficacy have not been established, an intramuscular or intravenous dose of 2.5 to 5 mg per kg of body weight every twenty-four hours has been recommended for sheep in the treatment of susceptible bacterial infections, based on pharmacokinetic data. See also the Withdrawal times section.

**Strength(s) usually available:**

U.S.—

Veterinary-labeled product(s):

- 22.7 mg per mL (Rx) [Baytril Injectable Solution 2.27%\(^{[R-104]}\)]
- 100 mg per mL (Rx) [Baytril 100 Injectable Solution\(^{[R-2]}\)].

Note: The more concentrated enrofloxacin injection, 100 mg per mL, is labeled only for use in cattle\(^{[R-2]}\), while the less concentrated injection, 22.7 mg per mL, is labeled for use in dogs.\(^{[R-104]}\) The product used for cattle contains different excipients than the injectable solution for dogs; the safety of using the cattle product in other species has not been demonstrated.\(^{[R-2]}\)

Canada—

Veterinary-labeled product(s):

- 50 mg per mL (Rx) [Baytril Injectable Solution\(^{[R-102]}\)].

**Withdrawal times:**

U.S.—\(^{[R-2]}\)—Federal law prohibits the extralabel use of enrofloxacin in food-producing animals and restricts enrofloxacin to use by or on the order of a licensed veterinarian.

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>28</td>
</tr>
</tbody>
</table>

Note: Not labeled for use in cattle intended for dairy production or in calves to be processed for veal.\(^{[R-2]}\) Subcutaneous injection can cause a local tissue reaction that is transient but can cause trim loss of edible tissue at slaughter.\(^{[R-2]}\)

Canada—There is no established withdrawal time for cattle in Canada because enrofloxacin is not labeled for use in cattle.

**Packaging and storage:** Store below 40°C (104°F), preferably between 15 and 30°C (59 and 86°F), unless otherwise specified by manufacturer. Protect from direct sunlight.\(^{[R-1; 2]}\) Do not freeze.\(^{[R-1; 2]}\)

**Caution:** Those who administer medication should avoid contact with their eyes and skin. If contact occurs, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. A physician should be consulted if irritation persists following exposure. In human beings, there is a risk of user photosensitization within a few hours of significant exposure to quinolones.

**USP requirements:** Not in USP.\(^{[R-105]}\)

\(^{1}\)Not included in Canadian product labeling or product not commercially available in Canada.

**MARBOFLOXACIN**

**ORAL DOSAGE FORMS**

**MARBOFLOXACIN TABLETS**

**Usual dose:** Bacterial infections—**Cats** and **dogs:** Oral. 2.75 to 5.5 mg per kg of body weight every twenty-four hours.\(^{[R-97; 101]}\)

Note: The 2.75 mg per kg dose was found to be clinically effective in the treatment of susceptible skin, soft tissue, and urinary tract infections.\(^{[R-97]}\)

For empiric treatment of probable *Pseudomonas aeruginosa* or *Staphylococcus* infections, the higher end of the dosage range may be preferable, pending susceptibility results.
**ORBIFLOXACIN**

**ORAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**ORBIFLOXACIN TABLETS**

**Usual dose**: Bacterial infections—Cats and dogs: Oral, 2.5 to 7.5 mg per kg of body weight every twenty-four hours.

Note: For empiric treatment of probable *Pseudomonas aeruginosa* or *Staphylococcus* infections, the higher end of the dosage range may be preferable, pending susceptibility results.

Table 1. Pharmacology/Pharmacokinetics—Intravenous administration.

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>Compound measured</th>
<th>Elimination half-life (hours)</th>
<th>$V_{D0}$ Area (L/kg)</th>
<th>$V_{D0}$, Steady state (L/kg)</th>
<th>Clearance (mL/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPROFLOXACIN</td>
<td><strong>Dogs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[R-117]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 to 10</td>
<td></td>
<td>2.2</td>
<td>3.06 ± 0.75</td>
<td>0.26 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>ENROFLOXACIN</td>
<td>Birds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[R-41]</td>
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<tr>
<td></td>
<td>10</td>
<td>Enrofloxacin</td>
<td>5.61 ± 0.54</td>
<td>2.82 ± 0.37</td>
<td>2.98 ± 0.32</td>
<td>5.71 ± 0.41</td>
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<tr>
<td></td>
<td>[R-50]</td>
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</tr>
<tr>
<td></td>
<td>10</td>
<td>Enrofloxacin</td>
<td>4.16 ± 0.19</td>
<td>2.20 ± 0.17</td>
<td>2.43 ± 0.19</td>
<td>2.2 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>[R-11]</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>10</td>
<td>Enrofloxacin</td>
<td>10.29 ± 0.45</td>
<td>4.31 ± 0.15</td>
<td>2.77 ± 0.09</td>
<td>4.8 ± 0.17</td>
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<td>[R-41]</td>
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<td>Enrofloxacin</td>
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<td>1.49 ± 0.52</td>
<td>1.62 ± 1.04</td>
<td>6.00 ± 3.17</td>
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<td>One day of age</td>
<td>Enrofloxacin</td>
<td>6.61 ± 1.12</td>
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<td>1.81 ± 0.1</td>
<td>3.16 ± 0.5</td>
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<td></td>
<td>One week old</td>
<td>Enrofloxacin</td>
<td>9.19 ± 1.46</td>
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<td>2.28 ± 0.14</td>
<td>6.5 ± 1</td>
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<tr>
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<td>Cattle, lactating</td>
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<td>Camel, [R-45]</td>
<td>Enrofloxacin</td>
<td>3.6 ± 0.89</td>
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<td>4.61 ± 1.03</td>
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<td>4.0 ± 0.3</td>
<td>9.3 ± 0.7</td>
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<td>1.25 to 5</td>
<td>Enrofloxacin</td>
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<td>7.0 ± 6.4</td>
<td>27.1 ± 16.2</td>
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<td>Ciprofloxacin</td>
<td>3.9 ± 1.3</td>
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<td>4.4 ± 1</td>
<td>3.7 ± 0.6</td>
<td>10.88 ± 0.68</td>
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Table 1. (Contd.)

<table>
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<tr>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>Elimination half-life (hours)</th>
<th>VolD Area (L/kg)</th>
<th>VolD, Steady state (L/kg)</th>
<th>Clearance (mL/min/kg)</th>
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</thead>
<tbody>
<tr>
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<td>10</td>
<td>Eurofloxacin 34.2</td>
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<td>Eurofloxacin 24.4</td>
<td>3.22</td>
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<tr>
<td>Foals Horses</td>
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<td>Eurofloxacin 30.4</td>
<td>2.56</td>
<td>2.34</td>
<td>0.97</td>
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<tr>
<td>Llamas Oryx</td>
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<td>Eurofloxacin 17.10 ± 0.09</td>
<td>2.49 ± 0.43</td>
<td>2.47 ± 0.04</td>
<td>1.73 ± 0.001</td>
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<td>Joeys Neonatal rabbits</td>
<td>7.5 (IP)</td>
<td>Eurofloxacin 5.01</td>
<td>2.03</td>
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<td>Dogs Dogs</td>
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<td>Cats Cats</td>
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<td>5.4 ± 1.1</td>
<td>1.2 ± 0.2</td>
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</table>

Note: IP = Intraperitoneal

Table 2. Pharmacology/Pharmacokinetics: Other systemic data

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg)/Route, Water temperature Number of doses</th>
<th>Compound measured Absorption half-life (hours)</th>
<th>Peak serum concentration (mcg/mL)</th>
<th>Time to peak serum concentration (hours)</th>
<th>Half-life, terminal (hours)</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPROFLOXACIN</td>
<td>Dogs[114]</td>
<td>10/PO Single Enrofloxacin 0.23 ± 0.07</td>
<td>2.75 ± 0.11</td>
<td>1.72 ± 0.19</td>
<td>6.39 ± 1.49</td>
<td>97</td>
</tr>
<tr>
<td>DIFLOXACIN</td>
<td>Dogs[116]</td>
<td>5/PO Single Enrofloxacin 0.17 ± 0.02</td>
<td>1.84 ± 0.16</td>
<td>0.66 ± 0.05</td>
<td>6.80 ± 0.79</td>
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<tr>
<td>ENROFLOXACIN</td>
<td>Birds[41]</td>
<td>10/IM Single Enrofloxacin 0.23 ± 0.07</td>
<td>2.75 ± 0.11</td>
<td>1.72 ± 0.19</td>
<td>6.39 ± 1.49</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Chickens[50]</td>
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<td>2.45 ± 0.11</td>
<td>1.43 ± 0.02</td>
<td>4.06 ± 0.06</td>
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<td>Chickens[51]</td>
<td>10/PO Single Enrofloxacin 0.92 ± 0.05</td>
<td>1.69 ± 0.08</td>
<td>2.52 ± 0.08</td>
<td>4.29 ± 0.1</td>
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<td>Ducks[42]</td>
<td>10/IM Single Enrofloxacin 0.99 ± 0.08</td>
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<td>8.52 ± 0.84</td>
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<tr>
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<td>Parrots[49]</td>
<td>15/IM Single Enrofloxacin 3.87 ± 0.27</td>
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<td>2.31 ± 0.09</td>
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<tr>
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<td>3/PO Single Enrofloxacin 0.31 ± 0.11</td>
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<td>2.59 ± 0.16</td>
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<tr>
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<td>15/PO Single Enrofloxacin 1.12 ± 0.11</td>
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<td>2.52 ± 0.33</td>
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<tr>
<td></td>
<td>30/PO Single Enrofloxacin 1.69 ± 0.23</td>
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<td>2.74 ± 0.37</td>
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### Table 2. (Contd.)

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<th>Species</th>
<th>Dose (mg/kg)/Route, Water temperature</th>
<th>Number of doses</th>
<th>Compound measured</th>
<th>Absorption half-life (hours)</th>
<th>Peak serum concentration (mcg/mL)</th>
<th>Time to peak serum concentration (hours)</th>
<th>Half-life, terminal (hours)</th>
<th>Bioavailability (%)</th>
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<tbody>
<tr>
<td><strong>Camels</strong></td>
<td>2.5/IM</td>
<td>Single</td>
<td>Enrofloxacin</td>
<td>0.76 ± 0.46</td>
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<td>6.36 ± 2.03</td>
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<td>Enrofloxacin</td>
<td>Not detected</td>
<td></td>
<td>1</td>
<td>10.58 ± 6.78</td>
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<tr>
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<td>2.5/SC</td>
<td>Every 24 hours  for 10 days</td>
<td>Enrofloxacin</td>
<td>0.2 ± 0</td>
<td>1.67 ± 0.11</td>
<td>0.6 ± 0.1</td>
<td>2.3 ± 0.5</td>
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<tr>
<td><strong>Cats</strong></td>
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<td>Enrofloxacin</td>
<td>0.5 ± 0.12</td>
<td>1.23 ± 0.27</td>
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<td>10 ± 8.5</td>
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<td>Not detected</td>
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<td>1</td>
<td>10.58 ± 6.78</td>
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<td>2.5/SC</td>
<td>Single</td>
<td>Enrofloxacin</td>
<td>0.5 ± 0.12</td>
<td>1.23 ± 0.27</td>
<td>1</td>
<td>10.58 ± 6.78</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>5/IM</td>
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<td>&gt; 3</td>
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<td>0.25 (from graph)</td>
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<td>100</td>
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<tr>
<td></td>
<td>5/PO</td>
<td>Single</td>
<td>Enrofloxacin</td>
<td>1.5 (from graph)</td>
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<td>&gt; 3</td>
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<td>100</td>
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<td><strong>Dogs</strong></td>
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<td>Enrofloxacin</td>
<td>0.2 ± 0.12</td>
<td>1.67 ± 0.11</td>
<td>0.6 ± 0.1</td>
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<td>100</td>
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<td><strong>Pacu</strong></td>
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<tr>
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<td>Ciprofloxacin</td>
<td>0.3 ± 0.03</td>
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<td>1.8 ± 0.6</td>
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<td>5/PO</td>
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<td>Enrofloxacin</td>
<td>0.27</td>
<td>6.44 ± 0.46</td>
<td>0.54 ± 0.06</td>
<td>12.5 ± 0.46</td>
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<td><strong>Trout</strong></td>
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<td>Enrofloxacin</td>
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<td>6.44 ± 0.46</td>
<td>0.54 ± 0.06</td>
<td>12.5 ± 0.46</td>
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<td>0.97 ± 0.6</td>
<td>1.8 ± 0.6</td>
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<td>Ciprofloxacin</td>
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<td>Enrofloxacin</td>
<td>0.02 ± 0.008</td>
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<td>2.25 ± 0.09</td>
<td>2.61 ± 0.15</td>
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<td>Ciprofloxacin</td>
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<td><strong>Sheep</strong></td>
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<td>Every 12 hours  for 15 days</td>
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<td>0.8 ± 1.17</td>
<td>2.62 ± 0.61</td>
<td>1 ± 0.35</td>
<td>57</td>
<td>100</td>
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<td></td>
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<td>Every 12 hours  for 3 days</td>
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<td>0.8 ± 1.17</td>
<td>2.62 ± 0.61</td>
<td>1 ± 0.35</td>
<td>57</td>
<td>100</td>
</tr>
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<td>Enrofloxacin</td>
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<td>0.37 ± 0.02</td>
<td>0.3 ± 0.03</td>
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<tr>
<td><strong>Pigs</strong></td>
<td>2.5/IM</td>
<td>Single</td>
<td>Enrofloxacin</td>
<td>1.4 ± 0.5</td>
<td>4.8 ± 1.9</td>
<td>83</td>
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<td>100</td>
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<tr>
<td><strong>Pythons</strong></td>
<td>5/IM</td>
<td>Single</td>
<td>Enrofloxacin</td>
<td>1.66 ± 0.42</td>
<td>5.75 ± 1.47</td>
<td>6.37</td>
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<tr>
<td><strong>Rabbits</strong></td>
<td>5/IM</td>
<td>Single</td>
<td>Ciprofloxacin</td>
<td>0.35 ± 0.21</td>
<td>13 ± 5.9</td>
<td>83</td>
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<td><strong>Sheep</strong></td>
<td>2.5/IM</td>
<td>Single</td>
<td>Enrofloxacin</td>
<td>0.07 ± 0.02</td>
<td>3.04 ± 0.34</td>
<td>0.17</td>
<td>1.81 ± 0.3</td>
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<td>Single</td>
<td>Ciprofloxacin</td>
<td>0.17 ± 0.04</td>
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<td>2.25 ± 0.11</td>
<td>3.65 ± 0.11</td>
<td>85</td>
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<td>5/IM</td>
<td>Single</td>
<td>Ciprofloxacin</td>
<td>0.17 ± 0.04</td>
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<td>2.25 ± 0.11</td>
<td>3.65 ± 0.11</td>
<td>85</td>
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<tr>
<td><strong>MARBOFLOXACIN</strong></td>
<td><strong>Cats</strong></td>
<td>6.2/PO</td>
<td>Single</td>
<td>4.8 ± 0.7</td>
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<td>12.7 ± 1.1</td>
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<td></td>
<td><strong>Dogs</strong></td>
<td>1/PO</td>
<td>Single</td>
<td>0.38 ± 0.35</td>
<td>0.83 ± 0.26</td>
<td>1.7 ± 1.2</td>
<td>14.7 ± 4.9</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td><strong>Dogs</strong></td>
<td>2/PO</td>
<td>Single</td>
<td>0.53 ± 0.24</td>
<td>1.38 ± 0.40</td>
<td>2.5 ± 1.2</td>
<td>14.0 ± 4.9</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td><strong>Dogs</strong></td>
<td>4/PO</td>
<td>Single</td>
<td>0.68 ± 0.59</td>
<td>2.93 ± 0.58</td>
<td>2.0 ± 1.1</td>
<td>12.5 ± 2.7</td>
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</table>
Table 2. (Contd.)

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg)/Route, Water temperature</th>
<th>Number of doses</th>
<th>Compound measured</th>
<th>Absorption half-life (hours)</th>
<th>Peak serum concentration (mcg/mL)</th>
<th>Time to peak serum concentration (hours)</th>
<th>Half-life, terminal (hours)</th>
<th>Bioavailability (%)</th>
</tr>
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<tbody>
<tr>
<td>Dogs</td>
<td>1/SC</td>
<td>Single</td>
<td>0.20 ± 0.11</td>
<td>0.78 ± 0.08</td>
<td>1.0 ± 0.6</td>
<td>11.5 ± 1.9</td>
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<td>2/SC</td>
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<td>1.52 ± 0.13</td>
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<td>13.0 ± 1.3</td>
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<td>4/SC</td>
<td>Single</td>
<td>0.25 ± 0.12</td>
<td>3.04 ± 0.24</td>
<td>1.3 ± 0.61</td>
<td>13.4 ± 2.8</td>
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<tr>
<td>[R-113]</td>
<td>2/PO</td>
<td>Single</td>
<td>1.47 ± 0.09</td>
<td>1.83 ± 0.17</td>
<td>9.07 ± 1.90</td>
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<tr>
<td></td>
<td>2/PO</td>
<td>Every 24 hours</td>
<td>for 8 days</td>
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<tr>
<td>[R-100]</td>
<td>2.7/PO</td>
<td>Single</td>
<td>2.0 ± 0.2</td>
<td>1.5 ± 0.3</td>
<td>10.7 ± 1.6</td>
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<tr>
<td></td>
<td>5.6/PO</td>
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<td>4.2 ± 0.5</td>
<td>1.8 ± 0.3</td>
<td>10.9 ± 0.6</td>
<td>94</td>
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<td><strong>ORBIFLOXACIN</strong></td>
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<td></td>
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<td>Cuts [R-98]</td>
<td>2.5/PO</td>
<td>Single</td>
<td>2.06 ± 0.6</td>
<td>1 ± 0.45</td>
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<tr>
<td>[R-113]</td>
<td>2.5/PO</td>
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<td>2.3 ± 0.3</td>
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<td>5.6 ± 1.1</td>
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<tr>
<td>[R-113]</td>
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<td>1.37 ± 0.01</td>
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<td>Maries</td>
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<td>2.41 ± 0.03</td>
<td>1.5</td>
<td>9.06 ± 1.33</td>
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</tbody>
</table>

Note IM=Intramuscular administration, PO=Oral administration, SC=Subcutaneous administration.

*These agar plate diffusion assays used bacillus subtilis or Klebsiella pneumoniae as the test organism and, therefore, measured enrofloxacin, ciprofloxacin, and any other unidentified metabolites with antimicrobial activity against it.

REFERENCES

86. Panel comment, Rec 8/5/99.
89. Panel comment, Rec 7/21/99.
93. Panel consensus, 1/6/00.
103. Panel consensus, 1/6/00.
112. Panel consensus, 1/6/00.
120. Panel comment, Rec 12/29/99.
121. Panel consensus, 1/6/00.
130. Panel consensus, 1/6/00.
133. New breakpoints of enrofloxacin (dogs/cats) approved by NCCLS. Bayer Animal Health paper.
145. Manufacturer comment, Rec 6/26/02.
LINCOMYCIN has been shown to have efficacy against many gram-positive bacteria and many anaerobic bacteria, but are not effective against most gram-negative organisms.

Lincomycin has been shown to have efficacy against Staphylococcus species, Streptococcus species (except Streptococcus faecalis), Erysipelothrix insidiosa, Leptospira pomona, and Mycoplasma species. The activity of lincomycin against obligate anaerobes is seldom addressed in published literature. According to the National Committee for Clinical Laboratory Standards in the United States, lincomycin is the class antibiotic for the lincosamide family and the lincomycin disk is used in in vitro testing to assess susceptibility to both clindamycin and lincomycin. Therefore, it is presumed that most anaerobes susceptible to clindamycin would likewise be susceptible to lincomycin, provided compensations for potency and kinetic disposition are made.

Clindamycin has a spectrum of activity that includes Staphylococcus species, Streptococcus species (except Streptococcus faecalis), and Mycoplasma species, as well as anaerobic organisms, such as Bacteroides species, Fusobacterium species, Clostridium perfringens (but not necessarily other clostridia), Actinomyces species, Peptostreptococcus species, and many Propionibacterium species.

### INDICATIONS

Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**Note:** For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

**CATEGORY:**
Antibacterial (systemic).

**GENERAL CONSIDERATIONS**

The lincosamides have a spectrum of activity that includes Staphylococcus species, Streptococcus species (except Streptococcus faecalis), and Mycoplasma species, as well as anaerobic organisms, such as Bacteroides species, Fusobacterium species, Clostridium perfringens (but not necessarily other clostridia), Actinomyces species, Peptostreptococcus species, and many Propionibacterium species.

### ACCEPTED

**Dysentery, swine (treatment)—**Pigs: Lincomycin hydrochloride for medicated feed and soluble powder are indicated in the treatment and control of swine dysentery caused by susceptible organisms.

**Enteritis, necrotic (treatment)—**Chickens: Lincomycin hydrochloride for medicated feed and soluble powder are indicated in the control of necrotic enteritis in chickens caused by susceptible organisms, such as Clostridium perfringens.

**Growth promotion and feed efficiency, increased—**Chickens and pigs:

Lincomycin hydrochloride for medicated feed is indicated for increased weight gain in growing-finishing pigs and for increased weight gain and feed efficiency in broiler chickens.

**Joint infections (treatment)—**Pigs: Lincomycin injection is indicated in the treatment of infectious arthritis caused by susceptible organisms, including susceptible Staphylococcus species, Streptococcus species, Erysipelothrix rhusiopathiae, and Mycoplasma species.

**Metritis (treatment)**—Dogs: Lincomycin injection, syrup, and tablets are indicated in the treatment of metritis caused by susceptible organisms.

**Osteomyelitis (treatment)—**Dogs: Clindamycin capsules and oral solution are indicated in the treatment of osteomyelitis caused by susceptible organisms, such as Staphylococcus aureus.

**Periodontal infections (treatment)—**

**Cats:**

Clindamycin oral solution is indicated in the treatment of periodontal infections caused by susceptible bacteria.

**Dogs:**

Clindamycin capsules and oral solution are indicated in the treatment of periodontal infections caused by susceptible bacteria.

**Porcine proliferative enteropathies (treatment)**—Pigs: Lincomycin hydrochloride for medicated feed is indicated in the control of porcine proliferative enteropathies (ileitis) caused by Lawsonia intracellularis.

**Pneumonia, bacterial (treatment)—**Pigs: Lincomycin injection and lincomycin hydrochloride for medicated feed are indicated in the treatment of pneumonia caused by susceptible Mycoplasma species.

**Respiratory tract infections (treatment)**—

**Cats:**

Lincomycin injection, syrup, and tablets are indicated in the treatment of respiratory tract infections caused by susceptible organisms.

**Dogs:**

Lincomycin injection, syrup, and tablets are indicated in the treatment of respiratory tract infections caused by susceptible organisms.

**Skin infections (treatment)**—Dogs: Lincomycin injection, syrup, and tablets are indicated in the treatment of skin infections, such as purulent dermatitis, caused by susceptible organisms. To assure efficacy in the treatment of skin infections, underlying primary disorders, such as allergic inhalant dermatitis, should be identified and controlled.

**Soft tissue infections (treatment)—**

**Cats:**

Clindamycin oral solution and lincomycin injection, syrup, and tablets are indicated in the treatment of soft tissue infections, including abscesses, caused by susceptible organisms.

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ACCEPTANCE NOT ESTABLISHED

Metritis (treatment)—Dogs: There are insufficient data to confirm specifically the efficacy of [clindamycin]¹ in the treatment of metritis in dogs; however, because lincomycin is indicated for this use, clindamycin can be expected to be at least equally effective.⁰¹⁵

Osteomyelitis (treatment)—[Cats]¹: There are insufficient data to confirm specifically the efficacy of clindamycin in the treatment of osteomyelitis in cats; however, the safety and predicted antimicrobial efficacy are supported by research.⁰¹⁶—⁰¹⁸

Respiratory tract infections (treatment)—Cats and dogs: There are insufficient data to confirm specifically the efficacy of [clindamycin]¹ in the treatment of respiratory infections in cats and dogs; however, because lincomycin is indicated for this use, clindamycin can be expected to be at least equally effective.⁰¹⁴—⁰¹⁵

Abscesses, laryngeal (treatment)¹—Cattle: There are insufficient data to confirm the efficacy and safety of lincomycin injection in the treatment of laryngeal abscesses in cattle. Reports of three cases showed a good response in laryngeal abscesses treated⁰⁴⁴

Arthritis, septic (treatment)¹—Cattle and sheep: There are insufficient data to confirm the efficacy and safety of lincomycin injection in the treatment of septic arthritis in cattle and sheep. Case reports of a dozen cases show a resolution of clinical signs in approximately one-half of refractory joint infections treated (mixed infections of streptococci, staphylococci, and Corynebacterium pyogenes).⁰⁴⁴

Mastitis (treatment)¹—Cattle: There are insufficient data to confirm the efficacy and safety of parenteral lincomycin in the treatment of caseous mastitis in cattle; however, there is evidence of distribution into milk in ruminants in concentrations sufficient to treat susceptible infections that are refractory to other antimicrobials.⁰¹⁴—⁰¹⁵ Although no studies have been performed to demonstrate the efficacy of lincomycin against gram-positive mastitis pathogens such as Staphylococcus or Corynebacterium, given lincomycin’s distribution and the susceptibility patterns of these organisms, lincomycin therapy may be a legitimate choice when other conventional treatments are deemed unlikely to be effective.

Toxoplasmosis (treatment)¹—Cats: There are insufficient data to establish the efficacy of clindamycin in the treatment of Toxoplasma gondii infection in cats; however, it is considered to have fewer side effects and perhaps to be more effective in treating some aspects of the disease than is pyrimethamine.⁰¹⁷—⁰¹⁹ Clindamycin may not effectively clear organisms from areas such as the central nervous system in chronically infected animals⁰¹⁸ and, in some cases, may be ineffective in resolving clinical signs involving the eye.⁰¹⁷

¹Not included in Canadian product labeling or product not commercially available in Canada.

REGULATORY CONSIDERATIONS

U.S.—Withdrawal times have been established for the use of lincomycin in chickens and pigs (see the Dosage Forms section). Lincomycin is not labeled for use in chickens producing eggs for human consumption.⁰⁴ ⁰⁴²

Canada—Withdrawal times have been established for the use of lincomycin in chickens and pigs (see the Dosage Forms section). Lincomycin is not labeled for use in chickens producing eggs for human consumption.⁰⁶ ⁰⁴¹

CHEMISTRY

Source:
Clindamycin hydrochloride—7-(3-S)-Chloro derivative of lincomycin.⁰²⁷
Lincomycin hydrochloride—Produced by the growth of a member of the lincolnensis group of Streptomyces lincolnensis (family Streptomycetaceae).⁰¹

Chemical name:
Clindamycin hydrochloride—7,8-diα-3-galacto-octopyranosido-6,12-dideoxy-6-[[1-(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-2-trans-monomohydrochloride.⁰²⁵

Molecular formula:
Clindamycin hydrochloride—C₁₉H₂₁CLN₂O₁₀SHCl • H₂O.⁰²⁵

Molecular weight:
Clindamycin hydrochloride—461.44.⁰²⁵
Lincomycin hydrochloride—461.01.⁰²⁵

Description:
Clindamycin Hydrochloride USP—White or practically white, crystalline powder. Is odorless or has a faint mercaptan-like odor. Is stable in the presence of air and light. Its solutions are acidic and are dextrorotatory.⁰²⁶
Lincomycin Hydrochloride USP—White or practically white, crystalline powder. Is odorless or has a faint odor. Is stable in the presence of air and light. Its solutions are acid and are dextrorotatory.⁰²⁶
Lincomycin Hydrochloride Injection USP—Clear, colorless to slightly yellow solution, having a slight odor.⁰²⁶

pKa:
Clindamycin—7.2⁰¹⁴
Lincomycin—7.6⁰¹⁴

Solubility:
Clindamycin Hydrochloride USP—Freely soluble in water, in dimethylformamide, and in methanol; soluble in alcohol; practically insoluble in acetone.⁰²⁶
Lincomycin Hydrochloride USP—Freely soluble in water; soluble in dimethylformamide: very slightly soluble in acetone.⁰²⁶

PHARMACOLOGY/PHARMACOKINETICS

Mechanism of action/effect: The lincosamides inhibit protein synthesis in susceptible bacteria by binding to the 50 S ribosomal subunits of bacterial ribosomes and preventing peptide bond formation.⁰⁴³ The lincosamides are usually considered bacteriostatic,⁰⁴³ however, when clindamycin is present at sufficient concentrations, it may act as a bactericidal antibiotic against sensitive organisms.⁰⁴³

Other actions/effects: Clindamycin may interfere with the attachment and entry of Toxoplasma gondii tachyzoites into host cells.⁰³³

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**Absorption:** Oral absorption of the lincosamides is rapid, but orally administered lincomycin is less well absorbed than clindamycin. Clindamycin—Oral absorption of clindamycin is high and is unaffected by food. Lincomycin—Oral absorption of lincomycin may be greatly reduced by the presence of food in the stomach.  

*Oral absorption:*  
- **Pigs:** 20 to 50%.  
- **Rats:** 45 to 60%.  
- **Intramuscular absorption:** Lincomycin hydrochloride is rapidly absorbed after intramuscular administration.  

**Distribution:** Clindamycin and lincomycin are widely distributed into most tissues, including respiratory tissue, soft tissue, bones, and joints. The lincosamides are weak bases (commercial preparations are acidic) and are very lipid soluble at physiologic pH (7.4). Tissue concentrations may be higher than serum concentrations. Small amounts are distributed into pancreatic and prostatic secretions. There is evidence that clindamycin hydrochloride accumulates in polymorphonuclear granulocytes. The lincosamides do not penetrate cerebrospinal fluid (CSF) well; however, in healthy cats, concentrations of clindamycin in brain tissue after 10 days of therapy were 10 to 20% of serum concentration and were consistently higher than CSF concentrations.  

*Volume of distribution (area)—Intravenous administration:*  
- **Clindamycin phosphate—Dogs:** 1.4 L per kg (L/kg).  
- **Lincomycin—Calves:** 6 weeks of age—1 to 1.2 L/kg (healthy calves or calves with induced Pasteurella haemolytica pneumonia).  
- **9 months of age—1.3 L/kg.**  

**Protein binding:**  
- **Clindamycin—Sheep:** Moderate (40 to 50%).  
- **Lincomycin—Cows:** Low to moderate (26 to 46%).  
- **Sheep:** Low (30 to 40%).  

Note: Human protein binding of lincomycin decreases with increased plasma concentrations; the range of protein binding varies from low to high.  

**Biotransformation:**  
- **Clindamycin—Active metabolites of clindamycin measured in urine along with parent compound include N-demethylclindamycin and clindamycin sulfoxide.**  
- **Lincomycin—The percentage of administered lincosamide metabolized by the liver is unknown.**  

**Half-life:** Elimination—Intravenous administration:  
- **Clindamycin phosphate—Dogs:** 3.2 hours.  
- **Lincomycin:**  
  - **Calves,** newborn to 2 weeks of age—3 hours.  
  - **Calves,** 4 weeks to 9 months of age—2 to 2.5 hours.  

**Time to peak concentration:**  
- **Clindamycin hydrochloride—**  
  - **Dogs:** Oral—1.3 hours (single dose of 5.5 to 11 mg per kg of body weight [mg/kg]).  
  - **Sheep:** Intramuscular—1 hour (dose of 20 mg/kg).  
- **Lincomycin hydrochloride—**  
  - **Dogs:** Intramuscular—1 hour (dose of 11 mg/kg).  
  - **Oral—2 to 4 hours (dose of 22 mg/kg).**  
  - **Sheep:** Intramuscular—1 hour (dose of 20 mg/kg).  

**Serum concentrations:**  
- **Peak serum concentration—**  
  - **Clindamycin hydrochloride—**  
    - **Sheep:** Intramuscular: 13.8 mcg/mL (single dose of 20 mg/kg).  
  - **Clindamycin phosphate—**  
    - **Dogs:** Intramuscular: 5.3 mcg/mL (dose of 11 mg/kg).  
  - **Lincomycin—**  
    - **Sheep:** Intramuscular: 12.6 mcg/mL (dose of 20 mg/kg).  

- **Serum concentration after multiple dosing—Clindamycin hydrochloride** (sample 12 hours after the last dose of an every-twelve-hour oral dose for 10 days):  
  - **Cats—**  
    - 3.5 mcg/mL (dose of 5.5 mg/kg).  
    - 5.4 mcg/mL (dose of 11 mg/kg).  
    - 6.5 mcg/mL (dose of 22 mg/kg).  

**Duration of action:**  
- **Clindamycin—**  
  - **Cats and dogs—**  
    - 12 hours, with an oral dose of 11 mg/kg.  
    - 24 hours, with an oral dose of 22 mg/kg.  
- **Lincomycin—**  
  - **Dogs—**  
    - Oral—For gram-positive organisms: 6 to 8 hours (22 mg/kg dose).  

Note: Efficacy studies based on a 22 mg/kg dose every 12 hours for 3 weeks in dogs show that duration of action for lincomycin is sufficient for it to be effective when administered every twelve hours.  

**Elimination:**  
- **Parent drug and metabolites are primarily excreted in the urine and bile.** Small amounts are excreted in intestinal contents and pancreatic and prostatic fluids. When lincomycin is administered orally to dogs, 77% of the dose is excreted in the feces and 14% of the dose is excreted in the urine. When administered intramuscularly, 38% of the dose is excreted in the feces and 49% is excreted in the urine.  

- **Less clindamycin than lincomycin is excreted in the urine.**  

**Clearance—Intravenous administration:**  
- **Clindamycin phosphate—**  
  - **Dogs:** 5.3 ml per minute per kg (ml/min/kg).  
- **Lincomycin—**  
  - **Calves:**  
    - 6 weeks of age—3.9 to 8.1 ml/min/kg.  
    - 9 months of age—4.4 ml/min/kg.  

**PRECAUTIONS TO CONSIDER**  
**CROSS-SENSITIVITY AND RELATED PROBLEMS**  
Animals sensitive to clindamycin may be sensitive to lincomycin and the reverse may also be true.  

**SPECIES SENSITIVITY**  
*Chinchillas, guinea pigs, hamsters, horses, ponies, and rabbits.* The use of oral clindamycin or lincomycin is generally contraindicated in
these species because of the risk of altering the gastrointestinal microflora and causing serious or fatal enterocolitis and diarrhea. Overgrowth of organisms such as Clostridium or Salmonella species has been suspected as the cause in many species. Cecal Escherichia coli, but not Clostridium species, have been cultured from rabbits showing adverse effects after lincomycin exposure.[R-9] Contamination of feed with lincomycin at or below feed additive concentrations used for pigs has caused severe or fatal diarrhea in rabbits, ponies, and horses.[R-7–9]

**Ruminants:** Ruminants exposed to oral lincomycin have also been reported to have side effects such as anorexia, ketosis, and sometimes severe diarrhea,[R-10; 12; 55] possibly caused by overgrowth of nonsusceptible bacteria; however, case reports and research studies using parental lincomycin have reported that only a small percentage of treated animals developed diarrhea and/or decreased milk production.[R-44–47]

Feeds contaminated with 3 to 24 parts per million (ppm) of lincomycin have caused ketosis and diarrhea in dairy cows.[R-12]. After treatment with oral lincomycin for Campylobacter, two thirds of a range flock of sheep died; however, the flock had a history of Salmonella infections and grazed in an area with some oxalate-containing range plants, both of which were believed to play a role in the losses.[R-10]

**PREGNANCY/REPRODUCTION**
The safety of clindamycin in pregnant or breeding animals has not been established.[R-1; 2; 13]

When lincomycin was given to pregnant dogs at 50 mg per kg of body weight (mg/kg) per day, no evidence of teratogenic effects on the embryos was seen.[R-3] Also, 75 mg of lincomycin per kg a day administered to breeding male and female rats during a breeding cycle had no observed effect on breeding or teratogenic effects on offspring.[R-3]

**LACTATION**
Clindamycin and lincomycin are distributed into milk.[R-14] With constant serum lincomycin concentrations, milk concentrations range from 2.5 to 6.2 times the serum concentration, depending on the pH of the milk.[R-14]

**PEDIATRICS**
No evidence of side effects was noted in newborn puppies and rats given lincomycin at doses of 30 to 90 mg/kg a day.[R-3]

**DRUG INTERACTIONS AND/OR RELATED PROBLEMS**
The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

*Anesthetics, hydrocarbon inhalation, such as:
  - Enflurane
  - Halothane
  - Isoflurane
  - Methoxyflurane, or

  - Neuromuscular blocking agents
    (concurrent use of these medications with clindamycin or lincomycin may enhance the neuromuscular blockade, resulting in respiratory depression or paralysis;[R-1; 48] caution is also recommended during surgery or the postoperative period; treatment with cholinesterase agents or calcium salts may help reverse the blockade[R-48])

**HUMAN DRUG INTERACTIONS**[R-61]
In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monographs Clindamycin (Systemic) and Lincomycin (Systemic) in USP DI Volume II; these drug interactions are intended for informational purposes only and may or may not be applicable to the use of clindamycin and lincomycin in the treatment of animals:

- **Antidiarrheals, adsorbent**
  (concurrent use of kaolin- or attapulgite-containing antidiarrheals with oral lincomycin may significantly decrease absorption of oral lincomycin; concurrent use with oral clindamycin may delay absorption; concurrent use should be avoided or patients should be advised to take adsorbent antidiarrheals not less than 2 hours before or 3 to 4 hours after oral lincosamides)

- **Antidiarrheals, antiperistaltic**
  (antiperistaltic agents, such as opiates, diphenoxylate, or loperamide, may prolong or worsen pseudomembranous colitis by delaying toxin elimination)

- **Antimyasthenics**
  (concurrent use of medications with neuromuscular blocking action may antagonize the effect of antimyasthenics on skeletal muscle; temporary dosage adjustments of antimyasthenics may be necessary to control symptoms of myasthenia gravis during and following concurrent use)

- **Chloramphenicol or Erythromycins**
  (may displace clindamycin or lincomycin from or prevent their binding to 50 S subunits of bacterial ribosomes, thus antagonizing the effects of the lincosamides; concurrent use is not recommended)

- **Opioid (narcotic) analgesics**
  (respiratory depressant effects of drugs with neuromuscular blocking activity may be additive to central respiratory depressant effects of opioid analgesics, possibly leading to increased or prolonged respiratory depression or paralysis [apnea]; caution and careful monitoring of the patient are recommended)

**LABORATORY VALUE ALTERATIONS**
The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):

Note: No significant laboratory value alterations have been reported in animals. Human laboratory value alterations have been reported and are included in this monograph.

**HUMAN LABORATORY VALUE ALTERATIONS**[R-61]
The following laboratory value alterations have been reported in humans, and are included in the human monographs Clindamycin (Systemic) and Lincomycin (Systemic) in USP DI Volume II; these laboratory value alterations are intended for informational purposes.
only and may or may not be applicable to the use of clindamycin and lincomycin in the treatment of animals:

With physiology/laboratory test values
- Alanine aminotransferase (ALT [SGPT]), serum, and
- Alkaline phosphatase, serum, and
- Aspartate aminotransferase (AST [SGOT]), serum

(values may be increased)

MEDICAL CONSIDERATIONS/CONTRAINDICATIONS
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

Risk-benefit should be considered when the following medical problems exist:

- Hepatic function impairment, severe
  (because clindamycin and lincomycin are metabolized by the liver) [R-1; 49], it is possible that severe hepatic function impairment could prolong the half-lives of these medications; adjustments in dosage might be required [R-177]
- Hypersensitivity to clindamycin or lincomycin [R-1; 3]
  (sensitivity or cross-sensitivity may occur)
- Renal function impairment, severe
  (lincomycin is eliminated by the kidneys of dogs to a greater degree than is clindamycin) [R-50]; very severe renal impairment may require dosage adjustments)

PATIENT MONITORING
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

- Culture and susceptibility, in vitro, and
- Minimum inhibitory concentration (MIC)
  (in vitro cultures and MIC tests should be done on samples collected prior to lincosamide administration to determine pathogen susceptibility)

Note: The clindamycin disk is used for in vitro susceptibility testing to assess susceptibility to both clindamycin and lincomycin [R-31].

SIDE/ADVERSE EFFECTS
Note: The pseudomembranous colitis reported in people as an adverse reaction to lincosamides as well as the colitis and diarrhea side effects reported in chinchillas, guinea pigs, horses, rabbits, and ruminants are considered to be caused by overgrowth of resistant organisms. Resistant Clostridium species are suspected, but other organisms or even other mechanisms may also be involved [R-40; 48].

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence more frequent

Chinchillas, guinea pigs, hamsters, horses, ponies, and rabbits [R-7–9; 11]

Enteroocolitis (anorexia; collapse; dehydration; diarrhea, watery and sometimes hemorrhagic)

Incidence less frequent

Cats and dogs

Anorexia; diarrhea; vomiting [R-1; 3; 54]

Note: Anorexia, diarrhea, and vomiting in cats and dogs are believed to result from local irritation because side effects have not been seen with parenteral treatment. Side effects are more likely with higher doses [R-54]

Ruminants

With lincomycin—

Anorexia; decreased milk production; diarrhea; ketosis

Note: Anorexia, decreased milk production, ketosis, and severe diarrhea have been reported to be most likely in ruminants administered lincomycin orally. [R-10; 12] However, some animals may develop adverse effects with parenterally administered lincomycin [R-45]

Incidence unknown
All species

Hypersensitivity reactions [R-1; 3]

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOtherSOME
Incidence more frequent

Cats

Lip smacking—with clindamycin oral solution [R-53]; salivation— with clindamycin oral solution [R-53]

Incidence less frequent or rare

Pigs

Anal swelling [R-41; 42]; diarrhea [R-41; 42]—transient; irritable behavior [R-41; 42]; skin reddening [R-41; 42]

Note: Anal swelling, diarrhea, irritable behavior, and skin reddening are generally self-limiting within 5 to 8 days.

HUMAN SIDE/ADVERSE EFFECTS [R-61]

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monographs Clindamycin (Systemic) and Lincomycin (Systemic) in USP DI Volume 1; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of clindamycin and lincomycin in the treatment of animals:

Incidence more frequent

Gastrointestinal disturbances; pseudomembranous colitis

Incidence less frequent

Fungal overgrowth; hypersensitivity; neutropenia; thrombocytopenia

Indicating possible pseudomembranous colitis and the need for medical attention if they occur after medication is discontinued

Abdominal or stomach cramps and pain, severe; abdominal tenderness; diarrhea, watery and severe, which may also be bloody; fever

OVERDOSE

For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

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CLIENT CONSULTATION
Medication should be administered for the full length of time prescribed. Any signs of anorexia, diarrhea, or vomiting should be reported to the veterinarian.

CLINDAMYCIN

SUMMARY OF DIFFERENCES

Pharmacology/pharmacokinetics: Highly absorbed after oral administration. Absorption is unaffected by the presence of food in the stomach.

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of the clindamycin base (not the hydrochloride salt).

CLINDAMYCIN HYDROCHLORIDE CAPSULES USP

Usual dose:
Osteomyelitis—Dogs: Oral, 11 to 33 mg (base) per kg of body weight every twelve hours.1
Periodontal infections and soft tissue infections—Dogs: Oral, 5.5 to 33 mg (base) per kg of body weight every twelve hours.1
[Skin infections]1—Dogs: Oral, 11 mg (base) per kg of body weight every twenty-four hours.1
Note: The above dose for the treatment of skin infections in dogs is based upon a clinical comparative efficacy study of clindamycin and lincomycin.2

Strength(s) usually available:
U.S. (R-1; 6)—Veterinary-labeled product(s): 25 mg (base) per mL (Rx) [AmTech Clindamycin Hydrochloride Oral Liquid; Antirobe Aquadrops; ClindaCure; Clinda-Guard; Clindrops; generic].

Canada (R-6)—Veterinary-labeled product(s): 25 mg (base) per mL (Rx) [Antirobe Aquadrops].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

USP requirements: Preserve in tight containers. Label oral solution to indicate that it is intended for veterinary use only. Contains the equivalent of the labeled amounts, within ±10%. Meets the requirements for Identification, Uniformity of dosage units, Deliverable volume, and pH (3.0–5.5).1

1Not included in Canadian product labeling or product not commercially available in Canada.

LINCOMYCIN

SUMMARY OF DIFFERENCES
Indications: Indicated in the treatment of swine dysentery; growth promotion and feed efficiency in chickens and pigs; joint infections in pigs; metritis in dogs; pneumonia in pigs; respiratory tract infections in cats and dogs; skin infections in dogs; and soft tissue infections in cats and dogs. Indicated in the control of necrotic enteritis in chickens.

Pharmacology/pharmacokinetics: Oral lincomycin is less well absorbed than intramuscular lincomycin; dosages are adjusted to compensate. Elimination of lincomycin is affected to a greater extent by severe renal
function impairment than is clindamycin. Absorption is reduced by the presence of food in the stomach.

**ORAL DOSAGE FORMS**

Note: The dosing and strengths of the dosage forms available are expressed in terms of lincomycin base (not the hydrochloride salt).

### LINCOMYCIN HYDROCHLORIDE FOR MEDICATED FEED

#### Usual dose:

**Growth promotion—**

**Chickens:** Oral, 2 to 4 grams (base) per ton of feed, fed as the only ration.\(^{[R-18]}\)

**Pigs:** Oral, 20 grams (base) per ton of feed, fed as the only ration.\(^{[R-48]}\)

**Mycoplasma pneumonia—**

**Pigs:** Oral, 200 grams (base) per ton of feed, fed as the only ration for twenty-one days.\(^{[R-18]}\)

**Necrotic enteritis**\(^{1}\)—

**Chickens:** Oral, 2 grams (base) per ton of feed, fed as the only ration.\(^{[R-48]}\)

**Porcine proliferative enteropathies (control)**\(^{1}\)—

**Pigs:** Oral, 100 grams (base) per ton of feed, fed as the only ration for twenty-one days or until signs of disease disappear. A dose of 40 grams (base) per ton of feed, fed as the only ration, may follow the above dose or be used in place of the 100-gram dose in animals that have not yet had symptoms.\(^{[R-18]}\).

**Swine dysentery—**

**Pigs:**

Control—Oral, 40 grams (base) per ton of feed, fed as the only ration.\(^{[R-38; 42]}\)

Treatment—Oral, 100 grams (base) per ton of feed (approximately 4.4 to 8.8 mg [base] per kg of body weight), fed as the only ration for twenty-one days or until signs of disease disappear.\(^{[R-18; 42]}\).

**Strength(s) usually available:**

#### U.S.\(^{[R-6]}\)

Veterinary-labeled product(s):

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 grams</td>
<td>per pound of premix (OTC) [Moorman’s LN 10]</td>
</tr>
<tr>
<td>20 grams</td>
<td>per pound of premix (OTC) [Lincomix 20 Feed Medication]</td>
</tr>
<tr>
<td>50 grams</td>
<td>per pound of premix (OTC) [Lincomix 50 Feed Medication]</td>
</tr>
</tbody>
</table>

#### Canada\(^{[R-6]}\)

Veterinary-labeled product(s):

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 grams</td>
<td>per kg of premix (OTC) [Lincomix 44 Premix; Lincomycin 44 Premix; Lincomycin 44G Premix].</td>
</tr>
<tr>
<td>110 grams</td>
<td>per kg of premix (OTC) [Lincomix 110 Premix; Lincomycin 110 Premix; Lincomycin 110G Premix].</td>
</tr>
</tbody>
</table>

**Withdrawal times:**

#### U.S.\(^{[R-18; 42]}\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>0</td>
</tr>
<tr>
<td>Pigs</td>
<td>0 or 6, depending on product</td>
</tr>
</tbody>
</table>

#### Canada\(^{[R-6]}\)

When mixed at 2.2 grams of lincomycin (base) per metric ton (1000 kg) of feed for chickens and 44 grams (base) of lincomycin per metric ton of feed for pigs:

**Whole withdrawal time:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>0</td>
</tr>
<tr>
<td>Pigs</td>
<td>0 or 6, depending on product</td>
</tr>
</tbody>
</table>

---

**LINCOMYCIN HYDROCHLORIDE SOLUBLE POWDER USP**

#### Usual dose:

**Necrotic enteritis**—

**Chickens:** Oral, 64 mg (base) per gallon of water, administered as the only source of drinking water for seven days.\(^{[R-22; 28; 41; 56]}\)

**Swine dysentery**—

**Pigs:** Oral, 250 mg (base) per gallon of water (approximately 8.4 mg [base] per kg of body weight) a day, administered as the only source of drinking water for five to ten days.\(^{[R-28; 41]}\)

**Strength(s) usually available:**

#### U.S.\(^{[R-6]}\)

Veterinary-labeled product(s):

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>per gram of powder (OTC) [Lincomix Soluble Powder; Lincosol Soluble Powder; GENERIC].</td>
</tr>
</tbody>
</table>

**Withdrawal times:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>0</td>
</tr>
<tr>
<td>Pigs</td>
<td>0 or 6, depending on product</td>
</tr>
</tbody>
</table>

---

**Additional information:**

Not for use in breeding swine or laying chickens.\(^{[R-18; 42]}\)

In preparing feeds, appropriate cleanout procedures should be followed to prevent cross-contamination of other feeds.\(^{[R-42]}\)

**USP requirements:** Not in USP\(^{[R-26]}\).
LINCOMYCIN HYDROCHLORIDE TABLETS

Usual dose:

Metritis\(^1\), or
Skin infections\(^1\)—Dogs: Oral, 22 mg (base) per kg of body weight every twelve hours or 15.4 mg (base) per kg of body weight every eight hours.\(^{[R-3]}\)
Respiratory tract infections\(^1\)—Cats and dogs: Oral, 22 mg (base) per kg of body weight every twelve hours or 15.4 mg (base) per kg of body weight every eight hours.\(^{[R-3]}\)
Soft tissue infections\(^2\)—Cats and dogs: Oral, 22 mg (base) per kg of body weight every twelve hours or 15.4 mg (base) per kg of body weight every eight hours.\(^{[R-3]}\)

Strength(s) usually available:

U.S.—\(^{[R-3, 6]}\)
Veterinary-labeled product(s):
100 mg (base) (Rx) [Lincoin].
200 mg (base) (Rx) [Lincoin].
500 mg (base) (Rx) [Lincoin].
Canada—\(^{[R-6]}\)
Veterinary-labeled product(s):
Not commercially available.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

LINCOMYCIN HYDROCHLORIDE SYRUP USP

Usual dose:

Metritis\(^1\); or
Skin infections\(^1\)—Dogs: Oral, 22 mg (base) per kg of body weight every twelve hours or 15.4 mg (base) per kg of body weight every eight hours.\(^{[R-3]}\)
Respiratory tract infections\(^1\)—Cats and dogs: Oral, 22 mg (base) per kg of body weight every twelve hours or 15.4 mg (base) per kg of body weight every eight hours.\(^{[R-3]}\)
Soft tissue infections\(^2\)—Cats and dogs: Oral, 22 mg (base) per kg of body weight every twelve hours or 15.4 mg (base) per kg of body weight every eight hours.\(^{[R-3]}\)

Strength(s) usually available:

U.S.—\(^{[R-3, 6]}\)
Veterinary-labeled product(s):
50 mg (base) per mL (Rx) [Lincoin Aquadrops].
Canada—\(^{[R-6]}\)
Veterinary-labeled product(s):
Not commercially available.

Packaging and storage: Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.\(^{[R-3, 4]}\) Store in a tight container.

LINCOMYCIN INJECTION USP

Usual dose:

Joint infections; or
Mycoplasma pneumonia\(^1\)—Pigs: Intramuscular, 11 mg (base) per kg of body weight every twenty-four hours for three to seven days.\(^{[R-4]}\)
Metritis\(^1\); or
Skin infections\(^1\)—Dogs: Intramuscular or intravenous, 22 mg (base) per kg of body weight every twenty-four hours or 11 mg (base) per kg of body weight every twelve hours.\(^{[R-3]}\)
Respiratory tract infections\(^1\); or
Soft tissue infections\(^2\)—Cats and dogs: Intramuscular or intravenous, 22 mg (base) per kg of body weight every twenty-four hours or 11 mg (base) per kg of body weight every twelve hours.\(^{[R-3]}\)

Note: For intravenous administration, the injection should be diluted with 5% glucose or normal saline and administered as a drip infusion.\(^{[R-1]}\)

Note: [Cattle]\(^2\)—Although the safety and efficacy have not been established for treatment of laryngeal abscesses, mastitis, or septic arthritis in cattle, a dose of 5 mg (base) lincomycin per kg of body
weight every twenty-four hours, administered intramuscularly for five to seven days, has been used. For deep-seated or severe infections, a dose of 10 mg (base) per kg of body weight every twelve hours has been recommended.

[Sheep]—Although the safety and efficacy have not been established for treatment of septic arthritis in sheep, cases have been reported that responded to 5 mg (base) per kg of body weight, administered intramuscularly every twenty-four hours for three to five days.

Strength(s) usually available: U.S.

Veterinary-labeled product(s):
- 25 mg (base) per mL (OTC) [Lincomycin Injectable; Lincomycin Sterile Solution; Lincomyx Injectable].
- 100 mg (base) per mL [Lincomycin Injectable [cats and dogs] (Rx); Lincomyx Injectable [pigs] (OTC); Lincomyx Injectable (OTC)].
- 300 mg (base) per mL (OTC) [Lincomycin Injectable; Lincomyx Injectable].

Canada

Veterinary-labeled product(s):
- 100 mg (base) per mL (OTC) [Lincomyx Injectable Solution].

Withdrawal times:

Note: There are no established withdrawal times for cattle or sheep in the United States or Canada because lincomycin is not approved for use in these species.

If lincomycin is administered to cattle at the dose of 5 mg (base) per kg of body weight for four days, evidence has been compiled by the Food Animal Residue Avoidance Databank (FARAD) that suggests a milk withholding time of 96 hours and a meat withdrawal time of 7 days would be sufficient to avoid residues. There is no available information to make recommendations for withdrawal times when lincomycin is administered to cattle concurrently with other medications or when doses greater than 5 mg (base) per kg of body weight every twenty-four hours are administered. Also, no recommendations can be made for withdrawal times when lincomycin is administered to sheep. If it is necessary to administer these doses, extended withdrawal times are recommended.

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>2</td>
</tr>
</tbody>
</table>

Canada

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>2</td>
</tr>
</tbody>
</table>

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I glass. Contains benzyl alcohol as a preservative. Contains an amount of Lincomycin Hydrochloride in Water for Injection equivalent to the labeled amount of lincomycin, within 10% to 20%. Meets the requirements for Bacterial endotoxins, Sterility, pH (3.0–5.5), and Particulate matter, and for Injections.

Developed: 07/17/96
Interim revision: 05/07/97; 10/15/99; 09/30/02; 04/04/03

REFERENCES
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27. Clindamycin package insert (Cleocin HCL, Pharmacia—US), Rev 9/02, Rec 1/14/03.
29. Veterinary Advisory Panel meeting, 2/1/96.
32. DSD comment, 8/91.
40. Panel comment, 11/17/95.
60. Panel comment, 11/28/95.
62. Clindamycin product overview for cats and dogs (Clindamycin, Pharmacia—Canada). Downloaded 2/26/03 from www.pharmaciaah.ca.
63. Lincomycin product overview for poultry and pigs (Lincomix 44, Pharmacia—Canada). Downloaded 2/26/03 from www.pharmaciaah.ca.
MACROLIDES Veterinary—Systemic

This monograph includes information on the following: Azithromycin; Clarithromycin; Erythromycin; Tilmicosin; Tylosin.

Some commonly used brand names are:

For veterinary-labeled products—

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocin-100</td>
<td>Erythromycin Base</td>
</tr>
<tr>
<td>Thiaocyanate</td>
<td></td>
</tr>
<tr>
<td>Erythro-200</td>
<td>Erythromycin Base</td>
</tr>
<tr>
<td>Gallmycinin</td>
<td>Erythromycin Base; Gallmycinin</td>
</tr>
<tr>
<td>Gallmycinin-PFC</td>
<td>Gallmycinin; Gallmycinin-PFC</td>
</tr>
<tr>
<td>Gallmycinin-50</td>
<td>Gallmycinin Base</td>
</tr>
<tr>
<td>Thiaocyanate</td>
<td></td>
</tr>
<tr>
<td>Gallmycinin-100</td>
<td>Gallmycinin Base</td>
</tr>
<tr>
<td>Gallmycin-200</td>
<td>Gallmycin-200 Base</td>
</tr>
<tr>
<td>Gallmycin-PFC</td>
<td>Gallmycin-PFC</td>
</tr>
<tr>
<td>Gallmycin Phosphate</td>
<td>Gallmycin Phosphate</td>
</tr>
<tr>
<td>Gallistat</td>
<td>Gallistat</td>
</tr>
<tr>
<td>Erythrocin</td>
<td>Gallistat Phosphate</td>
</tr>
<tr>
<td>Micotic</td>
<td>Micotic</td>
</tr>
<tr>
<td>Palmitol 90</td>
<td>Palmitol 90</td>
</tr>
<tr>
<td>Palmitol Premix</td>
<td>Palmitol Premix</td>
</tr>
</tbody>
</table>

For human-labeled products—

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocin</td>
<td>Erythromycin Base</td>
</tr>
<tr>
<td>Erythrocin E-C</td>
<td>Erythromycin Ethylsuccinate</td>
</tr>
<tr>
<td>Erythrocin-E-S</td>
<td>Erythromycin Lactobionate; Erythromycin Stearate</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Erythromycin S'</td>
<td>Erythromycin Stearate</td>
</tr>
<tr>
<td>Biaxin</td>
<td>Biaxin</td>
</tr>
<tr>
<td>Biaxin XL</td>
<td>Biaxin XL</td>
</tr>
<tr>
<td>E-Base</td>
<td>E-Base</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Erythrocin</td>
<td>Erythrocin</td>
</tr>
<tr>
<td>Erythrocin Enrup</td>
<td>Erythrocin Enrup</td>
</tr>
<tr>
<td>PC1</td>
<td>Erythrocin Enrup</td>
</tr>
<tr>
<td>Erythrocin Premix</td>
<td>Erythrocin Premix</td>
</tr>
<tr>
<td>Zithromax</td>
<td>Zithromax</td>
</tr>
</tbody>
</table>

Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:

Antibacterial (systemic).

INDICATIONS

Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

GENERAL CONSIDERATIONS

Macrolides are considered bacteriostatic at therapeutic concentrations but they can be slowly bactericidal, especially against streptococcal bacteria; their bactericidal action is described as time-dependent. The antimicrobial action of some macrolides is enhanced by a high pH and suppressed by low pH, making them less effective in abscesses, necrotic tissue, or acidic urine.[R-119] Erythromycin is an antibiotic with activity primarily against gram-positive bacteria, such as Staphylococcus and Streptococcus species, including many that are resistant to penicillins by means of beta-lactamase production. Erythromycin is also active against mycoplasma and some gram-negative bacteria, including Campylobacter and Pasteurella species.[R-1; 10–12] It has activity against some anaerobes, but Bacteroides fragilis is usually resistant. Some strains of Actinomycyes and Chlamydia are inhibited by erythromycin.[R-1; 2] Most Pseudomonas, Escherichia coli, and Klebsiella strains are resistant to erythromycin.[R-2] Cross-resistance to the other macrolides can also occur.[R-1]

Tilmicosin has in vitro activity against gram-positive organisms and mycoplasma and is active against certain gram-negative organisms,[R-51], such as Haemophilus somnus[R-49], Mannheimia (Pasteurella) haemolytica, and Pasteurella multocida.[R-51] However, M. haemolytica is more sensitive than P. multocida to tilmicosin. Other gram-negative organisms tested[R-91], including Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella[R-99], and Serratia species, are very resistant to tilmicosin.[R-91]. Some strains of Actinomycyes also are extremely resistant to tilmicosin.[R-99].

Tylosin has a spectrum of activity similar to that of erythromycin but is more active than erythromycin against certain mycoplasmas[R-51: 105]. Azithromycin, a macrolide labeled for human use, has some advantages over erythromycin in the treatment of infections in animals, including better oral absorption, a longer half-life, and a broader spectrum of activity than erythromycin[R-120; 122]. However, the activity of azithromycin against staphylococci is not as good as that of erythromycin. Azithromycin concentrates in tissues, particularly in leukocytes, macrophages and fibroblasts and is slowly released from leukocytes[R-119; 121]. The intracellular reservoir of azithromycin apparently produces effective drug concentrations in interstitial fluids even after the plasma concentrations have declined below detectable levels; plasma pharmacokinetic parameters have little correlation to the in vivo efficacy of azithromycin. Azithromycin can be delivered to infected tissues and early abscesses via leukocytes[R-119].

Clarithromycin, also labeled for human use, is tolerated better than erythromycin by human patients, has a broader spectrum of activity than erythromycin, and, like azithromycin, it also concentrates in leukocytes. In dogs, clarithromycin has a shorter half-life than erythromycin by human patients, has a broader spectrum of activity than erythromycin; it can be delivered to infected tissues and early abscesses via leukocytes[R-119; 124] and there is limited information for its clinical use in animals.

ACCEPTED

Abscesses, hepatic (prophylaxis)—Cattle: Tylosin phosphate for medicated feed is indicated for reduction in incidence of hepatic abscesses caused by susceptible Fusobacterium necrophorum and Actinomycyes pyogenes.[R-48; 49] Atrophic rhinitis (treatment)—Pigs: Tylosin phosphate for medicated feed is indicated for maintaining weight gain and feed efficiency in the presence of atrophic rhinitis infections.[R-49] Arthritis, infectious (treatment)—Pigs: Tylosin injection is indicated in the treatment of swine arthritis caused by susceptible Mycoplasma hyosynoviae.[R-51; 52] Coryza, infectious (prophylaxis)—Chickens: Erythromycin thiocyanate for medicated feed and [erythromycin phosphate powder for oral solution] are indicated as aids in the prevention of infectious coryza caused by susceptible organisms.[R-9; 54] Coryza, infectious (treatment)—Chickens: Erythromycin phosphate powder for oral solution is indicated as an aid in the control of infectious...
coryza caused by susceptible organisms, including *Haemophilus gallinarum*. \[R-3; 9\]

Diphtheria (treatment)\[3\]—Cattle, beef and nonlactating dairy: Tylosin injection is indicated in the treatment of diphtheria caused by susceptible *Fusobacterium necrophorum*. \[R-51; 52\]

Dysentery, swine (prophylaxis)\[4\]—Pigs: Tylosin phosphate for medicated feed is indicated in the prevention of swine dysentery \[R-48; 49\].

Dysentery, swine (treatment)\[5\]—Pigs: Tylosin phosphate for medicated feed is indicated in the control of swine dysentery caused by susceptible organisms. \[R-48; 49\]

Erysipelas (treatment)\[6\]—Sheep: Tylosin injection is indicated in the treatment of acute swine dysentery caused by susceptible *Treponema hyodysenteriae*, when followed by appropriate feed or water medication. \[R-51; 52\]

Tylosin tartrate powder for oral solution is indicated in the control and treatment of swine dysentery. \[R-50; 66\].

Enteritis (treatment)\[7\]—

Pigs, one week of age or older: Erythromycin injection is indicated in the treatment of scours, caused by susceptible organisms, in young pigs. \[R-7; 111\].

Turkeys: Erythromycin phosphate powder for oral solution is indicated in the control of enteritis (bluecomb) caused by susceptible organisms. \[R-3; 9\].

Enterotoxemia (prophylaxis)\[8\]—Lambs, newborn: Erythromycin injection is indicated in the prevention of enteritis in lambs. \[R-7; 111\].

Erysipelas (treatment)\[9\]—Pigs: Tylosin injection is indicated in the treatment of erysipelas caused by susceptible *Erysipelothrix rhusiopathiae*. \[R-51; 52\]; however, penicillin is considered the primary treatment of choice for this indication. \[R-88\].

Feed efficiency, improvement of 1; or weight gain, increased rate 2—

Chickens, including laying chickens: Tylosin phosphate for medicated feed is indicated for increased rate of weight gain and improving feed efficiency. \[R-49\].

Pigs: Tylosin phosphate for medicated feed is indicated for improving feed efficiency and growth promotion. \[R-48; 49\].

Leptospirosis—Sows, farrowing: Erythromycin injection is indicated in the management of leptospirosis in sows at farrowing time. \[R-7; 111\].

Metritis (treatment)\[10\]—

Cattle, beef and nonlactating dairy: Erythromycin injection and tylosin injection are indicated in the treatment of metritis caused by susceptible organisms. \[R-7; 51; 52; 111\]; however, therapeutic regimens often emphasize evacuation of uterine contents as the primary treatment.

Sows, at farrowing time: Erythromycin injection is indicated in the treatment of metritis caused by susceptible organisms. \[R-7; 111\]; however, therapeutic regimens often emphasize evacuation of uterine contents as the primary treatment.  

Pneumonia, bacterial (treatment)\[11\]—

Cattle: Erythromycin injection is indicated in the treatment of pneumonia and bovine respiratory disease caused by susceptible bacteria, including *Pasteurella multocida*. \[R-6; 7; 111\]

Tylosin injection is indicated in the treatment of pneumonia and bovine respiratory disease caused by susceptible bacteria, including *Pasteurella multocida* and *Actinomyces pyogenes*. \[R-51\].

Tilmicosin injection is indicated in the control of bovine respiratory disease in cattle at high risk for infection and in the treatment of bovine respiratory disease caused by susceptible bacteria, including *Mannheimia haemolytica*. \[R-51\]. In some regions, tilmicosin has been more effective than oxytetracycline in clinical resolution of calf pneumonia. \[R-75\].

Pigs: Erythromycin injection is indicated in the treatment of respiratory syndrome (pneumonia, bronchitis, and rhinitis). \[R-7; 111\].

Tilmicosin for medicated feed is indicated in the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*. \[R-107\]; however, parenteral tilmicosin should not be administered to pigs because of the risk of cardiovascular toxicity. \[R-53\].

Tylosin injection is indicated in the treatment of pneumonia caused by susceptible bacteria, including *P. multocida*. \[R-51; 52\].

[Calfes]: Tilmicosin injection is indicated in Canadian product labeling for the treatment of bovine respiratory disease associated with susceptible *M. haemolytica* or *Pasteurella multocida* during the first 30 days in the feedlot. \[R-65; 112\].

[Foals] 1: Erythromycin is used in the treatment of pneumonia caused by *Rhodococcus equi*. Some clinicians recommend the use of rifampin in combination with erythromycin in the treatment of this infection. \[R-4; 13; 14\]; however, comparative efficacy studies of erythromycin administered with and without rifampin have not been performed. See also *Pneumonia under Acceptance not established* below.

[Calves]: Tilmicosin injection is indicated in Canadian product labeling for the treatment of pneumonic pasteurellosis in lambs associated with susceptible *M. haemolytica*. \[R-6; 5; 112\].

Pododermatitis (treatment)\[12\]—Cattle, beef and nonlactating dairy: Erythromycin injection and tylosin injection are indicated in the treatment of pododermatitis caused by susceptible organisms. \[R-7; 51; 52; 111\].

Proliferative enteropathy, porcine (prophylaxis and treatment)\[13\]—Pigs: Tylosin phosphate for medicated feed is indicated in the prevention and control of porcine proliferative enteropathy (ileitis) associated with susceptible *Lawsonia intracellularis*. \[R-49\].

Respiratory disease, chronic (prophylaxis)\[14\]—Chickens and turkeys: Erythromycin thiocyanate for medicated feed and [erythromycin phosphate powder for oral solution] are indicated as aids in the prevention of chronic respiratory disease. \[R-54\].

Respiratory disease, chronic (treatment)\[15\]—

Chickens, broiler and replacement: Erythromycin thiocyanate for medicated feed and erythromycin phosphate powder for oral solution are indicated in the control of chronic respiratory disease in chickens due to susceptible *Mycoplasma gallisepticum*. \[R-3; 9; 54; 64\].

Tylosin tartrate powder for oral solution is indicated in the control of and as an aid in the treatment of chronic respiratory disease, and tylosin phosphate for medicated feed is indicated as an aid in the control of chronic respiratory disease caused by susceptible *M. gallisepticum*. \[R-49\].

Turkeys: Erythromycin thiocyanate for medicated feed and [erythromycin phosphate powder for oral solution] are indicated for reduction of lesions and to decrease the severity of chronic respiratory disease. \[R-9; 54; 64\].

Respiratory tract infections, bacterial (treatment)\[16\]—

Pigs: Erythromycin injection is indicated in the treatment of respiratory syndrome (bronchitis, pneumonia, and rhinitis). \[R-7; 111\].

Tilmicosin for medicated feed is indicated in the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*. \[R-107\]; however, parenteral tilmicosin should not be administered to pigs because of the risk of cardiovascular toxicity. \[R-53\].

Sheep: Erythromycin injection is indicated in the treatment of upper respiratory tract infections. \[R-7; 111\].
Sinusitis, infectious (treatment)—Turkeys: Tylosin tartrate powder for oral solution is indicated to maintain weight gain and feed efficiency in the presence of infectious sinusitis caused by susceptible *M. galliseptica*.[R-50]

[Enteritis, *Campylobacter* (treatment)]—Dogs: Erythromycin stearate is used in the treatment of diarrhea believed to be caused by susceptible *Campylobacter* species. Erythromycin treatment stops the shedding of *Campylobacter* in the feces; however, shedding often recurs shortly after discontinuation of therapy.[R-10–12] See also Enteritis, *Campylobacter* under Acceptance not established below.

[Pyoderma (treatment)]—Dogs: Erythromycin tablets are used in the treatment of pyoderma caused by susceptible *Staphylococcus* species. However, because drug-induced vomiting is a common side effect of administration, erythromycin is not considered the treatment of choice.[R-42–44]

[Synovitis, infectious (prophylaxis)]—Chickens and turkeys: Erythromycin phosphate powder for oral solution is indicated in the management of infectious synovitis.[R-9].

**ACCEPTANCE NOT ESTABLISHED**

[Chlamydial infections (treatment)]—Cats: There are no clinical studies to document the effectiveness of azithromycin in the treatment of chlamydial infections in cats. In vitro studies and clinical trials of azithromycin in urinary and respiratory tract chlamydial infections in human patients have demonstrated efficacy.[R-31–35; 111] and a pharmacokinetic study of azithromycin in cats allows for prediction of potentially effective dosing regimens.[R-120].

[Colitis, chronic (treatment)]—Dogs: There are insufficient data to establish the efficacy of tylosin in the treatment of chronic colitis in dogs and there is no available information on the mechanism of action for alleviation of colitis. However, tylosin tartrate powder for oral solution has been used in the U.S. in the treatment of chronic colitis in dogs. The use of tylosin in the treatment of colitis is typically reserved for patients that are not responsive to other forms of therapy, such as diet change, and for patients with chronic colitis for which specific causes have been ruled out.[R-84–86; 101; 102]

[Cryptosporidiosis (treatment)]—Cats and dogs: There is no treatment that has been clearly demonstrated to eradicate *Cryptosporidium* species infection in human beings.[R-32; 40] or animals; the zoonotic potential of this organism should be considered. Azithromycin can be administered to shorten the length of time oocysts are shed in cats and dogs; however, there are no clinical studies in these species to document efficacy in the treatment of cryptosporidiosis. There are studies of immunocompromised, human immunodeficiency virus (HIV)-positive patients that show some evidence of the efficacy of azithromycin in prevention, remission, and possibly eradication of infection with long-term administration.[R-41: 97]. Because of insufficient data, it is not possible at this time to recommend long-term dosing regimens that might be useful in the treatment of this infection in cats and dogs.

[Enteritis, *Campylobacter* (treatment)]—Dogs: *In vitro* studies have demonstrated that azithromycin may have up to 6 times the activity of erythromycin against susceptible *Campylobacter* strains, making it a potential treatment for this type of enteritis in dogs; however, no clinical studies have been performed.[R-57; 110].

[Mastitis (treatment)]—Cattle: There are insufficient data to establish the efficacy of systemic erythromycin in the treatment of acute and peracute mastitis caused by susceptible *Staphylococcus* and *Streptococcus* species; however, studies have shown that erythromycin is distributed into milk at antimicrobial concentrations under certain pH conditions and may be clinically effective.[R-45–47].

[Pneumonia, bacterial, (treatment)]—Foals: Although there is insufficient evidence to establish efficacy, pharmacokinetic studies suggest that azithromycin may be as effective as erythromycin, with less frequent dosing and fewer side effects, in the treatment of pneumonia caused by *Rhodococcus equi* in foals.[R-121; 122].

[Respiratory tract infections (treatment)]— Including,

[Bronchitis (treatment)]

[Laryngitis (treatment)]

[Pneumonia (treatment)]

[Tracheobronchitis (treatment)]

[Tracheitis (treatment)]—Cats and dogs: Although at one time Canadian tylosin tablets were available for the treatment of pneumonia and tracheobronchitis,[R-56], and the use of tylosin injection in the treatment of respiratory tract infections in cats and dogs has been approved by the U.S. Food and Drug Administration,[R-108], these uses are not included in United States or Canadian product labeling for tylosin. Studies performed during the original approval process showed that tylosin injection can be effective in the treatment of bronchitis, laryngitis, pneumonia, tracheobronchitis, or tracheitis in dogs and upper respiratory tract infections or pneumonitis in cats when the infection is caused by susceptible organisms.[R-108].

[Rocky Mountain spotted fever]—Dogs: There are insufficient data at this time to establish the efficacy of azithromycin in the treatment of Rocky Mountain spotted fever in dogs. A comparative therapeutic study of induced Rocky Mountain spotted fever in dogs showed that azithromycin, when given for a 3-day treatment regimen, was effective in improving platelet counts, slowing vascular leakage, and reducing fever; however, retinal vascular lesions remained unchanged. Overall, the response was not as good as the administration of doxycycline for 7 days. If azithromycin is administered to dogs for the treatment of Rocky Mountain spotted fever, longer term treatment may be more effective.[R-123–125]

1Not included in Canadian product labeling or product not commercially available in Canada.

**REGULATORY CONSIDERATIONS**

U.S.—

Erythromycin thiocyanate and tylosin tartrate are not labeled for use in chickens or turkeys producing eggs for human consumption.[R-8; 50; 54] Tilmicosin is not labeled for use in female dairy cattle 20 months of age or older,[R-51], veal calves, calves less than 1 month of age, or calves fed an all-milk diet. Tylosin injection is not labeled for use in lactating dairy cattle or preruminating calves.[R-51; 52] Withdrawal times have been established for erythromycin injection, erythromycin phosphate powder for oral solution, erythromycin thiocyanate, tilmicosin phosphate, tylosin injection, tylosin phosphate, and tylosin tartrate (see the Dosage Forms section).

Azithromycin and clarithromycin are not labeled for use in animals.

Canada—

Erythromycin phosphate, erythromycin thiocyanate, and tylosin tartrate are not labeled for use in chickens or turkeys producing eggs for human consumption.[R-8; 9] Neither tilmicosin nor tylosin base injection is labeled for use in lactating dairy cattle.[R-55; 65]
Withdrawal times have been established for erythromycin injection, erythromycin phosphate powder for oral solution, erythromycin thiocyanate, tilmicosin phosphate, tylosin injection, tylosin phosphate, and tylosin tartrate (see the Dosage Forms section).

Azithromycin and clarithromycin are not labeled for use in animals.

**CHEMISTRY**

**Source:**
Azithromycin and clarithromycin—Semisynthetically derived from erythromycin\[R-116; 119\].

Erythromycin—Produced from a strain of *Sarcophytopus erythraeus*\[R-7\].

Tilmicosin—Produced semisynthetically\[R-53\] by chemical modifications of desmycosin\[R-1\].

Tylosin—Produced by a strain of the actinomycete *Streptomyces fradiae*\[R-1\].

**Chemical group:**
Azalide antibiotic, a subclass of macrolides—Azithromycin\[R-116\].

Macrolide antibiotics (macrocyclic lactones)\[R-4; 117\]—Clarithromycin, erythromycin, tilmicosin, and tylosin.

**Chemical name:**
Azithromycin—1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-C-methyl-3-0-methyl-alpha-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[(3,4,6-trideoxy-3(dimethylamino)-beta-D-xylo-hexopyranosyl)oxy], dihydrate, [2R-(2R*, 3S*,4R*,5R*,8R*,10R*,11R*,12S*, 13S*,14R*)] 1\[R-16\].

Clarithromycin—Erythromycin, 6-O-methyl-1\[R-16\].

Erythromycin—Erythromycin 1\[R-16\].

Erythromycin estolate—Erythromycin, 2'-propanoate, dodecyl sulfate (salt)\[R-16\].

Erythromycin ethylsuccinate—Erythromycin 2'-(ethyl butanidoate)\[R-16\].

Erythromycin gluceptate—Erythromycin monoglucoheptonate (salt)\[R-16\].

Erythromycin lactobionate—Erythromycin mono(4-O-beta-D-galactopyranosyl-D-glucoside) (salt)\[R-16\].

Erythromycin stearate—Erythromycin octadecanoate (salt)\[R-16\].

Tilmicosin phosphate—Tylosin, 4'-O-d(2,6-dideoxy-3-C-methyl-alpha-L-ribo-hexopyranosyl)-20-deoxo-20(3,5-dimethyl-1-piperidinyl)-, [20cis, 20trans]- phosphate (1:1) (salt)\[R-16\].

Tylosin—(10E, 12E)-(3R, 4S, 5S, 6R, 8R, 14S, 15R)-14-[(6-deoxy-2, 3-dideoxy-beta-D-allo-heptopyranosyl)oxyethyl]-5-[[3,6-dideoxy-4-O(2,6-dideoxy-3-C-methyl-alpha-L-ribo-hexopyranosyl)-3-dimethylamino-beta-D-glycopyranosyl]oxy]-6-formylmethyl-3-hydroxy-4, 8, 12-trimethyl-9-oxoheptadeca-10, 12-dien-15-olide\[R-100\].

**Molecular formula:**
Azithromycin—C_{38}H_{72}N_{2}O_{12}·2H_{2}O\[R-16\].

Clarithromycin—C_{37}H_{67}NO_{13}\[R-16\].

Erythromycin—C_{36}H_{57}NO_{13}\[R-16\].

Erythromycin estolate—C_{37}H_{72}NO_{14}·C_{13}H_{22}O_{6}·S\[R-16\].

Erythromycin ethylsuccinate—C_{36}H_{57}NO_{13}\[R-16\].

Erythromycin gluceptate—C_{37}H_{72}NO_{13}·C_{13}H_{22}O_{6}\[R-16\].

Erythromycin lactobionate—C_{37}H_{72}NO_{13}·C_{13}H_{22}O_{6}\[R-16\].

Erythromycin stearate—C_{38}H_{71}NO_{13}·C_{13}H_{22}O_{6}\[R-16\].

Tilmicosin phosphate—C_{41}H_{69}NO_{13}·H_{2}O\[R-16\].

Tylosin—C_{46}H_{77}NO_{17}\[R-100\].

**Molecular weight:**
Azithromycin—785.02\[R-16\].

Clarithromycin—747.95\[R-16\].

Erythromycin—733.93\[R-16\].

Erythromycin estolate—1056.39\[R-16\].

Erythromycin ethylsuccinate—862.05\[R-16\].

Erythromycin gluceptate—960.1\[R-16\].

Erythromycin lactobionate—1092.2\[R-16\].

Erythromycin stearate—1018.40\[R-16\].

Tilmicosin phosphate—967.1\[R-16\].

Tylosin—916.1\[R-100\].

**Description:**
Azithromycin dihydrate—White, crystalline powder\[R-116\].

Clarithromycin USP—White to off-white, crystalline powder\[R-22\].

Erythromycin USP—White or slightly yellow, crystalline powder. Is odorless or practically odorless\[R-22\].

Erythromycin Estolate USP—White, crystalline powder. Is odorless or practically odorless\[R-22\].

Erythromycin Ethylsuccinate USP—White or slightly yellow crystalline powder. Is odorless or practically odorless\[R-22\].

Erythromycin Gluceptate—White powder. Is odorless or practically odorless, and is slightly hygroscopic. Its solution (1 in 20) is neutral or slightly acid.

Erythromycin Lactobionate for Injection USP—White or slightly yellow crystals or powder, having a faint odor. Its solution (1 in 20) is neutral or slightly alkaline\[R-22\].

Erythromycin Stearate USP—White or slightly yellow crystals or powder. Is odorless or may have a slight, earthy odor\[R-22\].

Tilmicosin USP—White to off-white amorphous solid\[R-22\].

Tylosin USP—White to buff-colored powder\[R-22\].

**pKa:**
Erythromycin base—8.8\[R-18; 19\].

Tilmicosin—7.4; 8.6\[R-94\].

Tylosin—7.1\[R-5; 58\].

**Solubility:**
Azithromycin—39 mg soluble per mL of water (pH 7.4) at 37 °C\[R-118\].

Clarithromycin USP—Soluble in acetone; slightly soluble in dehydrated alcohol, in methanol, and in acetonitrile; practically insoluble in water. Slightly soluble in phosphate buffer at pH values of 2 to 5\[R-22\].

Erythromycin USP—Slightly soluble in water; soluble in alcohol, in chloroform, and in ether\[R-22\].

Erythromycin Estolate USP—Soluble in alcohol, in acetone, and in chloroform; practically insoluble in water\[R-22\].

Erythromycin Ethylsuccinate USP—Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in polyethylene glycol 400\[R-22\].

Erythromycin Gluceptate—Freely soluble in water, in alcohol, and in methanol; slightly soluble in acetone and in chloroform; practically insoluble in ether.

Erythromycin Lactobionate for Injection USP—Freely soluble in water, in alcohol, and in methanol; slightly soluble in acetone and in chloroform; practically insoluble in ether\[R-22\].

Erythromycin Stearate USP—Practically insoluble in water; soluble in alcohol, in chloroform, in methanol, and in ether\[R-22\].

Tilmicosin USP—Slightly soluble in water and in n-hexane\[R-22\].

Tylosin USP—Freely soluble in methanol; soluble in alcohol, in amyl acetate, in chloroform, and in dilute mineral acids; slightly soluble in water\[R-22\].

Tylosin tartrate—Readily soluble in water, up to 600 mg per mL\[R-61\].
PHARMACOLOGY/PHARMACOKINETICS

Note: See also Table 1, Pharmacology/Pharmacokinetics at the end of this monograph.

Mechanism of action/effect: Bacteriostatic, with potential for a time-dependent bactericidal action, particularly with high concentrations. The macrolides are thought to enter the cell and reversibly bind to the 50S ribosomal subunit, inhibiting translocation of peptides, thereby inhibiting protein synthesis.

Absorption:
Azithromycin—Oral administration: Shown to be fairly well absorbed orally in cats (bioavailability of 58%), dogs (bioavailability of >90%), and foals (bioavailability of 39 to 56%).
Erythromycin—Oral administration:
Many oral erythromycin base preparations are coated to prevent degradation in the stomach. The higher pH of the intestine then permits absorption. However, absorption of enteric-coated and delayed-release dosage forms can be unpredictable in animals.
Erythromycin estolate and erythromycin ethylsuccinate are absorbed as inactive esters from the duodenum and then undergo hydrolysis to the free base. The stearate salt dissociates in the duodenum and is absorbed as the free base. It has been suggested that erythromycin phosphate also dissociates and is absorbed as the free base. Food in the stomach does not seem to affect significantly the absorption of the base or salt.
It is unclear whether any of the oral erythromycin preparations is absorbed more effectively than any other when administered to animals; however, it does appear that oral absorption in horses may be different from human absorption. In horses, oral erythromycin stearate and erythromycin phosphate produced peak plasma concentrations more quickly than did the ester formulations; the effect is the opposite of that seen in human studies.

Distribution:
Tylosin—Intramuscular administration: Bioavailability—Goats: 72.6% (15 mg per kg of body weight [mg/kg] dose).

Distribution:
Widely distributed in the body. Ion trapping and the high lipid solubility of the macrolides generally causes tissue concentrations to be higher (often many times higher) than serum concentrations.
Azithromycin—Tissue concentrations can be as much as 100 times serum concentrations and concentrations in leukocytes can be 200 to 300 times serum concentrations.
Cats: Azithromycin appears to distribute well, although sometimes slowly, into a variety of tissues. High tissue to plasma ratios are produced. In one study, lung, femur, eye, skin, and brain tissue concentrations of azithromycin were still rising when the last sample was taken, 72 hours after the dose.
Dogs: A single dose of azithromycin produced high tissue concentrations, often with a tissue to serum ratio of 100 to 1; azithromycin concentrations in eye and brain tissue exceeded serum concentrations by 20- and 1.2-fold, respectively.

Elimination:
Azithromycin—Oral administration:
Human data: 34 to 57 hours.

Half-life: Azithromycin in leukocytes—Foals: 49.2 hours.

Duration of action:
Tilmicosin—Cattle: Of the total subcutaneous dose administered, 24% has been recovered in the urine and 68% in the feces.

PRECAUTIONS TO CONSIDER

SPECIES SENSITIVITY

Erythromycin:
Cattle—Oral administration of erythromycin phosphate or erythromycin stearate has caused severe diarrhea in ruminating calves.

Because of this adverse effect and poor absorption, oral erythromycin administration in cattle is not recommended.

Horses—In foals treated with erythromycin, mild self-limiting diarrhea may develop. In adult horses, the risk of severe diarrhea makes the use of erythromycin controversial.
Tilmicosin:

All species—To avoid cardiotoxicity, tilmicosin should not be administered intravenously[81].

Human—Injection of tilmicosin may be lethal. Although there is little information on the effects of tilmicosin in people, a variable susceptibility to cardiotoxic reactions in other species warrants caution with human exposure and close monitoring of the cardiovascular system, particularly after accidental injection[81]. A physician should be consulted immediately in cases of accidental injection.[81]

Dogs—In laboratory dogs, tachycardia and decreased cardiac contractility have been noted in response to tilmicosin injection[100].

Goats—Administration of tilmicosin to goats at intramuscular or subcutaneous doses >10 mg per kg of body weight (mg/kg) is likely to lead to toxicity[81; 100].

Horses—Administration of tilmicosin to horses at intramuscular or subcutaneous doses >10 mg/kg is likely to lead to toxicity[81; 100].

Pigs—Injection of tilmicosin into swine can be fatal as a result of cardiovascular toxicity. Administration of epinephrine to treat cardiovascular toxicity due to intravenous tilmicosin administration has been associated with an increased risk of death.[81; 100]

Tilmosin: Horses—Injection of tilmicosin has been fatal to horses.[81; 52]

CROSS-SENSITIVITY AND/OR RELATED PROBLEMS

Patients that are hypersensitive to one macrolide may be hypersensitive to a different macrolide[116, 117].

PREGNANCY/REPRODUCTION

Azithromycin:

Fertility and reproduction—Rats and mice given azithromycin at doses of up to 200 mg/kg a day have shown no evidence of impaired fertility or harm to the fetus[116].

FDA human pregnancy category B.

Clarithromycin:

Fertility and reproduction—Male and female rats administered up to 160 mg/kg a day have shown no effect on estrous cycle, fertility, parturition, or viability of offspring[117].

Pregnancy—Monkeys administered oral doses of 150 mg/kg a day had embryonic loss, which was attributed to marked maternal toxicity at this dose. In utero fetal loss occurred in rabbits given intravenous doses of 33 mg per square meter of body surface area, which is equivalent to 17 times less than the maximum recommended human daily dose.

Clarithromycin was not found to be teratogenic in four rat studies or in two rabbit studies. Two additional studies in a different rat strain demonstrated a low incidence of cardiovascular anomalies at oral doses of 150 mg/kg a day administered during gestation days 6 through 15. Cleft palate was seen at doses of 500 mg/kg a day. Fetal growth retardation was seen in monkeys given an oral dose of 70 mg/kg a day, which produced plasma concentrations that were equivalent to two times the human serum concentrations.

FDA human pregnancy category C[114].

Erythromycin: Erythromycin crosses the placenta; however, there is no evidence of teratogenicity or other effects when female rats are fed erythromycin base during pregnancy.[177] In people, erythromycin estolate has been associated with reversible hepatotoxicity in some women during pregnancy.

Tilmicosin[87] and tilmicosin: Safety in breeding or pregnant animals has not been established.

LACTATION

Clarithromycin is excreted into milk[117]. The distribution of azithromycin into milk has not yet been demonstrated[116].

Erythromycin, tilmicosin, and tilmicosin concentrations in milk can be much higher than concentrations in serum.[26, 72, 74]

In cattle, tilmicosin is distributed into milk at effective antibacterial concentrations for susceptible pathogens, but detectable concentrations in milk are maintained for many weeks (up to 42 days)[87]. Tilmicosin should not be administered to lactating dairy cattle because of impractical withdrawal times[74].

In mastitis-free cattle, systemic tilmicosin is distributed into milk at concentrations that are therapeutic for some mastitis pathogens; however, tilmicosin is distributed into milk more readily as the pH of milk decreases. The pH of mastitic milk can approach 7.4 and decrease the diffusion of tilmicosin, interfering with the medication’s ability to reach therapeutic concentrations in milk against some organisms[79, 80].

PEDIATRICS

In animals up to 1 month of age, the hepatic clearance of macrolides may be slower than in adult animals.[1].

DRUG INTERACTIONS AND/OR RELATED PROBLEMS

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication. Beta-adrenergic antagonists, such as:

Propranolol (propranolol and other beta-adrenergic antagonists exacerbate the negative inotrophy of tilmicosin-induced tachycardia in dogs[51])

» Chloramphenicol or

» Florfenicol or

» Lincosamides or

» Macrolide antibiotics, other (chloramphenicol, florfenicol, and the lincosamides have mechanisms of action similar to the macrolides; they may be prevented from binding, or prevent a macrolide from binding, to the 50 S subunits of bacterial ribosomes; concurrent use is not recommended[81])

» Epinephrine (in pigs, the intravenous administration of epinephrine potentiates the lethality of intravenously administered tilmicosin[51])

Phenobarbital or Medications metabolized by microsomal mixed-function oxidases, other (concurrent use with erythromycin may decrease the effects of these medications because of induction of hepatic microsomal enzymes[87]).
HUMAN DRUG INTERACTIONS

In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monographs Azithromycin (Systemic), Clarithromycin (Systemic), or Erythromycins (Systemic) in USP DI Volume I; these drug interactions are intended for informational purposes only and may or may not be applicable to the use of macrolides in the treatment of animals:

Note: There are no tilmicosin or tylosin products labeled for use in people.

Anticoagulants, coumarin- or indanedione-derivative or Warfarin
(concurrent administration with macrolide antibiotics has been associated with increased anticoagulant effects; prothrombin time should be monitored carefully in patients receiving anticoagulants and macrolides concurrently)

Carbamazepine or
Cyclosporine or
Digoxin or
Hexobarbital or
Phenytoin or
Valproic acid
(concurrent use with macrolide antibiotics has been associated with increased serum concentration of these medications; monitoring of serum concentrations of medications administered concurrently is recommended to avoid toxicity)

Although no clinical cases of toxicity have been reported, concurrent use of oral antibiotics may increase serum digoxin concentrations in some individuals; in these individuals, alteration of gut flora by antibiotics may diminish digoxin conversion to inactive metabolites, resulting in increased serum digoxin concentrations; although limited data are available, this interaction has been reported with oral use of erythromycins, neomycin, and tetracyclines)

Midazolam or
Triazolam
(concurrent use with macrolide antibiotics may decrease the clearance of these medications, increasing the pharmacologic effect of midazolam or triazolam)

Penicillins
(since bacteriostatic drugs may interfere with the bactericidal effect of penicillins in the treatment of meningitis or in other situations in which a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy)

Rifabutin or
Rifampin
(concurrent use of rifabutin with azithromycin causes a 15% decrease in serum concentration of rifabutin
(concurrent use of rifabutin or rifampin with clarithromycin causes a decrease in the serum concentration of clarithromycin by greater than 50%)

Xanthines, such as:
Aminophylline
Caffeine
Oxtriphylline
Theophylline
(concurrent use of the xanthines [except dyphylline] with macrolides may decrease hepatic clearance of xanthines, resulting in increased serum concentrations and/or toxicity; dosage adjustment of the xanthines may be necessary during and after therapy with macrolides)
(concurrent administration of theophylline with clarithromycin has been shown to increase the area under the plasma concentration–time curve [AUC] of theophylline by 17%; monitoring of theophylline serum concentrations is recommended in patients receiving high doses of theophylline or in patients with theophylline serum concentrations in the upper therapeutic range)
(with erythromycin, this effect may be more likely to occur after 6 days of concurrent therapy because the magnitude of theophylline clearance reduction is proportional to the peak serum erythromycin concentrations)

For azithromycin
Antacids, aluminum- and magnesium-containing
(concurrent use with antacids decreases the peak serum concentration [Cmax] of azithromycin by approximately 24%, but has no effect on the area under the plasma concentration–time curve [AUC]; oral azithromycin should be administered at least 1 hour before or 2 hours after aluminum- and magnesium-containing antacids)

For clarithromycin
Pimozide
(concurrent administration of pimozide with clarithromycin has resulted in cardiac arrhythmias, including QTc-interval prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes; fatalities have also occurred; the most likely cause is the inhibition of hepatic metabolism of pimozide by clarithromycin; concurrent use is contraindicated)

Zidovudine
(concurrent administration with clarithromycin causes a decrease in the steady state concentration of zidovudine; doses of clarithromycin and zidovudine should be taken at least 4 hours apart)

For erythromycin
Hepatotoxic medications, other
(concurrent use of other hepatotoxic medications with erythromycin may increase the potential for hepatotoxicity)

Otoxic medications, other
(concurrent use with high-dose erythromycin in patients with renal function impairment may increase the potential for ototoxicity)

LABORATORY VALUE ALTERATIONS

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):

Note: Laboratory value alterations relating specifically to use of macro- lides in animals are rarely described. Human laboratory value alterations have been reported for erythromycin and are included in the following section.

HUMAN LABORATORY VALUE ALTERATIONS

The following laboratory value alterations have been reported in humans, and are included in the human monographs Azithromycin (Systemic), Clarithromycin (Systemic), or Erythromycins (Systemic) in USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may not be applicable to the use of macrolides in the treatment of animals:

Note: There are no tilmicosin or tylosin products labeled for use in people.

For azithromycin
With physiology/laboratory test values
Minimum inhibitory concentration (MIC) (in vitro cultures and MIC tests should be done on samples collected prior to macrolide administration to determine pathogen susceptibility)

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
All species
Allergic reactions—considered rare

Cats and dogs
Gastrointestinal effects (anorexia, diarrhea, vomiting)—particularly with erythromycin

Note: In dogs, it has been shown that intravenous erythromycin produces an increase in the electrical and motor activity of the stomach; this effect most likely occurs through cholinergic pathways. The effect produces an abrupt, powerful increase in gastric motility causing retrograde contractions leading to gastrointestinal effects, such as vomiting and retching. In one survey, 41% of pet owners reported that their dogs (19 of 46) vomited following administration of oral erythromycin stearate. This increase in gastric motility has not been shown to occur in response to tylosin and, although vomiting may occur in response to tylosin administration, it occurs infrequently.

Cattle
Diarrhea—associated with oral erythromycin dosage forms

Horses
Diarrhea, severe—with erythromycin; considered more likely in adult horses

Pigs
Diarrhea, erythema, and pruritis—with tylosin; edema, rectal, and partial anal prolapse—with erythromycin and tylosin

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME
All species
Pain and/or swelling at the site of injection—with subcutaneous injection in cattle; swelling is transient and usually mild

HUMAN SIDE/ADVERSE EFFECTS
In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monographs Azithromycin (Systemic), Clarithromycin (Systemic), or Erythromycins (Systemic) in USP DI Volume I: these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of macrolides in the treatment of animals:

Note: There are no tilmicosin or tylosin products labeled for use in people.

For azithromycin
Incidence more frequent—for injection form only
**Thrombophlebitis**
Incidence less frequent

**Gastrointestinal disturbances**
Incidence rare

**Acute interstitial nephritis; allergic reactions; dizziness; headache; pseudomembranous colitis**

*For clarithromycin*
Incidence less frequent

**Abnormal sensation of taste; gastrointestinal disturbances; headache**
Incidence rare

**Hepatotoxicity; hypersensitivity reaction; pseudomembranous colitis; thrombocytopenia**

*For erythromycin*
Incidence more frequent

**Gastrointestinal disturbances**
Incidence less frequent

**Hepatotoxicity; hypersensitivity; inflammation or phlebitis at the injection site—with parenteral erythromycins only; oral candidiasis; vaginal candidiasis**

**Cardiac toxicity, especially QT prolongation and torsades de points; loss of hearing, usually reversible; pancreatitis**

Note: Hepatotoxicity has been associated rarely with all erythromycin salts, but more frequently with erythromycin estolate. Reports suggest that a hypersensitivity mechanism may be involved. Liver function tests often indicate cholestasis. Symptoms typically appear within a few days to 1 to 2 weeks after the start of continuous therapy and are reversible when erythromycin is discontinued. However, hepatotoxicity reappears promptly on readministration to sensitive patients.

**Loss of hearing** is more likely to occur with administration of high doses (≥ 4 grams per day) in patients with renal or hepatic disease and/or in elderly patients. It appears to be related to high peak plasma concentrations, usually exceeding 12 mcg per mL. Hearing loss is usually reversible, although irreversible deafness has occurred. It occurs 36 hours to 8 days after treatment is started and begins to dissipate within 1 to 14 days after erythromycin is discontinued.

**OVERDOSE**

For more information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

For azithromycin: *Mice and rats*—The LD₅₀ for oral administration is 3000 to 4000 mg/kg.¹

For tilmicosin: Greater susceptibility to toxicity from parenterally administered tilmicosin has been shown in goats, horses, and pigs than in cattle.² In all species tested, the primary toxic effect is cardiotoxicity.²

Intravenous administration of tilmicosin is not recommended for use in any species because an intravenous dose of 10 mg or less per kg of body weight (mg/kg) causes signs of toxicity and, in some cases, death in calves, cattle, goats, horses, and sheep.² Subcutaneous doses of up to 30 mg/kg every 3 days for a total of three doses in cattle have been specified as the highest nontoxic dose in healthy cattle because the mild evidence of myocardial necrosis seen with three 50 mg/kg doses administered 72 hours apart was not found with a 30 mg/kg dosage regimen. Repeated subcutaneous doses of 150 mg/kg every 3 days resulted in one death following the third treatment and one death following the fourth treatment in cattle.² In contrast, three of four pigs administered a 20 mg/kg intramuscular dose of tilmicosin and four of four pigs given a 30 mg/kg dose died. In goats and horses, subcutaneous or intramuscular doses above 10 mg/kg may cause signs of toxicosis.²

Oral tilmicosin caused no ill effects in pigs when they were administered 2000 parts per million (ppm) in the only ration for 42 days or 4000 ppm for 21 days.³ Oral doses of 4 mg/kg a day administered to dogs for up to a year caused no observable adverse effects.³ The median lethal dose of oral tilmicosin in fasted rats is 800 mg/kg and in nonfasted rats is 2250 mg/kg.³

**CLINICAL EFFECTS OF OVERDOSE**

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

*For tilmicosin*—in order of their appearance

**Dogs**

- **Cardiovascular changes, including sinus tachycardia, myocardial depression, and reduced arterial pulse pressure** (tremors, rapid respiration, convulsions, and in severe cases, death)—noted with an intravenous dose of 2.5 mcg/kg.³

**TREATMENT OF OVERDOSE**

*For tilmicosin*: The treatment of tilmicosin-induced cardiotoxicosis is not yet well established. Tachycardia is believed to result in part from stimulation of cardiac beta-receptors. In dogs, this effect is partially blocked by propranolol; however, propranolol also potentiates the decreased cardiac contractility induced by tilmicosin.³ Dobutamine may partially remedy the cardiac depression in dogs.³ Epinephrine potentiated the lethality of intravenously administered tilmicosin in pigs.³

**VETERINARY DOSING INFORMATION**

Activity of the macrolides is highest in tissues and in environments with elevated pH.⁴ Organisms that develop resistance to one macrolide antibiotic may also be resistant to other macrolide antibiotics; this cross-resistance should be considered when alternative antibacterials are chosen.⁴ Bacterial resistance to erythromycin seems to be more of a problem with repeated or continuous use; resistance decreases rapidly when medication is discontinued.⁴

**FOR ORAL DOSAGE FORMS ONLY**

Tylosin is more stable than erythromycin in acid environments and therefore can be administered orally without enteric coating.⁵

**FOR PARENTERAL DOSAGE FORMS ONLY**

Only the gluceptate and the lactobionate salts of erythromycin can be administered intravenously. Other parenteral dosage forms must be administered by the intramuscular route only.
Cattle: The intramuscular route of administration for erythromycin is recommended to avoid the poor absorption and intestinal side effects associated with oral dosing and the poor absorption and more severe local reactions associated with subcutaneous administration. Even with intramuscular injection, the effect of erythromycin on edible tissues should be considered before administration. High-dose intravenous administration should be avoided unless the glucosylate or lactobionate forms are used because immediate side effects have been reported with such administration.

FOR TREATMENT OF ADVERSE EFFECTS

For anaphylaxis

Recommended treatment consists of the following:

- Parenteral epinephrine.
- Oxygen administration and breathing support.
- Parenteral fluid administration as needed.

Note: Parenteral epinephrine is not recommended treatment for tilmicosin toxicity because of adverse effects noted in pigs (see Overdose section); however, epinephrine is not contraindicated for anaphylaxis due to tilmicosin.

AZITHROMYCIN

SUMMARY OF DIFFERENCES

Pharmacology/pharmacokinetics: Distribution—Azithromycin concentrates in tissues, particularly in leukocytes, macrophages and fibroblasts and is slowly released from leukocytes. The intracellular reservoir of azithromycin produces effective drug concentrations in interstitial fluids even after the plasma concentrations have declined below detectable levels. Azithromycin can be delivered to infected tissues and early abscesses via leukocytes. Azithromycin is slowly released from leukocytes and is slowly released from granulocytes after reconstitution.

ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

AZITHROMYCIN FOR ORAL SUSPENSION USP

Usual dose:

Note: Dosing recommendations for the use of azithromycin in the treatment of animals are given with some caution advised. Unlike other antibiotics for which there is limited clinical efficacy and safety data, the ability of azithromycin to concentrate in tissues makes the typical dosing estimation based on pharmacokinetic data more challenging. The following are current recommendations for dosing; however, these may be supplanted as knowledge about azithromycin increases:

[MG/kg] and [dose]/—Although the safety and efficacy have not been established, an oral dose of 3 to 5 mg per kg of body weight every twenty-four hours for three to four days has been used to treat susceptible bacterial infections, based on pharmacokinetic data. For infections that require longer-term treatment, azithromycin has been administered for a maximum of 3 or 4 days a week; this is done either by administering the 3 to 5 mg per kg dose every other day or by administering the same dose once on three subsequent days (Monday, Tuesday, and Wednesday) each week, with no treatment on the other four days of the week.

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

- Not commercially available.

Human-labeled product(s):

- 20 mg per mL (when reconstituted according to manufacturer's instruction) (available in 300-mg bottles) (Rx) [Zithromax (sucrose)].
- 40 mg per mL (when reconstituted according to manufacturer's instruction) (available in 600-, 900-, and 1200-mg bottles) (Rx) [Zithromax (sucrose)].

Canada—

Veterinary-labeled product(s):

- Not commercially available.

Human-labeled product(s):

- 20 mg per mL (when reconstituted according to manufacturer's instruction) (available in 300-mg bottles) (Rx) [Zithromax (sucrose)].
- 40 mg per mL (when reconstituted according to manufacturer's instruction) (available in 600- and 900-mg bottles) (Rx) [Zithromax (sucrose)].

Packaging and storage:

Prior to reconstitution, store between 5 and 30 °C (41 and 86 °F) in a tight container.

After reconstitution, the pediatric oral suspension should be stored between 5 and 30 °C (41 and 86 °F) and used within 10 days.

Preparation of dosage form: For the pediatric suspension, add the volume of water indicated on manufacturer's product labeling to the bottle and shake well.

USP requirements: Preserve in tight containers. A dry mixture of Azithromycin and one or more buffers, sweeteners, diluents, antica-king agents, and flavors. Contains the labeled amount, within ±10%. Meets the requirements for Identification, Uniformity of dosage units (for solid packaged in single-unit containers), Deliverable volume, pH (9.0–11.0) [for solid packaged in single-unit containers], 8.5–11.0 [for solid packaged in multiple-unit containers], in the suspension constituted as directed in the labeling), and Water not more than 1.5%.

AZITHROMYCIN TABLETS

Usual dose: See Azithromycin For Oral Suspension USP.

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

- Not commercially available.
Human-labeled product(s):
- 250 mg (Rx) [Zithromax].
- 500 mg (Rx) [Zithromax].

Canada—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
- 250 mg (Rx) [Zithromax].
- 500 mg (Rx) [Zithromax].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container.

USP requirements: Not in USP\(^{[R-22]}\).

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PARENTERAL DOSAGE FORMS

AZITHROMYCIN FOR INJECTION

Usual dose:
Note: There are no data at this time to recommend dosing for parenteral azithromycin in animals.

Strength(s) usually available\(^{[R-115]}\);
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
- 500 mg (Rx) [Zithromax].

Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
- 500 mg (Rx) [Zithromax].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: To prepare the initial solution for intravenous infusion, add 4.8 mL of sterile water for injection to each 500-mg vial and shake until all of the medication is dissolved. Further dilute this solution by transferring it into 250 or 500 mL of a suitable diluent (see manufacturer’s package insert) to provide a final concentration of 2 or 1 mg per mL, respectively.

Stability: After reconstitution with sterile water for injection, the solution is stable for 24 hours when stored below 30 °C (86 °F). After dilution to 1 or 2 mg per mL in suitable diluent, solutions are stable for 24 hours at or below room temperature (30 °C [86 °F]), or for 7 days if stored at 5 °C (41 °F).

USP requirements: Not in USP\(^{[R-22]}\).

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CLARITHROMYCIN

ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

CLARITHROMYCIN FOR ORAL SUSPENSION USP

Usual dose:
Note: Dosing recommendations for the use of clarithromycin in the treatment of animals are given with caution advised. Unlike other antibiotics for which there is limited clinical efficacy and safety data, the ability of clarithromycin to concentrate in tissues makes the typical dosing estimation based on pharmacokinetic data more challenging. One pharmacokinetic study suggested that 10 mg per kg a day may be an effective dose for [dogs]\(^{1}\), but did not attempt to recommend duration of therapy\(^{[R-124]}\). There are no reports of specific dosing regimens in common usage.

Strength(s) usually available\(^{[R-115]}\):
When reconstituted according to manufacturer’s instructions—
U.S.:
Veterinary-labeled product(s)—Not commercially available.
Human-labeled product(s)—
- 25 mg per mL (Rx) [Biaxin].
- 50 mg per mL (Rx) [Biaxin].

Canada:
Veterinary-labeled product(s)—
Not commercially available.
Human-labeled product(s)—
- 25 mg per mL (Rx) [Biaxin].
- 50 mg per mL (Rx) [Biaxin].

Packaging and storage: Store between 15 and 30 °C (59 and 86 °F), in a well-closed container. Protect from light.

Preparation of dosage form: Add the total volume of water indicated on manufacturer’s product labeling, in two portions, shaking well after each addition.

Stability: After reconstitution, suspension retains its potency for 14 days. Do not refrigerate.

USP requirements: Preserve in tight containers. A dry mixture of Clarithromycin, dispersing agents, diluents, preservatives, and flavorings. Contains the labeled amount, within –10 to +15%, labeled amount being 25 mg or 50 mg per mL when constituted as directed in the labeling. Meets the requirements for Identification, pH (4.0–5.4, in the suspension constituted as directed in the labeling), Loss on drying (not more than 2.0%), and Deliverable volume.\(^{[R-22]}\)

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CLARITHROMYCIN TABLETS USP

Usual dose: See Clarithromycin for Oral Suspension USP.

Strength(s) usually available\(^{[R-116]}\);
U.S.—
Veterinary-labeled product(s):
Not commercially available.

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\(^{1}\)Not included in Canadian product labeling or product not commercially available in Canada.

MACROLIDES Veterinary—Systemic 129

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Human-labeled product(s):
250 mg (Rx) [Biaxin],
500 mg (Rx) [Biaxin].

Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [Biaxin],
500 mg (Rx) [Biaxin].

Packaging and storage: Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Protect from light. Preserve in tight containers.

USP requirements: Preserve in tight containers. Contain the labeled amount, within ±10%. Meet the requirements for Identification, Dissolution (80% in 30 minutes in 0.1 M Sodium acetate buffer in Apparatus 2 at 50 rpm), Uniformity of dosage units, and Loss on drying (not more than 6.0%). [R-22]

CLARITHROMYCIN EXTENDED-RELEASE TABLETS

Usual dose:
Note: There is no specific evidence that human extended-release dosage forms are completely absorbed by animals; therefore, reliable dose recommendations cannot be made.

Strength(s) usually available [R-116]:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
500 mg (Rx) [Biaxin XL].
Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
500 mg (Rx) [Biaxin XL].

Packaging and storage: Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Protect from light.

USP requirements: Not in USP. [R-22]

ERYTHROMYCIN BASE

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

ERYTHROMYCIN DELAYED-RELEASE CAPSULES USP

Usual dose:
Note: There is no specific evidence that human delayed-release dosage forms are completely absorbed by animals; therefore, reliable dose recommendations cannot be made.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [ERYC; generic].
500 mg (Rx) [ERYC; generic].

Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [Apo-Erythro E-C; ERYC-250; Novo-rythro Encap].
333 mg (Rx) [Apo-Erythro E-C; ERYC-333].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Contain the labeled amount, within –10% to +15%. Meet the requirements for Identification, Drug release (Method B: 80% in 60 minutes for Acid stage and 60 minutes for Buffer stage in Apparatus 1 at 50 rpm), and Water (not more than 7.5%). [R-22]

ERYTHROMYCIN TABLETS USP

Usual dose:
Note: There is no specific evidence that human delayed-release dosage forms are completely absorbed by animals; therefore, reliable dose recommendations cannot be made.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [generic].
500 mg (Rx) [generic].

Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [Apo-Erythro; Erythromid].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Contain the labeled amount, within –10% to +20%. Meet the requirements for Identification, Dissolution (70% in 60 minutes in 0.05 M phosphate buffer [pH 6.8] in Apparatus 2 at 50 rpm), Uniformity of dosage units, and Loss on drying (not more than 5.0%). [R-22]

ERYTHROMYCIN DELAYED-RELEASE TABLETS USP

Usual dose:
Note: There is no specific evidence that human delayed-release dosage forms are completely absorbed by animals; therefore, reliable dose recommendations cannot be made.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [Apo-Erythro E-C; ERYC-250; Novo-rythro Encap].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Contain the labeled amount, within –10% to +20%. Meet the requirements for Identification, Drug release (Method B: 70% in 60 minutes for Acid stage and 60 minutes for Buffer stage in Apparatus 1 at 50 rpm), and Water (not more than 7.5%). [R-22]

ERYTHROMYCIN DELAYED-RELEASE CAPSULES USP

Usual dose:
Note: There is no specific evidence that human delayed-release dosage forms are completely absorbed by animals; therefore, reliable dose recommendations cannot be made.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [ERYC; generic].
500 mg (Rx) [ERYC; generic].

Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [Apo-Erythro E-C; ERYC-250; Novo-rythro Encap].
333 mg (Rx) [Apo-Erythro E-C; ERYC-333].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Contain the labeled amount, within –10% to +20%. Meet the requirements for Identification, Drug release (Method B: 70% in 60 minutes for Acid stage and 60 minutes for Buffer stage in Apparatus 1 at 50 rpm), and Water (not more than 7.5%). [R-22]
Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [E-Mycin; Ery-Tab; Ilotycin; GENERIC].
333 mg (Rx) [E-Base; E-Mycin; Ery-Tab; PCE; GENERIC].
500 mg (Rx) [E-Base; Ery-Tab; PCE].
Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (Rx) [E-Mycin; GENERIC].
333 mg (Rx) [PCE].
500 mg (Rx) [Erybid].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. The label indicates that Erythromycin Delayed-release Tablets are enteric-coated. The labeling indicates the Drug Release Test with which the product complies. Contain the labeled amount, within –10% to +20%. Meet the requirements for Identification, Drug Release (Method B: 75% in 60 minutes for Acid stage and 60 minutes for Buffer stage in Apparatus 1 at 100 rpm for Test 1 and in Apparatus 2 at 75 rpm for Test 2). Uniformity of dosage units, and Water (not more than 6.0%).

PARENTERAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

ERYTHROMYCIN INJECTION USP
Usual dose:
Enteritis (scours)—Piglets, one week of age or older: Intramuscular, 11 mg per kg of body weight every twenty-four hours{R-111].
Enterotoxemia (lamb dysentery) (prophylaxis)—Lambs, newborn: Intramuscular, 5.5 mg per kg of body weight every twenty-four hours, as soon after birth as is practical{R-111].
Leptospirosis—Sows, farrowing: Intramuscular, 1.1 to 3.3 mg per kg of body weight every twenty-four hours{R-111].
Metritis—
Cattle: Intramuscular, 1.1 to 2.2 mg per kg of body weight every twenty-four hours{R-111].
Sows, farrowing: Intramuscular, 1.1 to 3.3 mg per kg of body weight every twenty-four hours{R-111].
Pneumonia, bacterial—
Cattle: Intramuscular, 2.2 mg per kg of body weight every twenty-four hours. Note: See product labeling for the above dosing recommendations with applicable withdrawal times.
For pneumonia pasteurellosis—Intramuscular, 15 mg per kg of body weight every twelve hours. Note: The above dose is higher than those stated on U.S. or Canadian product labeling.

Strength(s) usually available:
U.S.—{R-6; 8}
Veterinary-labeled product(s):
100 mg per mL (OTC) [Gallimycin-100].
200 mg per mL (OTC) [Gallimycin-200].
Canada—{R-7; 8}
Veterinary-labeled product(s):
200 mg per mL (OTC) [Erythro-200; Gallimycin-200].

Withdrawal times:
U.S.—{R-6}
For Gallimycin-200{R-6]:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>6</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal time states that it applies to a dose of 8.8 mg per kg of body weight every 24 hours and a course of therapy not exceeding 5 days. Higher doses or longer duration of treatment may increase withdrawal times. This is not labeled for use in lactating dairy cattle. To avoid excessive trim, cattle should not be slaughtered for 21 days after the last injection.

For Gallimycin-100{R-111]:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>14</td>
<td>72</td>
</tr>
<tr>
<td>Pigs</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply to a dose of 1.1 to 2.2 mg per kg of body weight for cattle, 1.1 to 3.3 mg per kg of body weight for pigs, and 1.1 mg per kg of body weight for sheep.

Canada—{R-7]
Note: Product labeling listing the above withdrawal times states that the recommended withdrawal times apply to doses of 2.2 to 4.4 mg per kg of body weight in cattle, 2.2 mg per kg of body weight in piglets, 2.2 to 6.6 mg per kg of body weight in pigs, 11 mg per kg of body weight in lambs, and 2.2 mg per kg of body weight in sheep; administered every 24 hours in each species. To avoid excessive trim, cattle should not be slaughtered for 21 days after the last injection; for pigs and sheep, the waiting period is 10 days.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

USP requirements: Preserve in multiple-dose containers. A sterile solution of Erythromycin in a polyethylene glycol vehicle. Label it to indicate that it is for veterinary use only. Label it to state that it is for intramuscular administration only. Contains the labeled amount, within –10% to +20%. Meets the requirements for Identification, Water (not more than 1.0%), and Sterility, and for Injections.

ERYTHROMYCIN ESTOLATE

SUMMARY OF DIFFERENCES
Pharmacology/pharmacokinetics: Absorption—Erythromycin estolate is absorbed as the ester from the duodenum and is hydrolyzed to free base in the body. [R-1; 18]

Side/adverse effects: In humans, erythromycin estolate has been associated with an increased risk of subclinical hepatotoxicity during pregnancy and an increased risk of cholestatic jaundice at any time. These effects have not been reported in animals; however, periodic liver function tests for animals receiving long-term erythromycin estolate therapy have been recommended. [R-2]

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that are either not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of erythromycin base (not the estolate salt).

ERYTHROMYCIN ESTOLATE CAPSULES USP

Usual dose: [Rhodococcus equi pneumonia] 1—Foals: Oral, 25 mg (base) per kg of body weight every six hours. [R-13; 14; 26]

Note: The above dose has also been administered concurrently with 5 mg rifampin per kg of body weight. [R-13; 14] The doses recommended are based on pharmacokinetic and clinical efficacy studies in foals. [R-13; 14; 26]

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (base) (Rx) [Ilosone; GENERIC].

Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (base) (Rx) [Ilosone; Novo-rythro].

Packaging and storage: Store between 2 and 8 °C (36 and 46 °F). Store in a tight container.

Auxiliary labeling:
• Refrigerate.
• Shake well.

USP requirements: Preserve in tight containers. Contains an amount of erythromycin estolate equivalent to the labeled amount of erythromycin, within –10% to +15%. Meets the requirements for Identification, Disintegration (30 minutes), Uniformity of dosage units, and Water (not more than 5.0%). [R-22]

ERYTHROMYCIN ESTOLATE ORAL SUSPENSION USP

Usual dose: See Erythromycin Estolate Capsules USP.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
25 mg (base) per mL (Rx) [Ilosone; GENERIC].
50 mg (base) per mL (Rx) [Ilosone; GENERIC].

Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
25 mg (base) per mL (Rx) [Ilosone; Novo-rythro].
50 mg (base) per mL (Rx) [Ilosone; Novo-rythro].

Packaging and storage: Store between 2 and 8 °C (36 and 46 °F). Store in a tight container.

Auxiliary labeling:
• Refrigerate.
• Shake well.

USP requirements: Preserve in tight containers, in a cold place. Contains one or more suitable buffers, colors, diluents, dispersants, and flavors. Contains an amount of erythromycin estolate equivalent to the labeled amount of erythromycin, within –10% to +15%. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume, and pH (3.5–6.5). [R-22]

ERYTHROMYCIN ESTOLATE TABLETS USP

Usual dose: See Erythromycin Estolate Capsules USP.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
250 mg (base) (Rx) [GENERIC].
500 mg (base) (Rx) [Ilosone].

Canada—
Veterinary-labeled product(s):
Not commercially available.

1 Not included in Canadian product labeling or product not commercially available in Canada.
Human-labeled product(s):
500 mg (base) (Rx) [Ilosone].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Label Tablets to indicate whether they are to be chewed before swallowing. Contain an amount of erythromycin estolate equivalent to the labeled amount of erythromycin, within –10% to +20% (+15%, if chewable). Meet the requirements for Identification, Disintegration (30 minutes [Note: Chewable tablets are exempt from this requirement]), Uniformity of dosage units, and Water (not more than 5.0%; if chewable, not more than 4.0%).\(^{[R-22]}\)

\(^{1}\)Not included in Canadian product labeling or product not commercially available in Canada.

**ERYTHROMYCIN ETHYLSUCCINATE**

**SUMMARY OF DIFFERENCES**

Pharmacology/pharmacokinetics: Absorption—
Absorbed as the ester, then hydrolyzed to free base in the body.\(^{[R-1]}\)

**Pigeons:** Orally administered erythromycin ethylsuccinate has a relative bioavailability of less than 10%.\(^{[R-27]}\)

**ORAL DOSAGE FORMS**

Note: The strengths of the dosage forms available are expressed in terms of the ethylsuccinate salt. In people, 400 mg of erythromycin ethylsuccinate produces approximately the same blood concentrations as 250 mg of erythromycin base.

1.17 grams of erythromycin ethylsuccinate equal 1 gram of erythromycin base.\(^{[R-90]}\)

**ERYTHROMYCIN ETHYLSUCCINATE ORAL SUSPENSION USP**

**Usual dose:**
Note: There are no dose recommendations specific to animals for this dosage form.

**Strength(s) usually available:**

**U.S.—**
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
40 mg per mL (Rx) [E.E.S.; Erythro; generic].
80 mg per mL (Rx) [E.E.S.; Erythro; generic].

Canada—
Not commercially available.

**Packaging and storage:** Store between 2 and 8 °C (36 and 46 °F). Store in a tight container.

**Stability:** After dispensing, suspensions do not require refrigeration if used within 14 days. Some manufacturers recommend storage in light-resistant containers to prevent discoloration.\(^{[R-16]}\)

**USP requirements:** Preserve in tight containers, and store in a cold place. A suspension of Erythromycin Ethylsuccinate containing one or more suitable buffers, colors, dispersants, flavors, and preservatives. Contains an amount of erythromycin ethylsuccinate equivalent to the labeled amount of erythromycin, within –10% to +20%. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume, and pH (6.5–8.5).\(^{[R-22]}\)

**ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION USP**

**Usual dose:** See Erythromycin Ethylsuccinate Oral Suspension USP.

**Strength(s) usually available:** When reconstituted according to manufacturer’s instructions—

**U.S.:**
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
40 mg per mL (Rx) [E.E.S.; Erythro; generic].
80 mg per mL (Rx) [E.E.S.; Erythro; generic].

**Canada:**
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
20 mg per mL (Rx) [Novo-Rythro].
40 mg per mL (Rx) [E.E.S.; Novo-Rythro].
80 mg per mL (Rx) [E.E.S.].

**Packaging and storage:** Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

**Stability:** After reconstitution, depending on the manufacturer or the specific product, suspensions do not require refrigeration if used within 14 days.

**USP requirements:** Preserve in tight containers. A dry mixture of Erythromycin Ethylsuccinate with one or more suitable buffers, colors, diluents, dispersants, and flavors. Contains an amount of erythromycin ethylsuccinate equivalent to the labeled amount of erythromycin, within –10% to +20%. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume, pH (7.0–9.0, in the suspension constituted as directed in the labeling), and Loss on drying (not more than 1.0%).\(^{[R-22]}\)

**ERYTHROMYCIN ETHYLSUCCINATE TABLETS USP**

**Usual dose:** See Erythromycin Ethylsuccinate Oral Suspension USP.

**Strength(s) usually available:**

**U.S.—**
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
400 mg (Rx) [E.E.S.; generic].

Canada—
Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
600 mg (Rx) [Apo-Erythro-ES; E.E.S.].
Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Label the chewable Tablets to indicate that they are to be chewed before swallowing. Contain an amount of erythromycin ethylsuccinate equivalent to the labeled amount of erythromycin, within –10% to +20%. Meet the requirements for Identification, Dissolution (75% in 45 minutes in 0.01 N hydrochloric acid in Apparatus 2 at 50 rpm for nonchewable tablets and 75% in 60 minutes in 0.1 M acetate buffer [pH 5.0] in Apparatus 2 at 75 rpm for Tablets labeled as chewable). Uniformity of dosage units, Loss on drying (not more than 4.0% [Note: Chewable Tablets are exempt from this requirement]), and Water (Chewable Tablets only, not more than 5.0%).

ERYTHROMYCIN ETHYLSUCCINATE TABLETS (CHEWABLE) USP

Usual dose: See Erythromycin Ethylsuccinate Oral Suspension USP.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
200 mg (Rx) [EryPed].
400 mg (Rx) [Erythrol].
Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
200 mg (Rx) [E.E.S. (scored); EryPed].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

USP requirements: Preserve in tight containers. Label the chewable Tablets to indicate that they are to be chewed before swallowing. Contain an amount of erythromycin ethylsuccinate equivalent to the labeled amount of erythromycin, within –10% to +20%. Meet the requirements for Identification, Dissolution (75% in 45 minutes in 0.01 N hydrochloric acid in Apparatus 2 at 50 rpm for nonchewable tablets and 75% in 60 minutes in 0.1 M acetate buffer [pH 5.0] in Apparatus 2 at 75 rpm for Tablets labeled as chewable). Uniformity of dosage units, Loss on drying (not more than 4.0% [Note: Chewable Tablets are exempt from this requirement]), and Water (Chewable Tablets only, not more than 5.0%).

STERILE ERYTHROMYCIN GLUCEPTATE USP

Usual dose: [Antibacterial]—Foals: Intravenous, 5 mg (base) per kg of body weight every four to six hours.

Size(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
1 gram (base) (Rx) [Ilotycin].
Canada—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
500 mg (base) (Rx) [Ilotycin].
1 gram (base) (Rx) [Ilotycin].

Packaging and storage: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: To prepare solution, add at least 10 mL of sterile water for injection to each 500-mg vial and at least 20 mL of diluent to each 1-gram vial. After initial dilution, solution may be further diluted to a concentration of 1 gram per L in 0.9% sodium chloride injection or 5% dextrose injection for slow, continuous infusion.

Stability: After reconstitution, initial dilutions (25 to 50 mg per mL) retain their potency for 7 days if refrigerated.

USP requirements: Preserve in Containers for Sterile Solids. It is Erythromycin Gluceptate suitable for parenteral use. Has a potency equivalent to not less than 600 mcg of erythromycin per mg, calculated on the anhydrous basis. In addition, where packaged for dispensing, contains an amount of erythromycin gluceptate equivalent to the labeled amount of erythromycin, within –10% to +15%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH (6.0–8.0, in a solution containing 25 mg per mL). Water (not more than 5.0%), and Particulate matter, and, where packaged for dispensing, Uniformity of dosage units, Constituted solutions, and Labeling under Injections.

ERYTHROMYCIN LACTOBIONATE

PARENTERAL DOSAGE FORMS

Note: The strengths of the dosage forms available are expressed in terms of erythromycin base (not the lactobionate salt).

ERYTHROMYCIN LACTOBIONATE FOR INJECTION USP

Usual dose:
Note: There are no dose recommendations specific to animals for this dosage form.

Size(s) usually available:
U.S.—
Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
500 mg (base) (Rx) [Erythrocin; Generic].
1 gram (base) (Rx) [Erythrocin; Generic].

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
500 mg (base) (Rx) [Erythrocin].
1 gram (base) (Rx) [Erythrocin].

**Packaging and storage:** Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Preparation of dosage form:** See manufacturer’s product labeling.

**Stability:**
After reconstitution, initial dilutions (50 mg per mL) retain their potency for 14 days if refrigerated, or for 24 hours at room temperature. Infusions prepared in piggyback infusion bottles retain their potency for 8 hours at room temperature, for 24 hours if refrigerated, or for 30 days if frozen.

Acidic infusions are unstable and lose potency rapidly. A pH of at least 5.5 is recommended for final dilutions, which should be administered completely within 8 hours after dilution.

**USP requirements:** Preserve in Containers for Sterile Solids. A sterile, dry mixture of erythromycin lactobionate and a suitable preservative. Contains an amount of erythromycin lactobionate equivalent to the labeled amount of erythromycin, within –10% to +20%. Meets the requirements for Constituted solution, Identification, Bacterial endotoxins, pH (6.5–7.5, in a solution containing the equivalent of 50 mg of erythromycin per mL), Water (not more than 5.0%), Particulate matter, and Heavy metals (not more than 0.005%), and for Injections.

**ERYTHROMYCIN PHOSPHATE**

**SUMMARY OF DIFFERENCES**

Pharmacology/pharmacokinetics: Absorption—
Erythromycin phosphate is presumed to dissociate in the duodenum and be absorbed as the free base.[R-18]

**Horses:** Erythromycin phosphate is absorbed at least as well as erythromycin estolate when administered orally.[R-18]

**ORAL DOSAGE FORMS**

Note: The dosing and strengths of the dosage form available are expressed in terms of erythromycin phosphate (not erythromycin base).

1.12 grams of erythromycin phosphate equal 1 gram of erythromycin base.[R-8]

**ERYTHROMYCIN PHOSPHATE POWDER FOR ORAL SOLUTION**

**Usual dose:**
Chronic respiratory disease—**Chickens:** Oral, 500 mg per gallon of water, administered as the only source of drinking water every twenty-four hours for five days.[R-3].

Coryza, infectious—**Chickens:** Oral, 500 mg per gallon of water, administered as the only source of drinking water for seven days.[R-3]

Enteritis—**Turkeys:** Oral, 500 mg per gallon of water, administered as the only source of drinking water for seven days.[R-3]

Note: Dosage ranges for birds are approximate, based on variable water consumption and animal size.

**Strength(s) usually available:**

**U.S.**—[R-3; 6; 8]

Veterinary-labeled product(s):
260 mg (231.2 mg erythromycin base) per gram (OTC) [Gallimycin PFC].

Canada—[R-8; 9]

Veterinary-labeled product(s):
130 mg (115.6 mg base) per gram (OTC) [Gallimycin; Gallistat].

260 mg (231.2 mg base) per gram (OTC) [Gallimycin PFC].

**Withdrawal times:**

U.S. and Canada—[R-3; 9]

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens and turkeys</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Products are not labeled for use in birds producing eggs for human consumption or in replacement pullets over 16 weeks of age.[R-3; 9].

Canadian product labeling lists the dose as 116 mg (base) per liter of water for chickens and turkeys.

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Stability:** Solutions should be discarded after 3 days.[R-8]

**USP requirements:** Not in USP.[R-22].

**ERYTHROMYCIN STEARATE**

**SUMMARY OF DIFFERENCES**

Pharmacology/pharmacokinetics: Absorption—Erythromycin stearate dissociates in the duodenum and is absorbed as the free base.[R-18]

**ORAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of erythromycin base (not the stearate salt).

**ERYTHROMYCIN STEARATE ORAL SUSPENSION**

**Usual dose:** [Enteritis, Campylobacter]—**Dogs:** Oral, 10 mg (base) per kg of body weight every eight hours.[R-10]

**Strength(s) usually available:**

**U.S.—**

Not commercially available.

Canada—

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
25 mg (base) per mL (Rx) [Erythrocin; Novo-rythro].

50 mg (base) per mL (Rx) [Erythrocin; Novo-rythro].

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Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:
- Refrigerate.
- Shake well.

USP requirements: Not in USP.

ERYTHROMYCIN STEARATE TABLETS USP

Usual dose: See Erythromycin Stearate Oral Suspension.

Strength(s) usually available:

U.S.—
- Veterinary-labeled product(s): Not commercially available.
- Human-labeled product(s):
  - 250 mg (base) (Rx) [Erythrocin; Erythrocin; Mg-E; Wintracin; generic].
  - 500 mg (base) (Rx) [Erythrocin; generic].

Canada—
- Veterinary-labeled product(s): Not commercially available.
- Human-labeled product(s):
  - 250 mg (base) (Rx) [Apo-Erythro-S; Erythrocin; Novo-rythro].
  - 500 mg (base) (Rx) [Apo-Erythro-S; Erythrocin].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Note: Some manufacturers recommend storage in light-resistant containers to prevent discoloration.

USP requirements: Preserve in tight containers. Contain an amount of erythromycin stearate equivalent to the labeled amount of erythromycin, within –10% to +20%. Meet the requirements for Identification, Dissolution (75% in 120 minutes in 0.05 M phosphate buffer [pH 6.8] in Apparatus 2 at 100 rpm), Uniformity of dosage units, and Loss on drying (not more than 5.0%).

ERYTHROMYCIN THIOCYANATE

ORAL DOSAGE FORMS

Note: 1.08 grams of thiocyanate salt equal 1 gram of erythromycin base.

ERYTHROMYCIN THIOCYANATE FOR MEDICATED FEED

Usual dose:

- Coryza, infectious (prophylaxis)—Chickens: Oral, 100 grams (93 grams of base) per ton of feed, fed as the only ration for seven to fourteen days.
- Respiratory disease, chronic (prophylaxis)—Chickens and turkeys: Oral, 100 grams (93 grams of base) per ton of feed, fed as the only ration from two days before stress until three to six days after stress.
- Respiratory disease, chronic (treatment)—Chickens and turkeys: Oral, 200 grams (185 grams of base) per ton of feed, fed as the only ration.

Strength(s) usually available:

U.S.—Veterinary-labeled product(s):
- 220 grams (203 grams of base) per kg of premix (OTC) [Erymycin-100].

Canada—Veterinary-labeled product(s):
- 110 grams (102 grams of base) per kg of premix (OTC) [Gallimycin-50].

Withdrawal times:

U.S.—
With a dose of 200 grams (185 grams of base) per ton of feed:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>2 (days)</td>
</tr>
<tr>
<td>Turkeys</td>
<td>0 (days)</td>
</tr>
</tbody>
</table>

Note: Product is not labeled for use in birds producing eggs for human consumption.

With a dose of 100 grams (93 grams of base) per ton of feed:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>1 (days)</td>
</tr>
<tr>
<td>Turkeys</td>
<td>0 (days)</td>
</tr>
</tbody>
</table>

Note: Product is not labeled for use in birds producing eggs for human consumption.

Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>1 (days)</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal time states that it applies to a dose of 220 grams per metric ton (1000 kg) of feed, fed as the only ration, to chickens.

Not labeled for use in chickens producing eggs for human consumption.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

USP requirements: Not in USP.

TILMICOSIN PHOSPHATE

ADDITIONAL DOSING INFORMATION

Tilmicosin injection should be given only by subcutaneous administration because intravenous administration is fatal with doses as low as 5 mg per kg of body weight.

Parenteral administration of tilmicosin to pigs by any route often is fatal.
ORAL DOSAGE FORMS
Note: The dosing and strengths of the dosage form available are expressed in terms of tilmicosin base (not the phosphate salt).

TILMICOSIN FOR MEDICATED FEED
Usual dose: Pneumonia, bacterial—Pigs: Oral, 181 to 383 grams per ton of feed, fed as the only ration for twenty-one days, beginning approximately seven days before an anticipated disease outbreak, if possible.\(^{[R-107; 114]}\).

Strength(s) usually available:\(^{[R-8]}\):
U.S.—Veterinary-labeled product(s):
200 grams (base) per kg (90.7 grams [base] per pound) of premix (Rx) [Pulmotil 90].
Canada—Veterinary-labeled product(s):
200 grams (base) per kg (OTC) [Pulmotil Premix].

Withdrawal times: U.S.\(^{[R-107]}\):

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
<th>Meats (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

Canada\(^{[R-114]}\):

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
<th>Meats (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: Tilmicosin should not be mixed in concentrates or feeds containing bentonite because bentonite may reduce the efficacy of tilmicosin\(^{[R-107]}\). Premix should be thoroughly mixed in feed before administration\(^{[R-107]}\).

Caution: Inhalation, oral exposure, and direct contact with eyes should be avoided\(^{[R-107]}\).

USP requirements: Not in USP.\(^{[R-22]}\)

PARENTERAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.
The dosing and strengths of the dosage form available are expressed in terms of tilmicosin base (not the phosphate salt).

TILMICOSIN INJECTION USP
Usual dose: Pneumonia, bacterial—
Cattle: Subcutaneous, 10 mg (base) per kg of body weight as a single dose.\(^{[R-53]}\).
[Calves] and [lambs]: Subcutaneous, 10 mg (base) per kg of body weight as a single dose.\(^{[R-65; 112]}\).

Strength(s) usually available:\(^{[R-8]}\):
U.S.—Veterinary-labeled product(s):
300 mg (base) per mL (Rx) [Micotil].
Canada—Veterinary-labeled product(s):
300 mg (base) per mL (Rx) [Micotil].

Withdrawal times: U.S.—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>28</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal time states that it applies to a dose of 10 mg (base) per kg of body weight administered once to cattle.
Not labeled for use in lactating cattle.
Tilmicosin should not be used in lactating dairy cows because of its extended antimicrobial activity in milk. A single subcutaneous tilmicosin dose of 10 mg per kg of body weight resulted in tilmicosin concentrations detectable in milk for 19 to 31 days when measured by high performance liquid chromatography or 14 to 21 days when measured by Bacillus stearothermophilus assay.\(^{[R-74]}\).

Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, cattle, lambs</td>
<td>28</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal time states that it applies to a dose of 10 mg (base) per kg of body weight administered once to cattle or lambs.\(^{[R-112]}\)
Not labeled for use in lactating dairy cattle, veal calves, calves weighing less than 70 kg, or lactating sheep.\(^{[R-92]}\).

Packaging and storage: Store at or below 30 °C (86 °F). Protect from light.\(^{[R-53]}\)

Caution: Injection of tilmicosin in humans may be fatal. Caution should be exercised to avoid self-injection. An automatically powered syringe should not be used for administration.\(^{[R-53]}\)

Auxiliary labeling:
- Keep out of the reach of children.
- Avoid contact with eyes.

USP requirements: Preserve in light-resistant Containers for Injections. Store at or below 30°. A sterile solution of Tilmicosin in a mixture of Propylene Glycol and Water for Injection, solubilized with the aid of Phosphoric Acid. Label the Injection to indicate that it is for veterinary use only. Contains the labeled amount, within ±10%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH.
(5.5–6.5). Particulate matter, and Content of propylene glycol (within ±20% of labeled amount)[R-22].

TYLOSIN BASE

SUMMARY OF DIFFERENCES
Pharmacology/pharmacokinetics: Tylosin is stable enough in acid environments to be administered orally without enteric coating.[R-58]

PARENTERAL DOSAGE FORMS
Note:Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

TYLOSIN INJECTION
Usual dose:
Arthritis, infectious1;
Erysipelas; or
Swine dysentery—Pigs: Intramuscular, 8.8 mg per kg of body weight every twelve hours[R-51];
Note: When used to treat swine dysentery, tylosin injection should be followed by administration of medication in feed or drinking water.[R-51]
Diphtheria1;
Metritis; or
Pododermatitis1—Cattle, beef and nonlactating dairy: Intramuscular, 17.6 mg per kg of body weight every twenty-four hours[R-51; 52; 55].
Pneumonia, bacterial—
Cattle, beef and nonlactating dairy: Intramuscular, 17.6 mg per kg of body weight every twenty-four hours[R-51; 55];
Pigs: Intramuscular, 8.8 mg per kg of body weight every twelve hours[R-51].
Note: In pigs, no more than 5 mL per injection site is recommended; in cattle, no more than 10 mL per injection site.[R-51; 52]
Note: [Cats]1 and [dogs]1—A dose of 6.6 to 11 mg per kg of body weight every twelve to twenty-four hours has been used in the treatment of respiratory tract infections in cats and dogs[R-108].

Strength(s) usually available[R-8]:
U.S.—
Veterinary-labeled product(s):
50 mg per mL (OTC) [Tylan 50].
200 mg per mL (OTC) [Tylan 200; TyloVed canine].
Canada—[R-55]
Veterinary-labeled product(s):
200 mg per mL (OTC) [Tylan 200; Tylocine 200].

Withdrawal times:
U.S.—[R-51; 52]

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>21</td>
</tr>
<tr>
<td>Pigs</td>
<td>14</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply to a dose of 17.6 mg per kg of body weight (mg/kg) for cattle and 2.2 to 8.8 mg/kg every 24 hours for pigs. Not for use in lactating dairy cattle.

To avoid excessive trim, swine should not be slaughtered for 21 days after treatment; cattle should not be slaughtered for 42 days after treatment.[R-55]

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Incompatibilities: To avoid precipitation, tylosin injection should not be mixed with other injectables.[R-51]

Caution:
Contact with human skin should be avoided.
Injection into pigs weighing less than 6.25 pounds should not be attempted unless the syringe is capable of accurately delivering 0.1 mL. Adverse reactions may occur from overdosage in piglets.[R-51; 52]

USP requirements: Not in USP.[R-22]

1Not included in Canadian product labeling or product not commercially available in Canada.

TYLOSIN PHOSPHATE
ORAL DOSAGE FORMS

TYLOSIN GRANULATED USP

Usual dose:
Abscesses, hepatic (prophylaxis)1—Cattle, beef: Oral, 8 to 10 grams per ton of feed (approximately 60 to 90 mg per animal a day), fed as the only ration[R-49].
Atrophic rhinitis1—Pigs: Oral, 100 grams per ton of feed, fed as the only ration[R-49].
Dysentery, swine—Pigs:
Prophylaxis—Oral, 100 grams per ton of feed, fed as the only ration for at least three weeks, followed by 40 grams per ton of feed, fed as the only ration[R-49].
Treatment—Oral, 40 to 100 grams per ton of feed, fed as the only ration for two to six weeks[R-48; 49].
Note: The dose shown for treatment with tylosin phosphate for medicated feed should follow an initial treatment with tylosin powder for oral solution in the drinking water for three to ten days[R-49; 100].
Feed efficiency, improvement of; or
Increased weight gain

**Chickens**: Oral, 4 to 50 grams per ton of feed, fed as the only ration.

*Veterinary-labeled product(s):*

- **Tylan 100**: 100 grams per ton of feed, fed as the only ration.
- **Tylan 40**: 40 grams per ton of feed, fed as the only ration.
- **Tylan 10**: 10 grams per ton of feed, fed as the only ration.

**Pigs**: Oral, 10 to 40 grams per ton of feed, fed as the only ration.

**Veterinary-labeled product(s):**

- **Tylan Soluble**: 22 grams per gallon (approximately 132 mg per kg of body weight a day) in the only source of drinking water for three to five days.
- **Tylan 10**: 2 grams (base) per gallon (approximately 110 mg per kg of body weight a day) in the only source of drinking water for three to five days.

**Withdrawal times:**

**U.S.**

When fed at doses of 10 to 100 grams of tylosin phosphate per ton of feed:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>0</td>
</tr>
</tbody>
</table>

When fed at doses of 800 to 1000 grams of tylosin phosphate per ton of feed:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>5</td>
</tr>
</tbody>
</table>

**Canada**

When fed at a dose of 110 grams of tylosin phosphate per metric ton (1000 kg) of feed:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>0</td>
</tr>
</tbody>
</table>

**Note:** Product labeling listing the above withdrawal time states that when tylosin premix is administered concurrently with tylosin tartrate in drinking water, a withdrawal time of two days is necessary.

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Preparation of dosage form:** Medication should be thoroughly mixed in feed before use. It should not be used in any feed containing more than 2% bentonite.

**Caution:** When handling and mixing medication, protective clothing and impervious gloves should be used. Contact with human skin should be avoided.

**USP requirements:** Preserve in well-closed, polyethylene-lined or polypropylene-lined containers, protected from moisture and excessive heat. Contains tylosin phosphate mixed with suitable carriers and inactive ingredients. Label it also to indicate that it is for animal use only. Label it to indicate that it is for manufacturing, processing, or repackaging. Contains the labeled amount, within ± 20%. Meets the requirement for Identification, Loss on drying (not more than 12.0%), Powder fineness, and Content of tylosins.

**TYLOSIN TARTARTE**

**ORAL DOSAGE FORMS**

**Note:** Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

1.1 grams of tylosin tartrate equals 1 gram of tylosin base. The dosing and strengths of the dosage forms available are expressed in terms of the base.

**TYLOSIN TARTARTE POWDER FOR ORAL SOLUTION**

**Usual dose:**

- **Dysentery, swine—Pigs:** Oral, 250 mg per gallon of water, as the only source of drinking water for three to ten days.
- **Respiratory disease, chronic—Chickens:** Oral, 2 grams (base) per gallon (approximately, 110 mg per kg of body weight a day) in the only source of drinking water for three to five days.
- **Sinusitis, infectious—Turkeys:** Oral, 2 grams per gallon (approximately 132 mg per kg of body weight a day) in the only source of drinking water for three to five days.

**Note:** [Dogs] — There are insufficient data to establish the efficacy of tylosin in the treatment of chronic colitis in dogs; however, an oral dose of 11 mg per kg of body weight every eight hours has been recommended.

**Note that reformulation is necessary for administration to dogs.**

**Size(s) usually available:**

**U.S.—**

Veterinary-labeled product(s):

- 100 grams (base) of powder (OTC) [Tylan Soluble].
Canada—
Veterinary-labeled product(s):
100 grams (base) of powder (OTC) [Tylosin Soluble].

Withdrawal times ([R-8]).

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat, days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>1</td>
</tr>
<tr>
<td>Turkeys</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply to a dose of 250 mg per gallon of drinking water for pigs and 2 grams per gallon of drinking water for chickens and turkeys. Product is not labeled for use in birds producing eggs for human consumption ([R-50]).

Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat, days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td>1</td>
</tr>
<tr>
<td>Pigs</td>
<td>2</td>
</tr>
<tr>
<td>Turkeys</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply to a dose of 1 gram per 4 L (approximately 1 gallon) of drinking water for 3 to 10 days for pigs, 2 grams per 4 L of drinking water for 3 to 5 days for chickens, and 2 grams per 4 L of drinking water for 3 to 5 days for turkeys. ([R-66])

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: A fresh solution of tylosin tartrate should be prepared every 3 days. Water should be added to powder (not powder added to water) when preparing the solution. ([R-50])

Caution: Contact with human skin should be avoided. Protective clothing and impervious gloves should be worn when mixing and handling solutions. ([R-50])

USP requirements: Not in USP. ([R-22])

1 Not included in Canadian product labeling or product not commercially available in Canada.

Table 1. Pharmacology/pharmacokinetics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein binding (%)</th>
<th>Elimination half-life (hr)</th>
<th>Volume of distribution (L/kg)</th>
<th>Clearance (mL/min/kg)</th>
<th>Route; Dose (mg/kg)</th>
<th>Tmax (hr)</th>
<th>Cmax (mcg/mL)</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cats ([R-120])</td>
<td></td>
<td>Terminal: 35</td>
<td>Steady state: 23</td>
<td>10.7</td>
<td>IV: 5</td>
<td>0.85</td>
<td>0.97</td>
<td>58</td>
</tr>
<tr>
<td>Dogs (beagles)</td>
<td></td>
<td>16–26*</td>
<td>29</td>
<td></td>
<td>IV: 24</td>
<td>0.13</td>
<td>4.2</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steady state: 12</td>
<td></td>
<td>PO: 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foals, 8– to 14-weeks</td>
<td></td>
<td>16</td>
<td>Area: 12.4</td>
<td>10</td>
<td>IV: 5</td>
<td>1.4</td>
<td>0.72</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terminal: 16.3</td>
<td>Steady state: 11.6</td>
<td></td>
<td>PO: 10</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foals, 6– to 10-weeks</td>
<td></td>
<td>20.3</td>
<td>Area: 22.3</td>
<td>10.4</td>
<td>PO: 10</td>
<td>1.8</td>
<td>0.57</td>
<td>56</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Steady state: 18.6</td>
<td></td>
<td>PO: 10</td>
<td>2 to 3</td>
<td>0.4</td>
<td>37</td>
</tr>
<tr>
<td>Human data ([R-113])</td>
<td></td>
<td>7–50†</td>
<td>11 to 14</td>
<td></td>
<td>PO: 500 mg</td>
<td>2.0</td>
<td>0.29</td>
<td>46</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Area: 12.4</td>
<td></td>
<td>total dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbits ([R-123])</td>
<td></td>
<td>14–29*</td>
<td>32</td>
<td></td>
<td>IV: 20</td>
<td>2.0</td>
<td>0.29</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steady state: 84</td>
<td></td>
<td>PO: 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>Terminal: 3.9</td>
<td>Steady state: 1.4</td>
<td>4.3</td>
<td>IV: 10</td>
<td>1.6</td>
<td>3.3</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PO: 10</td>
<td>1.7</td>
<td>3.5</td>
<td>79</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calves ([R-23])</td>
<td></td>
<td>2.2</td>
<td>Area: 1.5</td>
<td>7.8</td>
<td>IV: 15</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV/IM: 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle ([R-21])</td>
<td></td>
<td>18</td>
<td></td>
<td></td>
<td>IV: 12.5</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV: 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs ([R-62])</td>
<td></td>
<td>3.2</td>
<td>Area: 0.79</td>
<td>2.9</td>
<td>IV: 5 to 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horses, foals ([R-26])</td>
<td></td>
<td>1</td>
<td>Steady state: 2.7</td>
<td>21</td>
<td>IV: 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Area: 2.3 to 7.2</td>
<td></td>
<td>IV: 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mice ([R-62])</td>
<td></td>
<td>0.7</td>
<td>Steady state: 3.6</td>
<td>77</td>
<td>IV: 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigeons ([R-27])</td>
<td></td>
<td>0.9</td>
<td></td>
<td></td>
<td>IV: 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit ([R-62])</td>
<td></td>
<td>0.7</td>
<td>Steady state: 6.8</td>
<td>51</td>
<td>IV: 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat ([R-62])</td>
<td></td>
<td>0.7</td>
<td>Steady state: 9.3</td>
<td>73</td>
<td>IV: 25</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sheep ([R-21])</td>
<td></td>
<td>23</td>
<td></td>
<td></td>
<td>IV/IM: 20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 1. (Contd.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding (%)</th>
<th>Elimination</th>
<th>Distribution</th>
<th>Clearance (mL/min/kg)</th>
<th>Route: Dose (mg/kg)</th>
<th>Tmax (hr)</th>
<th>Cmax (mcg/mL)</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylosin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf, newborn</td>
<td>1.2</td>
<td>2.5</td>
<td>24.5</td>
<td>SC; 10</td>
<td>1.8</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf, 1 week</td>
<td>1.2</td>
<td>2.5</td>
<td>23.7</td>
<td>SC; 10</td>
<td>1</td>
<td>0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf, 7 weeks to 9 months</td>
<td>1.2</td>
<td>2.5</td>
<td>23.7</td>
<td>IV; 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicken [R-71]</td>
<td>30</td>
<td></td>
<td></td>
<td>IV/IM; 20</td>
<td>12.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chickens [R-71]</td>
<td>1.6</td>
<td>1.7</td>
<td>7.8</td>
<td>IV; 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs [R-68]</td>
<td>0.9</td>
<td></td>
<td>22</td>
<td>IV; 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goats [R-72]</td>
<td>38</td>
<td>1.7</td>
<td>6.8</td>
<td>IM; 15</td>
<td>4.2</td>
<td>2.4</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Sheep [R-70]</td>
<td>38</td>
<td>1.7</td>
<td>6.8</td>
<td>IV/IM; 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td></td>
<td></td>
<td>IV; 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Protein binding is concentration dependent, reported as increasing with decreasing concentration from 10 to 0.02 mg/L.
†Protein binding is concentration dependent, reported as increasing with decreasing concentration from 1 to 0.2 mcg/mL.

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METRONIDAZOLE Veterinary—Systemic

Some commonly used brand names for human-labeled products are: Apo-Metronidazole; Flagyl; Flagyl IV.; Flagyl IV. RTU; Metric 21; Metro IV.; Novomidazol; Prostat; and Trikacide.

Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:
Antibacterial (systemic); antiprotozoal.

INDICATIONS
Note: In other USP DI monographs, bracketed information in the Indications section refers to uses that are not included in U.S. product labeling, and superscript 1 refers to uses that are not included in Canadian product labeling. However, since metronidazole is not specifically approved for veterinary use, there is no product labeling identifying approved indications.

GENERAL CONSIDERATIONS
Metronidazole is effective in the treatment of systemic and enteric obligate anaerobic bacterial infections, including Clostridium species, Fusobacterium species[1-3], and penicillinase-producing strains of Bacteroides[2; 3]. Surgical therapy may be necessary to completely resolve isolated infections[3]. Metronidazole is not clinically effective against facultative anaerobes or obligate aerobes[1-4]. However, it is often combined with another antibiotic or antibiotics effective against aerobes to treat mixed bacterial infections[2]. Metronidazole is considered effective in the treatment of some protozoal infections in animals.

ACCEPTED
[Giardiasis (treatment)]1—Cats and dogs: Metronidazole is used to eliminate shedding of giardial cysts and treat associated diarrhea in cats and dogs.[6-7; 16] Environmental eradication is necessary for effective treatment. The infection may not be completely cleared in all animals[7].

ACCEPTANCE NOT ESTABLISHED
[Amebiasis, intestinal (treatment)]1;
[Balantidiasis, intestinal (treatment)]1; or
[Trichomoniasis, intestinal (treatment)]1—Cats and dogs: In human patients, metronidazole is used in the treatment of susceptible Balantidium coli, Entamoeba histolytica, and Trichomonas species[1-4; 5]. Metronidazole is also recommended in the treatment of enteric protozoal infections in cats and dogs, although the relationship between infection and clinical signs can be difficult to define.
[Bowel disease, inflammatory (treatment)]1—Cats and dogs: Although there are insufficient data to establish efficacy, metronidazole is used in the treatment of inflammatory bowel disease.
[Colitis, antibiotic-associated (treatment)]1; or
[Colitis, clostridial (treatment)]1—Horses: Although there are insufficient data to establish efficacy, metronidazole is used in the treatment of bacterial colitis caused by susceptible organisms, including Clostridium difficile[10-12].

[Encephalopathy, hepatic (treatment)]—Cats and dogs: Although there are insufficient data to establish efficacy, metronidazole is used to reduce gastrointestinal bacterial production of ammonia thought to contribute to clinical signs in hepatic encephalopathy.

[Endometritis (treatment)]1—Horses: Although there are insufficient data to establish efficacy, metronidazole is used in combination with other antibiotics in the treatment of endometritis, including infections caused by penicillinase-producing anaerobic bacteria[13].

[Helicobacter species infections (treatment)]1—Cats and dogs: Although the treatment of Helicobacter pylori in human gastrointestinal disease has had major clinical impact, there is currently little evidence to suggest that these organisms significantly affect gastrointestinal function in cats and dogs or that metronidazole, in combination with another antibiotic and bismuth subsalicylate or subcitrate, will produce long-term eradication of Helicobacter species in these species[22-26].

[Irritable bowel (treatment)]1, including
[Bone and joint infections (treatment)]1; or
[Central nervous system infections (treatment)]1; or
[Intra-abdominal infections (treatment)]1; or
[Perioperative infections, colorectal (prophylaxis)]1; or
[Respiratory tract infections, lower (treatment)]1; or
[Septicemia, bacterial (treatment)]1; or
[Skin and soft tissue infections (treatment)]1—Cats, dogs, and horses: Although there are insufficient clinical research data to establish efficacy, metronidazole is used in the treatment of many types of anaerobic bacterial infections in animals. In human patients, metronidazole is indicated, usually in combination with other antibiotics, in the prevention of perioperative infections during colorectal surgery and in the treatment of bone and joint infections; central nervous system infections; intraoperative infections; lower respiratory tract infections, including pleuropneumonia and lung abscess; septicemia; and skin and soft tissue infections caused by susceptible species, including Bacteroides and Clostridium species[1-4; 5]. There are limited pharmacokinetic data and case reports available pertaining to the use of metronidazole in the treatment of these types of infections in animals[8-9; 12; 14; 16; 19-21; 28].

[Periodontal infections (treatment)]1—Cats and dogs: Metronidazole is used in the treatment of periodontal infections in cats and dogs[15; 17; 18]. It may be administered for destructive periodontal diseases as part of a treatment plan that also includes one or more of the following: dental scaling, gingival crevicular lavage, periodontal surgery, or regular teeth cleaning[17].

REGULATORY CONSIDERATIONS
U.S.—
The Food and Drug Administration has not approved the use of metronidazole in animals. The use of nitroimidazoles in food animals is strictly prohibited.

Canada—
Metronidazole is not approved for use in food-producing animals. There are no established withdrawal times.
CHEMISTRY

Chemical group: Nitroimidazoles.

Chemical name:
- Metronidazole—1H-Imidazole-1-ethanol, 2-methyl-5-nitro.[R-29]
- Metronidazole hydrochloride—1H-Imidazole-1-ethanol, 2-methyl-5-nitro-hydrochloride.[R-29]

Molecular formula:
- Metronidazole—C₆H₉N₃O₃[ R-29]
- Metronidazole hydrochloride—C₆H₉N₃O₃· HCl.[R-29]

Molecular weight:
- Metronidazole—171.15[R-29]
- Metronidazole hydrochloride—207.61.[R-29]

Description: Metronidazole USP—White to pale yellow, odorless crystals or crystalline powder. Is stable in air, but darkens on exposure to light.[R-10]

Solubility: Metronidazole USP—Sparingly soluble in water and in alcohol; slightly soluble in ether and in chloroform.[R-10]

PHARMACOLOGY/PHARMACOKINETICS

Mechanism of action/effect: Metronidazole is reduced as it enters the target cell where it interacts with bacterial or protozoal DNA, causing a loss of helical structure and strand breakage in the DNA; these effects inhibit nucleic acid synthesis and cause death of the cell.

Absorption: Metronidazole is moderately well absorbed from the gastrointestinal tract.[R-21; 13; 17]

Distribution: Horses—In one pharmacokinetic study of horses, peak metronidazole concentrations in peritoneal fluid, synovial fluid, and cerebrospinal fluid were 65%, 92%, and 30% of peak serum concentrations.[R-21] With an oral dose of 7.5 mg/kg every 6 hours, endometrial penetration was poor.[R-21]

Biotransformation: Hepatic, metabolized primarily by side-chain oxidation and glucuronide synthesis.

Pharmacokinetic data:

Table 1. Intravenous administration.

<table>
<thead>
<tr>
<th>Species</th>
<th>Half-life of elimination (hours)</th>
<th>Volume of distribution (L/kg)</th>
<th>Clearance (mL/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs[R-37]</td>
<td>4.48 ± 0.89</td>
<td>Area: 0.95 ± 0.10</td>
<td>2.49 ± 0.54</td>
</tr>
<tr>
<td>Horse[R-11]</td>
<td>2.9</td>
<td>Area: 1.70 ± 0.24</td>
<td>6.67 ± 0.83</td>
</tr>
<tr>
<td>[R-21]</td>
<td>3.11 ± 0.21</td>
<td>Area: 0.74 ± 0.01</td>
<td>2.8 ± 0.18</td>
</tr>
<tr>
<td>[R-19]</td>
<td>3.27 ± 0.65</td>
<td>Steady state: 0.69 ± 0.01</td>
<td>2.8 ± 0.08</td>
</tr>
</tbody>
</table>

Table 2. Oral administration.

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>Cmax (mcg/mL)</th>
<th>Tmax (hour)</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs[R-37]</td>
<td>44</td>
<td>42*</td>
<td>1*</td>
<td>59 to 100</td>
</tr>
<tr>
<td>Horse[R-11]</td>
<td>25</td>
<td>12.6 ± 2.4</td>
<td>1 to 2</td>
<td>85.0 ± 18.6</td>
</tr>
<tr>
<td>[R-19]</td>
<td>20</td>
<td>22 ± 8</td>
<td>1.1 ± 0.6</td>
<td>74 ± 18</td>
</tr>
<tr>
<td>[R-21]</td>
<td>15</td>
<td>13.9 ± 2.18</td>
<td>0.67</td>
<td>97 ± 5.7</td>
</tr>
</tbody>
</table>

*Read from graph.
†Two horses with pleuropneumonia yielded similar kinetic results to that of healthy mares in this study.

PRECAUTIONS TO CONSIDER

CARCINOGENICITY/MUTAGENICITY

Metronidazole has been shown to be a carcinogen in mice and rats with chronic oral administration. It has also been shown to be mutagenic in in vitro assays.[R-1; 4]

PREGNANCY/REPRODUCTION

Pregnancy—Metronidazole readily crosses the placenta and enters the fetal circulation.[R-1] No teratogenic effects were seen in the pups of rats that had received 250 mg per kg of body weight (mg/kg) a day for 1 to 12 days, or 100 mg/kg a day for 40 days. However, spermatogenesis in male rats was affected by the administration of 100 mg/kg a day.

LACTATION

Metronidazole is distributed into milk at concentrations similar to plasma concentrations[R-1; 4]. Risk-benefit should be considered carefully when metronidazole is used in nursing animals.

DRUG INTERACTIONS AND/OR RELATED PROBLEMS

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive:

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with metronidazole.

Cimetidine
(hepatic metabolism of metronidazole may be decreased when metronidazole and cimetidine are used concurrently, possibly resulting in delayed elimination and increased serum metronidazole concentrations[R-6]; dosage of metronidazole may need to be adjusted)

Phenobarbital
(phenobarbital may induce microsomal liver enzymes, increasing metronidazole’s metabolism and resulting in a decrease in half-life and plasma concentration[R-5]; dosage of metronidazole may need to be adjusted)

SIDE/ADVERSE EFFECTS

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION

Neurologic disturbances (ataxia, nystagmus, seizures, tremors, weakness)—with high dosage in cats, dogs, and horses[R-31; 32]

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME

Anorexia; neutropenia; vomiting

THOSE NOT INDICATING NEED FOR MEDICAL ATTENTION

Reddish brown urine

HUMAN SIDE/ADVERSE EFFECTS[R-5]

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are
included in the human monograph *Metronidazole (Systemic)* in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of metronidazole in the treatment of animals:

Incidence more frequent

**Central nervous system (CNS) effects; gastrointestinal disturbance**

Incidence less frequent or rare

**Change in taste sensation; CNS toxicity, including ataxia and encephalopathy; dark urine; dryness of mouth; hypersensitivity: leukopenia; pancreatitis; peripheral neuropathy**—usually with high doses or prolonged use: **seizures**—usually with high doses: **thrombocytopenia**—reversible: **thrombophlebitis; unpleasant or sharp metallic taste; urinary tract effects, including frequent or painful urination and inability to control urine flow; vaginal candidiasis**

### OVERDOSE

For information in cases of overdose or unintentional ingestion, **contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center** (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

Lethal dose—**Dogs:** 250 mg per kg of body weight (mg/kg) a day induced central nervous system dysfunction within 4 to 6 days and death within a week of onset of signs\textsuperscript{[R-32]}.  

**Horses:** Oral, 15 to 25 mg (base) per kg of body weight every six hours\textsuperscript{[R-31]}.  

Note: Anorexia may occur in horses treated with the above dose; therefore, some clinicians recommend use of a lower oral dose of 10 mg per kg of body weight every twelve hours\textsuperscript{[R-40]}.  

For susceptible *gram-negative anaerobic* infections in horses, one study recommended an alternative dosage regimen of 15 mg per kg of body weight as an initial dose, followed by 7.5 mg per kg of body weight every six hours\textsuperscript{[R-21]}.  

Contents of the capsule can be mixed with molasses or administered via nasogastric tube.\textsuperscript{[R-11; 13; 34]}

**Hepatic encephalopathy**\textsuperscript{1; or} **[Inflammatory bowel disease]**\textsuperscript{1}—**Cats and dogs:** Oral, 7.5 mg (base) per kg of body weight every twelve hours.

### CLINICAL EFFECTS OF OVERDOSE

The following effects have been selected on the basis of their potential clinical significance—not necessarily inclusive:

**Dogs,** with doses of 65 to 129 mg/kg a day:\textsuperscript{[R-32]}

**Ataxia; head tilt; nystagmus** (spontaneous, positional, vertical);  

**seizures**

Note: Ataxia and nystagmus were noted consistently in a report on five cases of toxicosis. Signs appeared within 7 to 12 days of initiating therapy. In dogs that survived complications of neurologic dysfunction, signs gradually resolved over 1 to 2 weeks after ending metronidazole administration\textsuperscript{[R-32]}.  

**ORAL DOSAGE FORMS**

Note: In other USP DI monographs, bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling, and superscript 1 refers to categories of use and/or indications that are not included in Canadian product labeling. However, since metronidazole is not specifically approved for veterinary use, there is no product labeling identifying approved indications.

The dosing and strengths of the dosage forms available are expressed in terms of metronidazole base.

**METRONIDAZOLE CAPSULES**

**Usual dose:**

[Bacterial infections, anaerobic]\textsuperscript{1; or} **[Protozoal infections]**\textsuperscript{3}—

**Cats and dogs:** Oral, 15 mg (base) per kg of body weight every twelve hours\textsuperscript{[R-38]}.

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**USP requirements:** Preserve in well-closed, light-resistant containers. Contain the labeled amount, within ±10%. Meet the requirements for Identification, Dissolution (85% in 60 minutes in 0.1 N hydrochloric acid in Apparatus 1 at 100 rpm), and Uniformity of dosage units\(^{[R-10]}\).

**PARENTERAL DOSAGE FORMS**

Note: In other USP DI monographs, bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling, and superscript 1 refers to categories of use and/or indications that are not included in Canadian product labeling. However, since metronidazole is not specifically approved for veterinary use, there is no product labeling identifying approved indications. The dosing and strengths of the dosage forms available are expressed in terms of metronidazole base.

**METRONIDAZOLE INJECTION USP**

**Usual dose:**

Note: Reliable dosing information is not available for the use of parenteral metronidazole in animals. However, for situations in which oral administration is not a viable option, injectable forms are used by following dosing regimens similar to oral dosage forms.

**Strength(s) usually available:**

**U.S.—**

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (base) per 100 mL (Rx) [Flagyl I.V. RTU; Metro I.V.; generic].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (base) per 100 mL (Rx) [Flagyl; generic].

**Withdrawal times:** There are no established withdrawal times since metronidazole is not approved for use in food-producing animals.

**Packaging and storage:** Prior to reconstitution, store below 30 °C (86 °F), in a light-resistant container, unless otherwise specified by manufacturer.

**Preparation of dosage form:**

Metronidazole hydrochloride for injection must not be given by direct intravenous injection, since the initial dilution has an extremely low pH (0.5 to 2.0). It must be diluted further and neutralized prior to administration.\(^{[R-35]}\)

To prepare initial dilution for intravenous infusion, add 4.4 mL of sterile water for injection, bacteriostatic water for injection, 0.9% sodium chloride injection, or bacteriostatic sodium chloride injection to each 500-mg vial, to provide a concentration of 100 mg per mL (pH 0.5 to 2.0). The resulting solution should be further diluted in 100 mL of 0.9% sodium chloride injection, 5% dextrose injection, or lactated Ringer’s injection. The final dilution must be neutralized with approximately 5 mEq of sodium bicarbonate injection per 500 mg of metronidazole (final pH 6 to 7). Since carbon dioxide gas is produced during neutralization, it may be necessary to relieve the pressure in the final container. The final concentration should not exceed 8 mg per mL, since neutralization decreases the solubility of metronidazole and precipitation may occur.\(^{[R-35]}\)

**Stability:**

After reconstitution, solutions retain their potency for 96 hours if stored below 30 °C (86 °F) in room light. Diluted and neutralized solutions retain their potency for 24 hours. Neutralized solutions should not be refrigerated, because precipitation may occur.

**Incompatibilities:**\(^{[R-35]}\)

Metronidazole should not be used with aluminum (needles or hubs) that would come into contact with the medication. Intravenous admixtures of metronidazole with other medications are not recommended.

**USP requirements:** Not in USP\(^{[R-10]}\).

Revised: 07/28/94; 09/30/02
Interim revision: 06/05/95; 06/20/96; 05/19/97; 7/21/98
04/05/03

**REFERENCES**

31. Panel comment, Rec. 5/03.
PENICILLIN G Veterinary—Intramammary-Local†

Some commonly used brand names for veterinary-labeled products are Go-dry and Masti-Clear.

Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

†Not commercially available in Canada.

CATEGORY:
Antibacterial (intradammary-local).

INDICATIONS

GENERAL CONSIDERATIONS

The spectrum of activity of penicillin G includes many aerobic and anaerobic gram-positive organisms. Penicillin G is highly susceptible to beta-lactamases and has little activity against organisms that can produce these enzymes. In addition, penicillin G is ineffective against bacteria that are resistant to certain other mechanisms, such as having a relatively impermeable cell wall. Therefore, penicillin G has little activity against many staphylococci and most gram-negative bacteria.

ACCEPTED

Mastitis (treatment)†—Cattle: Penicillin G is indicated in the treatment of mastitis in cattle†R-1; 2; 7 caused by susceptible organisms such as Streptococcus agalactiae†R-7; 20. Intramammary therapy alone is indicated only in the treatment of subacute mastitis manifested by mild inflammatory changes in the milk or udder. Acute or purulent mastitis, in which gross inflammatory changes in the milk or udder or systemic signs appear, requires administration of other medications also, which may include systemic antibiotics and/or supportive therapy.†R-8

REGULATORY CONSIDERATIONS

U.S.—
Withdrawal times have been established for penicillin G procaine intramammary infusion (see the Dosage Forms section†R-11).

CHEMISTRY

Source: Produced by the mold Penicillium.†R-8
Chemical group: Beta-lactam antibiotics.†R-8; 9
Chemical name: Penicillin G procaine—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3, 3-dimethyl-7-oxo-6-[(phenylacetyl)laminoo]-, [2S-(2 alpha,5 alpha,6 beta)]-, compd. with 2-(diethylamino)ethyl 4-aminobenzoate (1:1) monohydrate.†R-10
Molecular formula: Penicillin G procaine
C13H20N2O2 · C14H20N2O2 · H2O†R-10
Molecular weight: Penicillin G procaine—588.72.†R-10
Description: Penicillin G Procaine USP—White crystals or white, very fine, microcrystalline powder. Is odorless or practically odorless, and is relatively stable in air. Its solutions are dextrorotatory. Is rapidly inactivated by acids, by alkali hydroxides, and by oxidizing agents†R-17.
pKa: 2.7†R-11; 12
Solubility: Penicillin G Procaine USP—Slightly soluble in water; soluble in alcohol and in chloroform†R-17.

PHARMACOLOGY/PHARMACOKINETICS

Mechanism of action/effect: The penicillins produce their bactericidal effect by inhibiting cross-linkages during bacterial cell wall synthesis.†R-9
Penicillin G must penetrate the cell wall to attach to specific proteins on the outer surface of the bacterial cell membrane. In actively growing cells, the binding of penicillin within the cell wall leads to interference with production of cell wall peptidoglycans and subsequent lysis of the cell in a hypo- or iso-osmotic environment†R-9; 11

Distribution: Medications infused into a teat are considered to be fairly evenly distributed in that quarter of the healthy mammary gland; however, in an udder affected by moderate to severe mastitis, the presence of edema, blockage of milk ducts, and reduced blood circulation causes uneven distribution.†R-14 After penicillin G procaine is infused into a mammary gland, it is also partially distributed into the other quarters of the gland†R-4; 15 into the local lymph circulation, and to some degree into the plasma and other tissues†R-16

Peak serum concentration: In healthy animals, after intramammary administration of 400 mg (404,000 Units) of penicillin G procaine in combination with the same amount of dihydrostreptomycin sulfate, the peak serum concentration of penicillin G is 0.07 mcg/mL at 4 hours.†R-16

PRECAUTIONS TO CONSIDER

PATIENT MONITORING

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

Bacteriologic pathogen identification in milk
(milk samples should be tested 3 weeks after the end of treatment; mastitis is not considered bacteriologically cured until samples show an absence of the mastitis-causing organisms†R-21)

Clinical signs
(although a resolution of clinical signs of mastitis is not an indication that a bacteriologic cure has been achieved†R-18, monitoring of the clinical condition of the mammary gland, teat, and milk produced can aid in diagnosis of a recurrence of mastitis or initial diagnosis of mastitis in another cow in the herd)

Somatic cell count
(somatic cell counts performed on milk to monitor the dairy herd are used primarily to maintain milk quality, but also to approximately assess the overall effectiveness of mastitis control programs that may include antibiotic treatment of cows†R-5)

SIDE/ADVERSE EFFECTS

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
Cows

Allergic reactions—theoretically possible locally or systemically
OVERDOSE
For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0800; a fee may be required for consultation) and/or the drug manufacturer.

CLIENT CONSULTATION
Treatment of mastitis in dairy cattle is best achieved by a comprehensive mastitis control program in which herd management is the primary focus. The program should include good maintenance of milking equipment and constant evaluation of milking procedures and teat health as well as strategic treatment of clinical cases of mastitis.\textsuperscript{R-7}

VETERINARY DOSING INFORMATION
Antibiotic therapy in the dry cow is measurably more effective than treatment during lactation.\textsuperscript{R-7, 18}

Choice of antibiotic for treatment of mastitis should be based on knowledge of culture and sensitivity of pathogens causing mastitis in the cow and the dairy herd.\textsuperscript{R-19}

Before administration of intramammary penicillin G procaine, the following steps should be performed:\textsuperscript{R-1}

- The udder should be milked out completely and the teats washed with warm water and a disinfectant. Care should be taken to avoid washing excess dirt down from the udder onto the teat ends.\textsuperscript{R-6}
- The area should be dried thoroughly. An effective germicidal teat dip should be applied for one minute and then each teat wiped with a separate cotton ball soaked with an antiseptic such as 70% alcohol.
- Persons performing the treatment should wash and dry their hands before each treatment.
- The tip of the syringe should be inserted into the teat end as little as possible\textsuperscript{R-6} and the contents of the syringe should be injected into each streak canal while the teat is held firmly. The medication should then be gently massaged up the teat canal into the udder.
- An effective teat dip is recommended on all teats following treatment.

For the lactating cow, treated quarters should not be milked for at least six hours after treatment but should be milked at regular intervals thereafter.\textsuperscript{R-2}

INTRAMAMMARY DOSAGE FORMS

PENICILLIN G PROCAINE INTRAMAMMARY INFUSION USP

\textbf{Usual dose:} Antibacterial\textsuperscript{1}—Cattle:

- Dry cow (nonlactating)—Intramammary, 100,000 Units into each quarter of the udder at the time of drying-off.\textsuperscript{R-1}
- Lactating cow—Intramammary, 100,000 Units into each affected quarter of the udder every twelve hours for a maximum of three doses.\textsuperscript{R-2}

\textbf{Strength(s) usually available:}

- U.S.—\textsuperscript{R-1, 2}
  - Veterinary-labeled product(s): 100,000 Units per 10 mL (OTC) [Go-dry (dry cow only); Masti-Clear (lactating cow only)].

- Canada—\textsuperscript{R-1}
  - Veterinary-labeled product(s): Not commercially available.

\textbf{Withdrawal times:}

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows</td>
<td>Nonlactating</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Lactating</td>
<td>3</td>
</tr>
</tbody>
</table>

\textbf{Packaging and storage:} Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.\textsuperscript{R-1, 2}

\textbf{USP requirements:} Preserve in well-closed disposable syringes. A suspension of Penicillin G Procaine in a suitable vegetable oil vehicle. Label it to indicate that it is for veterinary use only. Contains an amount of penicillin G procaine equivalent to the labeled amount of penicillin G, within –10% to +15%. Meets the requirements for Identification and Water (not more than 1.4%).\textsuperscript{R-17}

\textsuperscript{1}Not included in Canadian product labeling or product not commercially available in Canada.

Interim revision: 04/24/96; 05/19/97; 07/08/98; 10/15/99; 06/30/02/28/03

REFERENCES
PENICILLIN G Veterinary—Systemic

Some commonly used brand names are:
For veterinary-labeled products—Agri-cillin; Ambi-pen; Aquacillin; Benzaprol; Combidicillin; Combidicillin AG; Depocillin; Derapen SQ/LA; Duo-Pen; Duplocillin LA; Durapen; Hi-Penicin 300; Longistil; Microcillin; Pen-Aqueous; Pen G Injection; Penmed; Penro; Pot-Pen; Propen LA; R-Pen; Twin-pen; and Ultropen LA.
For human-labeled products—Pfizerpen.

CATEGORY:
Antibacterial (systemic).

INDICATIONS
Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

GENERAL CONSIDERATIONS
The spectrum of activity of penicillin G includes many aerobic and anaerobic gram-positive organisms. Aerobes susceptible to penicillin G include most beta-hemolytic streptococci, beta-lactamase-negative staphylococci, Actinomyces species, some Bacillus anthracis, Corynebacterium species, and Erysipelothrix rhusiopathiae. Most species of anaerobes, including Clostridium species, but excluding beta-lactamase-producing Bacteroides species, are also susceptible to penicillin G. Penicillin G is easily inactivated by beta-lactamases and has little efficacy against organisms that can produce these enzymes. In addition, penicillin G is ineffective against those bacteria that are resistant by other mechanisms, such as having a relatively impermeable cell wall. Therefore, penicillin G has little activity against many staphylococci and most gram-negative bacteria.

ACCEPTED
Blackleg (treatment)—Cattle and [sheep]: Penicillin G is indicated in the treatment of blackleg caused by susceptible organisms such as Clostridium chauvoei in cattle and sheep. [R-6; 6]
Erysipelas (treatment)—Pigs and turkeys: Penicillin G is indicated in the treatment of infections caused by Erysipelothrix rhusiopathiae (insidiosa) in pigs and turkeys. [R-6; 9]
Pharyngitis (treatment); or Rhinitis (treatment)—Cattle: Penicillin G is indicated in the treatment of bacterial rhinitis or pharyngitis caused by susceptible organisms such as Actinomyces pyogenes. [R-6]
Pneumonia, bacterial (treatment)—Cattle, sheep, [horses] [R-6; 7], and [pigs] [R-10]: Penicillin G is indicated in the treatment of bacterial pneumonia caused by susceptible organisms in cattle, sheep, [horses], and [pigs]; however, for bacterial pneumonia in cattle, sheep, and pigs, penicillin G is not considered the drug of first choice pending culture and sensitivity results. [R-85; 87]
Strangles (treatment)—Horses: Penicillin G is indicated in the treatment of strangles caused by Streptococcus equi. [R-7] however, it may be effective only during the acute phase of the infection. [R-11]
[Actinomycosis (treatment)]—Cattle: Penicillin G is indicated in the treatment of actinomycosis, and may be most effective for infections which pathogens other than Actinomyces species are not yet involved. [R-6; 14]
[Arthritis, septic (treatment)]—Cattle, horses, pigs, and sheep: [R-6] Penicillin G is indicated in the treatment of septic arthritis caused by susceptible bacteria in cattle, horses, pigs, and sheep. [R-15; 16]
[Leptospirosis (treatment)]—Cattle, dogs, horses, and pigs [R-6; 17], and pigs: [R-6] Penicillin G is indicated in the treatment of acute leptospirosis in cattle, dogs, horses, and pigs. The chronic shedding stage of leptospirosis is often treated with tetracycline; penicillin G administered alone will not clear the carrier state. [R-73; 85]
[Malignant edema (treatment)]—Cattle: [R-6] Penicillin G is indicated in the treatment of malignant edema caused by susceptible Clostridium septicum in cattle.
Metritis (treatment)—Cattle, horses, pigs, and sheep: [R-6] Penicillin G is indicated in the treatment of metritis caused by susceptible organisms in cattle, horses, pigs, and sheep [R-20; 21]; however, therapeutic regimens often emphasize evacuation of uterine contents as the primary treatment. [R-85]
[Pyelonephritis (treatment)]—Cattle: Penicillin G is indicated in the treatment of pyelonephritis caused by susceptible organisms such as Corynebacterium renale in cattle. [R-6; 22; 23]
[Skin and soft tissue infections (treatment)]—
Cattle: Penicillin G is indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including those associated with calf diphtheria, foot rot, the umbilicus, and wounds. [R-10]
Horses: Penicillin G is indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including those associated with the umbilicus and with wounds. [R-6]
Pigs: Penicillin G is indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including those associated with the umbilicus. [R-6]
Sheep: Penicillin G is indicated in the treatment of skin and soft tissue infections caused by susceptible organisms, including those associated with post-surgical tail docking and castration site infections, and also those associated with the umbilicus. [R-6; 10]
[Tetanus (treatment)]—Cats, cattle, dogs, horses, and pigs: [R-6] Penicillin G is indicated in the treatment of Clostridium tetani in cats, cattle, dogs, horses, and pigs in conjunction with tetanus antitoxin and supportive therapy. [R-6]

1Not included in Canadian product labeling or product not commercially available in Canada.

REGULATORY CONSIDERATIONS
U.S.—
Administration of penicillin G procaine to animals may produce procaine concentrations in the blood and urine that violate equine and greyhound racing commission prohibitions. [R-91; 92]
Penicillin G is not for use in turkeys producing eggs for human consumption or for use in horses intended for food. [R-7; 8]
Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension USP combination is not labeled for use in lactating cattle or preruminating calves. [R-5]
Some brands of Penicillin G Procaine Injectable Suspension USP are not labeled for use in preruminating cattle. [R-53]
Withdrawal times have been established for Penicillin G Potassium USP, Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension USP, and Penicillin G Procaine Injectable Suspension USP (see the Dosage Forms section).\[R-5; 7; 8; 26]\n
Canada—

Administration of penicillin G procaine to animals may produce procaine concentrations in the blood and urine that violate equine and greyhound racing commission prohibitions.\[R-84]\n
Penicillin G is not labeled for use in turkeys producing eggs for human consumption.\[R-9]\n
Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension USP combination is not labeled for use in lactating cattle.\[R-27; 28]\n
Withdrawal times have been established for Penicillin G Potassium USP, Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension USP, and Penicillin G Procaine Injectable Suspension USP (see the Dosage Forms section).\[R-9; 27; 28]\n
CHEMISTRY

**Source:** Produced by the mold *Penicillium.*\[R-1]\n
**Chemical group:** Beta-lactam antibiotics.\[R-1; 29]\n
**Chemical name:**

- Penicillin G benzathine—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, [2S-(2alpha,5alpha,6beta)-], compd. with N,N’-bis(phenylmethy)-1,2-ethanediamine (2:1), tetrahydrate.\[R-10]\n- Penicillin G potassium—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, monopotassium salt, [2S-(2alpha,5alpha,6beta)-].\[R-10]\n- Penicillin G procaine—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, [2S+(2alpha,5alpha,6beta)-], compd. with 2-(diethylamino)ethyl 4-aminobenzoate (1:1) monohydrate.\[R-10]\n- Penicillin G sodium—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, [2S-(2alpha,5alpha,6beta)-], monosodium salt.\[R-10]\n
**Molecular formula:**

- Penicillin G benzathine—(C16H20N2S)2C16H2O2N24H2O.\[R-10]\n- Penicillin G potassium—C16H11KNO3S.\[R-10]\n- Penicillin G procaine—C16H11N2O4S-C16H2O2N24H2O.\[R-10]\n- Penicillin G sodium—C17H17N2NaO3S.\[R-10]\n
**Molecular weight:**

- Penicillin G benzathine—981.19.\[R-10]\n- Penicillin G potassium—372.48.\[R-10]\n- Penicillin G procaine—588.72.\[R-10]\n- Penicillin G sodium—356.37.\[R-10]\n
**Description:**

- Penicillin G Benzathine USP—White, odorless, crystalline powder.\[R-51]\n- Penicillin G Potassium USP—Colorless or white crystals or white, crystalline powder. Is odorless or practically so, and is moderately hygroscopic. Its solutions are dextrorotatory. Its solutions retain substantially full potency for several days at temperatures below 15 °C, but are rapidly inactivated by acids, by alkali hydroxides, by glicerin, and by oxidizing agents.\[R-51]\n- Penicillin G Procaine USP—White crystals or white, very fine, micro-crystalline powder. Is odorless or practically odorless, and is relatively stable in air. Its solutions are dextrorotatory. It is rapidly inactivated by acids, by alkali hydroxides, and by oxidizing agents.\[R-61]\n
Penicillin G Sodium USP—Colorless or white crystals or white to slightly yellow, crystalline powder. Is odorless or practically odorless, and is moderately hygroscopic. Its solutions are dextrorotatory. Is relatively stable in air, but is inactivated by prolonged heating at about 100 °C, especially in the presence of moisture. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15 °C. Its solutions are rapidly inactivated by acids, alkali hydroxides, oxidizing agents, and penicillinase.\[R-51]\n
**pKa:** 2.7.\[R-2; 12]\n
**Solubility:**

- Penicillin G Benzathine USP—Very slightly soluble in water; sparingly soluble in alcohol.\[R-51]\n- Penicillin G Potassium USP—Very soluble in water, in saline TS, and in dextrose solutions; sparingly soluble in alcohol.\[R-51]\n- Penicillin G Procaine USP—Slightly soluble in water; soluble in alcohol and in chloroform.\[R-51]\n
PHARMACOLOGY/PHARMACOKINETICS

See also Table 1. Pharmacokinetic Parameters at the end of this monograph.

Note: With the exception of information in Table 1, pharmacokinetic data in this section are based on intravenous administration of potassium or sodium penicillin G.

**Mechanism of action/effect:** The penicillins produce their bactericidal effect by inhibition of bacterial cell wall synthesis.\[R-29]\n
Penicillin G must penetrate the cell wall to attach to specific proteins on the inner surface of the bacterial cell membrane. In actively growing cells, the binding of penicillin within the cell wall leads to interference with production of cell wall peptidoglycans and subsequent lysis of the cell in a hypo- or iso-osmotic environment.\[R-4; 29; 33]\n
**Absorption:**

Gastric absorption of penicillin G is poor in many species because it is rapidly hydrolyzed in the acid environment of the stomach or abomasum.\[R-41]\n
Only 15 to 30% of penicillin G may be absorbed by the oral route in a fasted animal and that percent decreases when there is food in the stomach.\[R-14]\n
The sodium and potassium salts of penicillin G are the only dosage forms that are suitable for intravenous administration. They are also the most quickly absorbed from intramuscular or subcutaneous sites of administration.\[R-4; 14; 35]\n
Procaine penicillin G is more slowly absorbed from intramuscular administration than are the sodium or potassium salts and so produces more sustained but lower plasma concentrations.\[R-4; 15]\n
Benzathine penicillin G is the least soluble of the dosage forms and so is the most slowly absorbed; the longest sustained but lowest plasma concentrations of penicillin G are produced.\[R-4; 15]\n
The rate of absorption from intramuscular injections of some penicillin dosage forms, such as procaine penicillin G, can vary depending on the injection site; injections into the neck muscle in cattle and horses produce more rapid absorption and higher plasma concentrations than do injections into the gluteal muscle. Also, procaine penicillin G is more completely absorbed in steers when injected intramuscularly than when administered subcutaneously.

**Distribution:** Volume of distribution—

*Drodunaries:* 0.34 ± 0.079 liter per kg (L/kg).\[R-59]*
Penicillins have been shown to cross the placenta; however, no teratogenic problems have been associated with the use of penicillin G during pregnancy in studies of mice, rabbits, and rats, or during clinical use in many species. No well-controlled studies have been performed for most species.\[R-75]\]

**PREGNANCY/REPRODUCTION**

Penicillins have been shown to cross the placenta; however, no teratogenic problems have been associated with the use of penicillin G during pregnancy in studies of mice, rabbits, and rats, or during clinical use in many species. No well-controlled studies have been performed for most species.\[R-75]\]

**LACTATION**

Penicillin G is distributed into milk\[R-2; 4\]; in food animals the distribution is sufficient to cause violative residues. However, the concentrations of penicillin produced in milk are subtherapeutic for most bacteria.\[R-85]\]

In some species, approximately 1% of an intramuscular injection of sodium penicillin G was distributed into the milk.\[R-11]\]

**PROTEIN BINDING**

- **Cattle**—Low \( (28.5\%)\)[R-38; 39]
- **Dogs**—Moderate \( (60\%)\)[R-40]
- **Horses**—Moderate \( (52–54\%)\)[R-39; 41]
- **Rabbits**—Low \( (35\%)\)[R-39; 42]
- **Sheep**—Low \( (30.4\%)\)[R-38; 39]

**ELIMINATION**

**Horses:** Elimination—
- Calves, newborn to 15 days: 26.6 minutes \[R-60\]
- Dogs: 30 minutes \[R-60\]
- Dromedaries: 49 minutes \[R-59\]
- Horses: 48 to 53 minutes \[R-41; 57\]
- Sheep: 42 minutes \[R-59\]
- Turkeys: 30 minutes \[R-62\]

**Horses:**

- Newborn: \( 2.98 \pm 0.52 \) mL/min/kg \[R-60\]
- Five days: \( 4.83 \pm 1.45 \) mL/min/kg \[R-60\]
- Ten days: \( 3.11 \pm 1 \) mL/min/kg \[R-60\]
- Fifteen days: \( 4.65 \pm 1.18 \) mL/min/kg \[R-60\]

**Sheep:**

- Newborn: \( 0.604 \pm 0.205 \) L/kg \[R-59\]

**Half-life:**

- **Dogs:** 30 minutes \[R-60\]
- **Horses:** 48 to 53 minutes \[R-41; 57\]
- **Sheep:** 42 minutes \[R-59\]
- **Turkeys:** 30 minutes \[R-62\]

**Drug Interactions and/or Related Problems**

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive \( (\ast = \text{major clinical significance})\):

- **Combination Therapy**
  - **Antibacterials, bacteriostatic, such as:** Chloramphenicol or Tetracycline
    - (because penicillin G acts only on cells that are actively reproducing, bacteriostatic antibiotics such as chloramphenicol or tetracycline may decrease the efficacy of penicillin G by depressing the activity of target cells\[R-43\]; however, the clinical significance of this interference is not well documented\[R-66\]).
  - **Phenytoin**
  - (the concomitant administration of phenytoin with penicillin G may cause higher plasma concentrations of penicillin G, resulting in lower distribution of penicillin G to the tissues\[R-44\]).

**Medical Considerations/Contraindications**

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive \( (\ast = \text{major clinical significance})\).

**Except under special circumstances, this medication should not be used when the following medical problems exist:**

- **Hypersensitivity to penicillin**
  - (some reactions, such as hemolytic anemia in horses\[R-49\], may be much more likely to occur in an animal that has had a previous reaction to penicillin G)
  - **Hypersensitivity to procaine**\[R-64\]
  - (some sources recommend intradermal procaine testing of animals suspected of procaine sensitivity before administering procaine penicillin G\[R-61\]).

**Risk-benefit should be considered when the following medical problems exist:**

- **Erysipelas in pigs**
  - (administration of procaine penicillin has caused recurrence or exacerbation of signs of erysipelas including abortion, cyanotic ears, fever of 39.5 to 41 °C, inappetance, lassitude, vomiting, and shivering\[R-50\]).

**Renal function impairment**

(because penicillin G is primarily excreted by the kidneys, unnecessary accumulation of medication in the plasma and tissues may occur\[R-45\]; also, the sodium or potassium content of intravenous penicillin G dosage forms should be considered)

**Pediatrics**

In neonates that have not yet developed full renal function, excretion of penicillin G occurs at a slower rate than it does in a mature animal.\[R-60; 75\]

**Drug Interactions and/or Related Problems**

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive \( (\ast = \text{major clinical significance})\):

**Combination Therapy**

- **Antibacterials, bacteriostatic, such as:** Chloramphenicol or Tetracycline
  - (because penicillin G acts only on cells that are actively reproducing, bacteriostatic antibiotics such as chloramphenicol or tetracycline may decrease the efficacy of penicillin G by depressing the activity of target cells\[R-43\]; however, the clinical significance of this interference is not well documented\[R-66\]).
  - **Phenytoin**
  - (the concomitant administration of phenytoin with penicillin G may cause higher plasma concentrations of penicillin G, resulting in lower distribution of penicillin G to the tissues\[R-44\]).

**Medical Considerations/Contraindications**

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive \( (\ast = \text{major clinical significance})\).

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**Renal function impairment**

(because penicillin G is primarily excreted by the kidneys, unnecessary accumulation of medication in the plasma and tissues may occur\[R-45\]; also, the sodium or potassium content of intravenous penicillin G dosage forms should be considered)
Patient Monitoring
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; * = major clinical significance):

- Culture and susceptibility, in vitro, and minimum inhibitory concentration (MIC)
- (in vitro cultures and MIC test should be done on samples collected prior to penicillin administration to determine pathogen susceptibility)

Potassium or sodium, serum
(determination of concentrations of serum sodium or potassium may be necessary in animals receiving high doses or long-term therapy with potassium or sodium penicillin G, particularly in those patients with severe renal function impairment, other pre-existing electrolyte imbalance, or congestive heart failure)

Side/Adverse Effects
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

Those Indicating Need for Medical Attention
Incidence unknown

- Allergic reactions, specifically anaphylaxis
  - Contact dermatitis
  - Serum sickness–like syndromes
  - Urticaria
  - Overgrowth of nonsusceptible organisms
  - Procaine toxicity
  - Procaine toxicity

Note: Multiple cases of procaine toxicity have been reported in pig herds being treated for erysipelas. Signs included abortion, cyanotic ears, fever of 39.5 to 41°C, inappetance, lassitude, vomiting, and shivering.

Horses
- Allergic reactions, specifically anaphylaxis
- Immune-mediated hemolytic anemia
- Proximal muscle weakness

Note: Proximal muscle weakness is seen in horses receiving procaine-containing formulations in higher doses.

Those Indicating Need for Medical Attention Only If They Continue or Are Bothersome
Incidence more frequent

- Pain at site of injection
- With higher doses

Human Side/Adverse Effects
In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Penicillins (Systemic) in USP DI Volume I: these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of penicillin G in the treatment of animals:

- Incidence more frequent

Gastrointestinal reactions; headache; oral candidiasis; vaginal candidiasis
Incidence less frequent

- Allergic reactions, specifically anaphylaxis
- Exfoliative dermatitis
- Serum sickness–like reactions
- Skin rash, hives, or itching

Clostridium difficile colitis; hepatotoxicity; interstitial nephritis; leukopenia or neutropenia; mental disturbances; pain at site of injection; platelet dysfunction or thrombocytopenia; seizures
Note: Clostridium difficile colitis may occur up to several weeks after discontinuation of these medications.

Interstitial nephritis is seen primarily with methicillin, and to a lesser degree with nafcillin and oxacillin, but may occur with any penicillin.

Mental disturbances are toxic reactions to the procaine content of penicillin G procaine; this reaction may be seen in patients who receive a large single dose of the medication, as in the treatment of gonorrhea.

Seizures are more likely to occur in patients receiving high doses of a penicillin and/or patients with severe renal function impairment.

Overdose
For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-444-0000; a fee may be required for consultation) and/or the drug manufacturer.

Veterinary Dosing Information
For Parenteral Dosage Forms Only
To prevent procaine toxicity, keeping procaine penicillin at proper storage temperature and following shelf life recommendations are recommended to avoid any degradation of the product.

For Treatment of Adverse Effects
Recommended treatment consists of the following:

- For anaphylaxis
  - Parenteral epinephrine
  - Oxygen administration and respiratory support.

- For procaine toxicity
  - If seizures occur, sedation with diazepam and/or barbiturates.
  - Oxygen administration and respiratory support as needed.
  - Treatment for cardiovascular collapse if necessary.

Oral Dosage Forms
Penicillin G Potassium for Oral Solution USP
Usual dose: Antibacterial—Turkeys: Oral, administered as the sole source of drinking water at a concentration of 1,500,000 Units per gallon (395,000 Units per L) for five days.

Size(s) usually available

- Veterinary-labeled product(s):
  - 384,000,000 Units (OTC) [R-Pen].
  - 500,000,000 Units (OTC) [R-Pen; GENERIC].
Canada—[R-9]
Veterinary-labeled product(s):
100,000,000 Units (OTC) [Pot-Pen],
500,000,000 Units (OTC) [Pot-Pen; GENERIC],
15,000,000,000 Units (OTC) [GENERIC].

Withdrawal times:
U.S.—[R-8; 26] and Canada—[R-9]

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkeys</td>
<td>1</td>
</tr>
</tbody>
</table>

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Store in a tight container.

Preparation of dosage form:
U.S.—Dissolve 384,000,000 Units in 256 Gallons (969 L) to produce the final 1,500,000 Units per Gallon (3.8 L) solution.\[R-8\]
Canada—Dissolve 100,000,000 Units in 88.7 Gallons (337 L) to produce the final 1,128,600 Units per Gallon (3.8 L) solution.\[R-9\]

Stability: Gravity flow water systems require preparation of fresh solutions every 12 hours. Automatic watering systems require fresh solution preparation every 24 hours.\[R-8\]

USP requirements: Preserve in tight containers. A dry mixture of Penicillin G Potassium and one or more suitable buffers, colors, diluents, flavors, and preservatives. Contains the labeled number of Penicillin G Units when constituted as directed in the labeling, within –10% to +30%. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume (multiple-unit containers), pH (5.5–7.5, in the solution constituted as directed in the labeling), and Water (not more than 1.0%).\[R-51\]

PARENTERAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

PENICILLIN G BENZATHINE AND PENICILLIN G PROCAINE INJECTABLE SUSPENSION USP
Note: Penicillin G benzathine and penicillin G procaine combination has been replaced by other more effective medications. Although products containing penicillin G procaine and penicillin G benzathine combined may be effective in the treatment of extremely sensitive organisms, the plasma concentration of penicillin G produced by the administration of recommended doses of penicillin G benzathine drops to such a low level after 12 to 48 hours that it becomes ineffective in the treatment of most systemic infections.\[R-78; 79\] No dosage of these penicillin G procaine and penicillin G benzathine combinations can be recommended as likely to be effective for many infections caused by penicillin-sensitive organisms.\[R-88\] Even when administered at label doses, the risk exists for residues, which are 30 to 60 times the maximum limit, to occur at the injection site.\[R-80\]

Strength(s) usually available\[R-46\]:
U.S.—
Veterinary-labeled product(s):
150,000 Units of penicillin G benzathine and 150,000 Units of penicillin G procaine per mL (Rx) [Ambi-Pen; Combicillin; Combicillin AG; Duo-Pen; Durapen; Twin-Pen; GENERIC].

Canada—
Veterinary-labeled product(s):
150,000 Units of penicillin G benzathine and 150,000 Units of penicillin G procaine per mL (Rx) [Benzapro; Duplocillin LA; Longisil].

Withdrawal times:
U.S.—[R-26]

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle, beef</td>
<td>30</td>
</tr>
</tbody>
</table>

Note: Products bearing labeling listing the above withdrawal time state that it is based on a dose of 4400 Units of penicillin G benzathine and 4400 Units of penicillin G procaine per kg (2000 Units of each per pound) of body weight administered subcutaneously every 48 hours for two treatments and is not applicable to higher doses or longer administration.\[R-5\]

Canada—[R-27; 28]

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle, beef</td>
<td>14</td>
</tr>
</tbody>
</table>

Note: Products bearing labeling listing the above withdrawal time state that it is based on a dose of 4286 to 4500 Units of penicillin G benzathine and 4286 to 4500 Units of penicillin G procaine per kg of body weight administered intramuscularly and is not applicable to higher doses or longer administration.\[R-27; 28; 61\]

Packaging and storage: Store between 2 and 8 °C (36 and 46 °F). Protect from freezing.\[R-6\]

Preparation of dosage form: The vial should be warmed to room temperature and shaken well to insure a uniform suspension.\[R-5\]

USP requirements: Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass. A sterile suspension of Penicillin G Benzathine and Penicillin G Procaine or when labeled for veterinary use only, of Penicillin G Benzathine and Penicillin G Procaine, in Water for Injection. Where it is intended for veterinary use only, it is so labeled. May contain one or more suitable buffers, preservatives, and suspending agents. Contains the labeled amounts, within –10% to +15%. Meets the requirements for Identification, Crystallinity, pH (5.0–7.5), Limit of soluble penicillin G and procaine (where it is prepared from penicillin G procaine and is labeled for veterinary use only, not more than 1%), and for Bacterial endotoxins, and Sterility under Penicillin G Procaine Suspension, and for Injections.\[R-51\]
PENICILLIN G POTASSIUM FOR INJECTION USP

Usual dose: [Antibacterial]—

Cats and dogs: Intravenous or intramuscular, 20,000 to 40,000 Units per kg of body weight every six to eight hours.  

Horses: Intravenous or intramuscular, 20,000 Units per kg of body weight every six to eight hours.

Size(s) usually available:  
U.S.—[R-66; 67]  
Veterinary-labeled product(s):  
Not commercially available.

Human-labeled product(s):  
1,000,000 Units (Rx) [GENERIC].
5,000,000 Units (Rx) [Pfizerpen; GENERIC].
10,000,000 Units (Rx) [GENERIC].
20,000,000 Units (Rx) [Pfizerpen; GENERIC].

Canada—[R-68]  
Veterinary-labeled product(s):  
Not commercially available.

Human-labeled product(s):  
1,000,000 Units (Rx) [GENERIC].
5,000,000 Units (Rx) [GENERIC].
10,000,000 Units (Rx) [GENERIC].

Packaging and storage: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form:  
To prepare initial dilution for intramuscular or intravenous use, see manufacturer’s labeling.

To prepare for further dilution for intravenous use, see manufacturer’s labeling.

Stability: After reconstitution, solutions retain their potency for 24 hours at room temperature or for 7 days if refrigerated.

Incompatibilities:  
Penicillin G potassium is rapidly inactivated by oxidizing and reducing agents, such as alcohols and glycols.  
Extemporaneous admixtures of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation. Do not mix these antibacterial agents in the same intravenous bag, bottle, or tubing.

Additional information:  
Human guidelines recommend that daily doses of 10,000,000 Units or more should be administered by slow intravenous infusion or by intermittent piggyback infusion to avoid causing or exacerbating possible electrolyte imbalance.

The potassium content and sodium content (derived from sodium citrate buffer) of penicillin G potassium for injection are approximately 1.7 mEq (66.3 mg) and 0.3 mEq (6.9 mg), respectively, per 1,000,000 Units of penicillin G.

Constituted solution, Identification, Crystallinity, Bacterial endotoxins, Sterility, pH (6.0–8.5, in a solution containing 60 mg per mL or, where packaged for dispensing, in the solution constituted as directed in the labeling), Loss on drying (not more than 1.5%), and Particulate matter, and for Uniformity of dosage units and Labeling under Injections.

PENICILLIN G PROCaine INJECTABLE SUSPENSION USP

Usual dose: Antibacterial—  
[Cats and dogs]: Intramuscular, 20,000 to 40,000 Units per kg of body weight every twelve to twenty-four hours.

Cattle, pigs, and sheep: Intramuscular, [24,000 to 66,000] Units per kg of body weight every twenty-four hours.

Horses: Intramuscular, [20,000 Units per kg of body weight every twelve to twenty-four hours.]

Not commercially available.

Human-labeled product(s):  
300,000 Units per mL (OTC) [Agri-cillin; Aquacillin; Microcillin; Pen-Aqueous; GENERIC].

Canada—  
Veterinary-labeled product(s):  
300,000 Units per mL (OTC) [Depocillin; Derapen SQ/LA; Hi-Pencin 300; Pen-Aqueous; Pen G Injection; Penmed; Penpro; Propen LA; Ultrapen LA; GENERIC].

Note: Penicillin G procaine should not be administered subcutaneously at high doses because doing so produces significant local inflammation and hemorrhage, as well as medication deposits that can contribute to residue problems. The maximum dose per injection site of penicillin G procaine should be 3,000,000 Units (10 mL); injection sites should be different for each succeeding treatment.

Note: Some Canadian products, such as Derapen SQ/LA, Propen LA, and Ultrapen LA, list their strengths and dosing in terms of milligrams rather than international units (IU).

procaine penicillin G contains 1009 penicillin G IU per mg.

Withdrawal times:  
U.S.—[R-7; 26; 53]

Species | Meat (days) | Milk (hours)
---|---|---
Cattle | 4 | 48
Calves (nonruminating) | 7 |  
Sheep | 8 |  
Swine | 6 |  

Note: Products bearing labeling with the above withdrawal times list a dose of 6600 Units per kg of body weight administered intramuscularly once every 24 hours. Treatment should not exceed five days in lactating cattle or seven days in sheep, swine, or nonlactating cattle for these withdrawal times to apply.
Note: Products bearing labeling with the above withdrawal times list a dose of 6600 Units per kg of body weight administered intramuscularly once every 24 hours. Treatment should not exceed four days for these withdrawal times to apply. These products are not labeled for use in pre-ruminating calves.[R-26; 53; 70]

Canada—[R-6; 81]

When administered at a dose of 6670 Units per kg of body weight every twenty-four hours:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>5</td>
<td>72</td>
</tr>
</tbody>
</table>

When administered at a dose of 15,000 Units per kg of body weight every twenty-four hours:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>8</td>
</tr>
</tbody>
</table>

When administered at a dose of 21,000 Units per kg of body weight every twenty-four hours:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>Sheep</td>
<td>10</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: The Canadian Bureau of Veterinary Drugs has published results of tissue residue studies and calculated withdrawal times for use of penicillin G procaine administered at doses that are higher than U.S. label doses[R-80; 82; 83]. Some of these withdrawal times are now listed in the labeling of Canadian products, as shown above, with the exception of the withdrawal calculated for the highest dose. If penicillin G is administered at the extra-label dose of 60,000 Units per kg of body weight every 24 hours, there is some evidence to suggest that a withdrawal time of 21 days would be sufficient to avoid residues in sheep and non-lactating cattle and that a withdrawal time of 15 days would be sufficient for pigs. For Derapen SQ/LA, Propen LA, and Ultrapen LA:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular dose</td>
<td>21</td>
</tr>
<tr>
<td>Subcutaneous dose</td>
<td>14</td>
</tr>
<tr>
<td>Pigs</td>
<td>10</td>
</tr>
</tbody>
</table>

Note: Products bearing labeling with the above withdrawal times list 20 mg per kg of body weight as a single intramuscular or subcutaneous dose in cattle or a single intramuscular dose in pigs. The dose may be repeated in seventy-two hours.

**Packaging and storage**: Store between 2 and 8 °C (36 and 46 °F). Protect from freezing.[R-53; 70]

**Preparation of dosage form**: The vial should be warmed to room temperature and shaken well to insure a uniform suspension.[R-53]

**Additional information**: Some animals may develop procaine toxicity, which can result in acute neurologic signs.[R-48]. Administration of penicillin G procaine to racing horses may produce violative procaine concentrations in urine for more than two weeks.[R-91; 92]

**USP requirements**: Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass, in a refrigerator. A sterile suspension of Penicillin G Procaine or, where labeled for veterinary use only, of sterile penicillin G procaine, in Water for Injection and contains one or more suitable buffers, dispersants, or suspending agents, and a suitable preservative. It may contain procaine hydrochloride in a concentration not exceeding 2.0%. Where it is intended for veterinary use, the label so states. Contains an amount of penicillin G procaine equivalent to the labeled amount of penicillin G, within –10% to +15%, the labeled amount being not less than 300,000 Penicillin G Units per mL or per container. Meets the requirements for Identification, Crystallinity, Bacterial endotoxins, Sterility, pH (5.0–7.5), and Penicillin G and procaine contents, and for Injections.[R-81]

**PENICILLIN G SODIUM FOR INJECTION USP**

**Usual dose**: [Antibacterial]¹—See Penicillin G Potassium for Injection USP.

**Strength(s) usually available**: U.S.—

Veterinary-labeled product(s): Not commercially available.

Human-labeled product(s):

- 5,000,000 Units (Rx) [generic].

Canada—

Veterinary-labeled product(s): Not commercially available.

Human-labeled product(s):

- 1,000,000 Units (Rx) [generic].
- 5,000,000 Units (Rx) [generic].
- 10,000,000 Units (Rx) [generic].

**Packaging and storage**: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.

**Preparation of dosage form**: To prepare initial dilution for intramuscular or intravenous use, see manufacturer’s labeling for instructions.

**Stability**: After reconstitution, solutions retain their potency for 24 hours at room temperature or for 7 days if refrigerated.[R-68]

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Incompatibilities:
Penicillin G sodium is rapidly inactivated by acids, alkalis, and oxidizing agents and in carbohydrate solutions at alkaline pH.
Extemporaneous admixtures of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation. Do not mix these antibacterials in the same intravenous bag, bottle, or tubing.3 29 71

Additional information:R-68
Human guidelines recommend that daily doses of 10,000,000 Units or more should be administered by slow intravenous infusion to avoid causing or exacerbating electrolyte imbalance.
The sodium content is approximately 2 mEq (2 mmol) per 1,000,000 Units of penicillin G. This should be considered in patients on a restricted sodium intake.

USP requirements: Preserve in Containers for Sterile Solids. It is sterile Penicillin G Sodium or a sterile mixture of penicillin G sodium and not less than 4.0% and not more than 5.0% of Sodium Citrate, of which not more than 0.15% may be replaced by Citric Acid. Contains the labeled amount of Penicillin G, within −10% to +20%, and where it contains Sodium Citrate it has a potency of not less than 1420 and not more than 1667 Penicillin G Units per mg. Meets the requirements for Constituted solution, Identification, Crystallinity, Bacterial endotoxins, Sterility, pH (6.0–7.5, in a solution containing 60 mg per mL). Loss on drying (not more than 1.5%), and Particulate matter, and for Uniformity of dosage units and Labeling under Injections.R-64

1Not included in Canadian product labeling or product not commercially available in Canada.

Developed: 04/27/95
Interim revision: 07/19/95; 07/11/96; 7/15/98; 11/5/99; 09/30/02; 04/05/03

Table 1. Pharmacokinetic parameters.

<table>
<thead>
<tr>
<th>Species</th>
<th>Penicillin G dosage form</th>
<th>Dose (Units/kg)</th>
<th>Route/site of administration*</th>
<th>Cmax (mcg/mL)</th>
<th>Tmax (hours)</th>
<th>Duration† of action (hours)</th>
<th>Target† minimum serum conc. (mcg/mL)</th>
<th>Disappearance rate constant (hour−1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves (6–9 mo.)</td>
<td>PotassiumR-55</td>
<td>10,000</td>
<td>IM/neck</td>
<td>4.71 ± 3.86</td>
<td>1 to 1.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>ProcaineR-55</td>
<td>30,000</td>
<td>IM/neck</td>
<td>1.55 ± 0.33</td>
<td>1.5 to 6</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>ProcaineR-56</td>
<td>66,000</td>
<td>IM/neck</td>
<td>4.24 ± 1.08</td>
<td>6.00 ± 0.00</td>
<td>–</td>
<td>–</td>
<td>0.08 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>ProcaineR-56</td>
<td>66,000</td>
<td>SC/neck</td>
<td>1.85 ± 0.27</td>
<td>5.33 ± 0.67</td>
<td>–</td>
<td>–</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>ProcaineR-56</td>
<td>24,000</td>
<td>IM/gluteal</td>
<td>0.99 ± 0.04</td>
<td>5.33 ± 0.67</td>
<td>–</td>
<td>–</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>After 5-day administration</td>
<td>ProcaineR-56</td>
<td>66,000</td>
<td>IM/gluteal</td>
<td>2.63 ± 0.27</td>
<td>6.00 ± 0.00</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>During 7-day administration:</td>
<td>ProcaineR-609</td>
<td>11,000</td>
<td>IM/not stated</td>
<td>0.72</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.04 ± 0.00</td>
</tr>
<tr>
<td>Horses</td>
<td>SodiumR-57</td>
<td>10,000</td>
<td>IV/jugular</td>
<td>–</td>
<td>1.68</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20,000</td>
<td>IV/jugular</td>
<td>–</td>
<td>2.92</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40,000</td>
<td>IV/jugular</td>
<td>–</td>
<td>3.90</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>ProcaineR-57</td>
<td>10,000</td>
<td>IM/gluteal</td>
<td>–</td>
<td>4.90</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20,000</td>
<td>IM/gluteal</td>
<td>–</td>
<td>18.75</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td>40,000</td>
<td>IM/gluteal</td>
<td>–</td>
<td>&gt;24</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>ProcaineR-56</td>
<td>22,000</td>
<td>IM/gluteal</td>
<td>–</td>
<td>1.42 ± 0.22</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fawns (0–7 days)</td>
<td>ProcaineR-58</td>
<td>22,000</td>
<td>IM/seminemembranous</td>
<td>2.17 ± 0.27</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Legend: IM = intramuscular; IV = intravenous; SC = subcutaneous.
†The durations of action in this study were based on a specific minimum target serum concentration considered by that researcher to be a value high enough to treat penicillin-susceptible organisms.
‡This study gave the stated dose once every 24 hours and monitored serum concentrations for 7 days. The Cmax shown here was the highest measured; values stayed below 0.31 after the first day and went as low as 0.12 mcg/mL.

REFERENCES
6. Penpro package insert (Sanofi Sante Animale—Canada), Rec 7/22/94.
9. Pot-Pen package labeling (Sanofi Sante Animale—Canada), Rec 7/22/94.
10. Penicillin procaine G package insert (Pfizer Sante Animale—Canada), Rec 8/2/94.
85. Panel comment, 11/21/94.
87. Panel comment, 11/15/94.
88. Panel comment, 11/29/94.
89. Panel comment, 11/17/94.
91. Panel comment, 11/15/94.
PIRLIMYCIN Veterinary—Intramammary-Local

Some commonly used brand names are Pirsue Aqueous Gel and Pirsue Sterile Solution. Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:
Antibacterial (intramammary-local).

INDICATIONS

GENERAL CONSIDERATIONS

Pirlimycin is a lincosamide antibiotic with activity primarily against gram-positive organisms, including Staphylococcus and Streptococcus species. It is considered more active than clindamycin against Staphylococcus aureus. Pirlimycin is not active against gram-negative bacteria, such as Escherichia coli.

ACCEPTED

Mastitis (treatment)—Cows, lactating: Pirlimycin is indicated in the treatment of clinical and subclinical mastitis caused by Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae, and Streptococcus uberis. In refractory cases of chronic Staphylococcus aureus mastitis, administration of intramammary pirlimycin at recommended doses is sufficient to control but does not eliminate the pathogen. Intramammary therapy alone is indicated only in the treatment of subacute or subclinical mastitis manifested by mild changes in the milk or udder. Cows with acute or peracute mastitis, which involves gross changes in the milk or udder or systemic signs, should be given other medications also, which may include systemic antibiotics and/or supportive therapy.

REGULATORY CONSIDERATIONS

U.S. and Canada—Withdrawal times have been established for cattle. See the Dosage Forms section.

CHEMISTRY

Source: Semisynthetic derivative of lincomycin.

Chemical group: Lincosamide antibiotic.

Chemical name: Pirlimycin hydrochloride—L-threo-alpha-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[(4-ethyl-2-piperidinylcarbonyl)amino]-1-thio-, monohydrochloride, monohydrate, (2S-cis).

Molecular formula: Pirlimycin hydrochloride—\( \text{C}_{17}\text{H}_{31}\text{ClN}_{2}\text{O}_{5}\text{S} \cdot \text{HCl} \cdot \text{H}_{2}\text{O} \).

Molecular weight: Pirlimycin hydrochloride—465.43.

pKa: 8.5.

PHARMACOLOGY/PHARMACOKINETICS

Mechanism of action/effect: Pirlimycin is bacteriostatic at therapeutic concentrations. The lincosamides inhibit protein synthesis in susceptible bacteria by binding to the 50 S ribosomal subunits of bacterial ribosomes and preventing peptide bond formation.

Absorption: Almost one half of the dose is absorbed systemically after intramammary administration.

Distribution: Pirlimycin is lipophilic and diffuses readily across tissue membranes.

Biotransformation: Pirlimycin is eliminated primarily as parent drug when administered by the intramammary route; however, 4% of the dose is oxidized by the liver to pirlimycin sulfoxide.

Peak concentrations: Based on two intramammary doses of 50 mg each, given 24 hours apart—Blood: 0.025 mcg per mL (mcg/mL) 2 and 6 hours after the second 50-mg intramammary dose.

Mammary tissue: 10 mcg per gram (mcg/gram) 10 hours after the second dose.

Milk: > 150 mcg/mL in the first assay sample, taken 4 hours after each dose.

Liver concentration:
Total—The concentration of pirlimycin and metabolites (primarily pirlimycin sulfoxide) in the liver 4 days after the second 50-mg intramammary dose is 2.18 mcg/gram.

Parent compound (marker residue)—The concentration of pirlimycin in the liver 2 days after the second 50-mg intramammary dose is 2.33 mcg/gram; the concentration falls below 0.5 mcg/gram by 21 days after the second dose.

Mammary tissue concentration: Based on two intramammary doses of 50 mg each, given 24 hours apart—The mammary tissue concentration 4 days after the second dose is 0.927 mcg/gram.

Milk concentration: Based on a 50-mg intramammary dose at 0 and 24 hours, the milk pirlimycin concentration 12 hours after the second infusion of medication is measured to be 8 to 18 mcg/mL and by 36 hours the concentration is less than 1 mcg/mL.

Elimination: When pirlimycin is administered by the intramammary route, approximately 51% of the original dose is distributed into the milk. 10% into the urine, and 24% into the feces. Of the total dose, 68% is recovered as unchanged pirlimycin.

PRECAUTIONS TO CONSIDER

PATIENT MONITORING

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; = major clinical significance):

Bacteriologic pathogens in milk (milk samples should be tested three weeks after treatment with pirlimycin is discontinued; mastitis is not considered bacteriologically cured until samples show an absence of the mastitis-causing organism; for refractory Staphylococcus aureus mastitis, in which control, but not elimination, is achieved, S. aureus...
can reappear in milk cultures by 10 hours after the second treatment.[R-45]

**SIDE/ADVERSE EFFECTS**

Note: All clinical efficacy and toxicity studies performed with intramammary pirlimycin in cows have shown it to be nonirritating.[R-11] No serious adverse effects associated with the use of pirlimycin in cows have been documented. The Food and Drug Administration Adverse Drug Experience reporting program has received only one report of urticaria, possibly drug-related, in three cows that responded well to treatment for the urticaria.[R-16]

**OVERDOSE**

For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

**CLIENT CONSULTATION**

Treatment of mastitis in dairy cattle is best achieved by a comprehensive mastitis control program in which herd management is the primary focus. The program should include good maintenance of milking equipment and constant evaluation of milking procedures and teat health as well as strategic treatment of clinical cases of mastitis.[R-9]

**VETERINARY DOSING INFORMATION**

The choice of antibiotic for the treatment of mastitis should be based on knowledge of the culture and sensitivity of the pathogens causing mastitis in the cow and the dairy herd.

Before administration of intramammary pirlimycin, the following steps should be performed:

- The udder should be milked out completely and the teats washed with warm water and a disinfectant. Care should be taken to avoid washing excess dirt down from the udder onto the teat ends. The area should be dried thoroughly. An effective germicidal teat dip should be applied for one minute and then each teat wiped with a separate cotton ball soaked with an antiseptic such as 70% isopropyl alcohol.
- Persons performing the treatment should wash and dry their hands before each treatment.
- To administer pirlimycin, the tip of the syringe should be inserted into the teat end as little as possible and the contents of the syringe should be injected into each streak canal while the teat is held firmly.
- The medication should then be gently massaged up the teat canal into the gland cistern.
- Following treatment, an effective teat dip is recommended on all teats.

**INTRANAMMARY DOSAGE FORMS**

**PIRLIMYCIN INTRANAMMARY INFUSION**

**Usual dose:** Mastitis—**Cows,** lactating: Intramammary, 50 mg administered into each affected quarter, followed by a second dose administered twenty-four hours later.[R-1; 17]
14. Manufacturer comment, Rec 7/22/96.
16. The Food and Drug Administration Center for Veterinary Medicine Adverse Drug Experience Summaries, Center for Veterinary Medicine, Food and Drug Administration, Rockville, MD. 10/18/96.
POTENTIATED SULFONAMIDES Veterinary—Systemic

This monograph includes information on the following: Ormetoprim and Sulfadimethoxine; Pyrimethamine and Sulfadiazine oral solution; Sulfadiazine and Trimethoprim; Sulfadoxine and Trimethoprim; Sulfamethoxazole and Trimethoprim.

Some commonly used brand names are:

For veterinary-labeled products—

- Bimotrim [Sulfadiazine and Trimethoprim]
- Borgal [Sulfadiazine and Trimethoprim]
- Potensulf [Sulfadiazine and Trimethoprim]
- Primor 120 [Ormetoprim and Sulfadimethoxine]
- Primor 240 [Ormetoprim and Sulfadimethoxine]
- Prime 600 [Ormetoprim and Sulfadimethoxine]
- Primor 1,200 [Ormetoprim and Sulfadimethoxine]
- Quinnoxine-S [Pyrimethamine and Sulfaquinoxaline]
- Rofenaid 40 [Ormetoprim and Sulfadimethoxine]
- Romet 30 [Ormetoprim and Sulfadimethoxine]
- Romet-30 [Ormetoprim and Sulfadimethoxine]
- Bactrim DS [Sulfamethoxazole and Trimethoprim]
- Cotrim DS [Sulfamethoxazole and Trimethoprim]
- Cotrim Pediatric [Sulfamethoxazole and Trimethoprim]
- Nu-Cotrimox [Sulfamethoxazole and Trimethoprim]

For human-labeled products—

- Septra [Sulfamethoxazole and Trimethoprim]
- Septra DS [Sulfamethoxazole and Trimethoprim]
- Sulfamethoxazole and Trimethoprim
- Sulfadoxine and Trimethoprim
- Sulfamethoxazole and Trimethoprim
- Sulfadoxine and Trimethoprim
- Sulfonamides and Trimethoprim
- Tribrissen [Sulfadiazine and Trimethoprim]
- Tribrissen DS
- Tucoprim Powder
- Nu-Cotrimox DS
- Nu-Cotrimox
- Quinnoxine-S
- Sulfaquinoxaline-S
- Tribrissen 120
- Tribrissen 480
- Tribrissen 960
- Tribrissen 44%
- Tribrissen 40% Powder
- Tribrissen 50%
- Tribrissen 960
- Tribrissen 40%
- Tribrissen 44%
- Tribrissen 50%
- Tribrissen S/S
- Primor 120
- Primor 240
- Primor 600
- Primor 1,200
- Cotrim DS
- Cotrim
- Nu-Cotrimox
- Romet-30
- Bactrim DS
- Romet 30
- Bimotrim
- Borgal
- Quinnoxine-S
- Rofenaid 40
- Romet 30
- Romet-30
- Bactrim DS
- Bactrim
- Cotrim DS
- Cotrim
- Nu-Cotrimox
- Nu-Cotrimox
- Romet 30
- Romet-30
- Bactrim DS
- Bactrim
- Cotrim DS
- Cotrim
- Nu-Cotrimox
- Nu-Cotrimox

Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:

- Antibacterial (systemic); antiprotozoal (systemic).

INDICATIONS

Note: Bracketed information in the Indications section refers to uses that are either not included in U.S. product labeling or are for products not commercially available in the U.S.

Information identified by a superscript 1 refers to uses that are either not included in Canadian product labeling or are for products not commercially available in Canada.

GENERAL CONSIDERATIONS

The combined and synergistic activities of the two agents in each type of potentiated sulfonamide produce antibacterial activity against a wide range of infections caused by gram-positive and gram-negative bacteria, some protozoa under certain conditions. The minimum inhibitory concentrations against specific susceptible bacteria for each antibiotic are generally lowered when the antibiotics are administered in the potentiated sulfonamide combination. The resistance developed to the potentiated sulfonamides is lower than that to each individual agent. This is an important benefit because of the common resistance to sulfonamides and rapid development of resistance to diaminopyrimidines when used alone. Cross-resistance between sulfonamides is considered complete and often occurs between pyrimidines.

ACCEPTED

Coccidiosis (prophylaxis)—

- Chickens: Ormetoprim and sulfadimethoxine premix is indicated in the prevention of coccidiosis caused by susceptible Eimeria acervulina, E. brunetti, E. maxima, E. necatrix, and E. tenella. [Pyrimethamine and sulfadiazine combination is indicated in the prevention of coccidiosis, caused by susceptible organisms.] Potentiated sulfonamides may be more effective in the treatment of E. acervulina than of E. tenella.

Partridges, chukar: Ormetoprim and sulfadimethoxine premix is indicated in the prevention of coccidiosis caused by susceptible Eimeria kohfidii and E. legioniensis.

Turkeys: Ormetoprim and sulfadimethoxine premix is indicated in the prevention of coccidiosis caused by susceptible Eimeria adenoeides, E. gallopavonis, and E. melagravis. [Pyrimethamine and sulfadiazine combination is indicated in the prevention of coccidiosis caused by susceptible organisms.]

Coccidiosis (treatment)—Chickens and turkeys: Pyrimethamine and sulfadiazine oral solution is indicated to aid in the treatment of susceptible coccidia.

Colibacillosis (prophylaxis)—Chickens, broiler and replacement, and ducks: Ormetoprim and sulfadimethoxine premix is indicated in the prevention of colibacillosis caused by susceptible Escherichia coli.

Colibacillosis (treatment)—Ducks: Ormetoprim and sulfadimethoxine premix is indicated in the control of colibacillosis caused by susceptible E. coli.

[Species]: Sulfadiazine and trimethoprim injection is indicated in the treatment of colibacillosis caused by susceptible organisms.
[Pigs]: Sulfadiazine and trimethoprim oral suspension\(^{R-10}\) and sulfadoxine and trimethoprim injection\(^{R-11}\) are indicated in the treatment of neonatal colibacillosis caused by susceptible E. coli \(^{R-10}\).

Enteric sepsis (treatment)\(^3\)—Catfish: Ormetoprim and sulfadimethoxine premix\(^{R-7; 16}\) is indicated in the control of enteric sepsis caused by susceptible Edwardsiella ictaluri.

Fowl cholera (prophylaxis)\(^1\)—Chickens and turkeys: Ormetoprim and sulfadimethoxine premix\(^{R-6}\) is indicated in the prevention of fowl cholera caused by susceptible Pasteurella multocida.

Fowl cholera (treatment)\(^1\)—Ducks: Ormetoprim and sulfadimethoxine premix\(^{R-6}\) is indicated in the control of fowl cholera caused by susceptible Pasteurella multocida.

Furunculosis (treatment)—Salmon and trout: Ormetoprim and sulfadimethoxine premix\(^{R-7; 16}\) is indicated in the control of furunculosis caused by susceptible Aeromonas salmonicida.

Gastrointestinal tract infections, bacterial (treatment)—Treatment of gastroenteritis with antimicrobials should rely on a specific diagnosis and knowledge of pathogen susceptibility.

Dogs: Sulfadiazine and trimethoprim [injection]\(^{R-8; 95}\) and tablets\(^{1\text{R-2; 11}}\) are indicated in the treatment of acute gastrointestinal tract infections.

[Cats]: Sulfadiazine and trimethoprim injection\(^{R-8}\) and tablets\(^{1\text{R-11}}\) are indicated in the treatment of acute gastrointestinal tract infections.

Infectious coryza (prophylaxis)\(^1\)—Chickens: Ormetoprim and sulfadimethoxine premix\(^{R-6}\) is indicated in the prevention of infectious coryza caused by susceptible Haemophilus gallinarum.

New duck disease (treatment)\(^1\)—Ducks: Ormetoprim and sulfadimethoxine premix\(^{R-6}\) is indicated in the control of new duck disease caused by susceptible Riemerella anatipestifer.

Respiratory tract infections, bacterial (treatment)—

Dogs: Sulfadiazine and trimethoprim [injection]\(^{R-8; 95}\) and tablets\(^{1\text{R-2; 11}}\) are indicated in the treatment of acute bacterial respiratory tract infections caused by susceptible organisms.

Horses: Sulfadiazine and trimethoprim injection\(^{R-96; 146}\), oral paste, and oral powder\(^{1\text{R-4}}\) are indicated in the treatment of bacterial pneumonia caused by susceptible organisms.

[Cats]: Sulfadiazine and trimethoprim injection\(^{R-8}\) and tablets\(^{1\text{R-11}}\) are indicated in the treatment of respiratory tract infections caused by susceptible organisms.

Skin and soft tissue infections (treatment)—

Dogs: Ormetoprim and sulfadimethoxine tablets\(^{1\text{R-5}}\) are indicated in the treatment of skin and soft tissue infections caused by susceptible E. coli and Staphylococcus intermedius. Sulfadiazine and trimethoprim injection\(^{R-8}\) and tablets\(^{1\text{R-2; 11}}\) are indicated in the treatment of abscesses and infected wounds caused by susceptible organisms.

Horses: Sulfadiazine and trimethoprim injection\(^{R-96; 146}\), oral paste\(^{1\text{R-3; 18}}\), and oral powder\(^{1\text{R-4}}\) are indicated in the treatment of abscesses and infected wounds caused by susceptible organisms.

[Cats]: Sulfadiazine and trimethoprim injection\(^{R-8}\) and tablets\(^{1\text{R-11}}\) are indicated in the treatment of bacterial infections, such as abscesses and wounds, caused by susceptible organisms.

Strangles (treatment)—Horses: Sulfadiazine and trimethoprim injection\(^{R-96; 146}\), oral paste\(^{1\text{R-3; 18}}\), and oral powder\(^{1\text{R-4}}\) are indicated in the treatment of abscesses and infected wounds caused by susceptible organisms.

Urinary tract infections (treatment)—Dogs: Ormetoprim and sulfadimethoxine tablets\(^{R-126}\) and sulfadiazine and trimethoprim tablets\(^{3\text{R-2}}\) are indicated in the treatment of acute urinary tract infections caused by susceptible organisms.

Urogenital tract infections (treatment)\(^1\)—Horses: Sulfadiazine and trimethoprim injection\(^{R-96; 146}\). oral paste, and oral powder\(^{1\text{R-4}}\) are indicated in the treatment of acute urogenital tract infections\(^{R-1}\).

[Arthritis, bacterial (treatment)]—Pigs: Sulfadoxine and trimethoprim injection\(^{R-11; 15}\) is indicated in the treatment of bacterial arthritis caused by susceptible organisms.

[Enteritis, bacterial (treatment)]—

Cattle: Sulfadiazine and trimethoprim injection\(^{R-13; 14}\) is indicated in the treatment of enteritis caused by susceptible E. coli or Salmonella.

Pigs: Sulfadiazine and trimethoprim oral suspension\(^{R-10}\) and sulfadoxine and trimethoprim injection\(^{R-13; 14}\) are indicated in the treatment of post-weaning scour caused by susceptible E. coli.

[Mastitis (treatment)]; or

[Metritis (treatment)]—Sows: Sulfadoxine and trimethoprim injection\(^{R-11; 15}\) is indicated in the treatment of mastitis-metritis-agalactia syndrome caused by susceptible organisms.

[Perioperative infections (treatment)]—Horses: Sulfadiazine and trimethoprim oral paste\(^{R-18}\) and injection\(^{R-9}\) are indicated in the treatment of postoperative bacterial infections caused by susceptible organisms.

[Pneumonia, bacterial (treatment)]—

Cattle: Sulfadiazine and trimethoprim injection\(^{R-13; 14}\) is indicated in the treatment of bacterial pneumonia, including bovine pneumonic pasteurellosis (shipping fever), caused by susceptible organisms.

Pigs: Sulfadoxine and trimethoprim combination\(^{R-14; 15}\) is indicated in the treatment of bacterial pneumonia caused by susceptible organisms.

[Pododermatitis (treatment)]—Cattle: Sulfadiazine and trimethoprim injection\(^{R-13; 14}\) is indicated in the treatment of pododermatitis caused by susceptible organisms.

[Septicemia (treatment)]—

Cattle: Sulfadiazine and trimethoprim injection\(^{R-13; 14}\) is indicated in the treatment of septicemia caused by susceptible organisms.

Dogs: Sulfadiazine and trimethoprim injection\(^{R-96; 146}\) is used in the treatment of septicemia caused by susceptible organisms.

[Vibrio anguillarum infection]—Salmon: Sulfadiazine and trimethoprim combination oral powder\(^{R-22}\) is indicated in the treatment of infections caused by susceptible Vibrio anguillarum\(^{R-64}\).

ACCEPTANCE NOT ESTABLISHED

Distemper, canine (treatment)—Dogs: Although U.S. product labeling includes the use of sulfadiazine and trimethoprim in the treatment of secondary bacterial infections associated with canine distemper\(^{R-2}\), and this use may be appropriate in bacterial infections that are susceptible to this medication, the use of these antimicrobials in the treatment of distemper-associated infections is not considered more appropriate or more generally accepted than in the treatment of bacterial infections associated with other viral infections.

Bacterial infections (treatment)—Horses: There is insufficient controlled studies to support the efficacy and safety of [sulfamethoxazole and trimethoprim combination] in the treatment of bacterial infections in foals and horses; however, based on pharmacokinetic data, the combination is used in the treatment of susceptible infections\(^{R-31–33}\).
[Protozoal infections (treatment)]—Horses: There are insufficient data to support the efficacy and safety of sulfadiazine and trimethoprim combination in the treatment of protozoal infections in foals and horses; however, based on pharmacokinetic data, the combination is used in the treatment of susceptible infections [R-11–13]. Prior to the availability of approved products (ponazuril, toltrazuril) to treat equine protozoal myeloencephalitis, administration of sulfadiazine and trimethoprim in combination with pyrimethamine was clinically useful in treating horses with this disease [R-147]. In vitro studies also show efficacy of potentiated sulfonamides against Sarcocystis neurona [R-148].

[Meningitis, bacterial (treatment)]—Dogs: There are insufficient data to support the efficacy of sulfadiazine and trimethoprim combination in the treatment of bacterial meningitis in dogs; however, it has been used for this indication [R-138].

[Nocardiosis (treatment)]—Cats and dogs: There are insufficient data to support the efficacy of sulfadiazine and trimethoprim or sulfamethoxazole and trimethoprim in combination in the treatment of nocardiosis in cats and dogs; however, these medications are used in the treatment of nodacardial infections. Sulfonamides have been considered the treatment of choice and there is some evidence [R-128–133] to suggest that sulfadiazine and trimethoprim or sulfamethoxazole and trimethoprim are efficacious in the treatment of these infections [R-128, 131]. Ormetoprim and sulfadimethoxine combination could also be effective in the treatment of nocardiosis, based on a pharmacokinetic profile similar to that of trimethoprim with sulfadiazine or sulfamethoxazole [R-1138].

Because of a variability in the susceptibility of Nocardia species, culture and sensitivity tests should be performed, if possible. Surgical drainage should be provided for any abscesses or draining tracts [R-130, 131]. Sulfaquinoxaline and trimethoprim combination administered alone may not be effective in the treatment of cerebral nocardiosis [R-132].

[Pneumonia (treatment)]—Calves, nonruminating: Until recently, Canadian sulfadiazine and trimethoprim boluses were labeled for use in the treatment of bacterial pneumonia in calves [R-12]. Such a product has not been available in the United States. Although there are no sulfadiazine and trimethoprim products labeled for use in calves in the United States or Canada at this time, oral sulfadiazine and trimethoprim tablets might be used in the treatment of susceptible infections, such as bacterial pneumonia, in calves. For more information, see Sulfadiazine and Trimethoprin Tablets in the Dosage Forms section of this monograph.

[Prostate infection (treatment)]—Dogs: There are insufficient data to support the efficacy of trimethoprim in combination with sulfadiazine or sulfamethoxazole in the treatment of prostate infections caused by susceptible organisms in dogs; however, pharmacokinetic studies show that these trimethoprim and sulfonamide combinations are distributed into prostate fluid at therapeutic concentrations [R-485]. Ormetoprim and sulfadimethoxine combination also could be effective in the treatment of prostatitis, based on a pharmacokinetic profile similar to that of trimethoprim with sulfadiazine or sulfamethoxazole [R-1138].

Not included in Canadian product labeling or product not commercially available in Canada.

REGULATORY CONSIDERATIONS

U.S.—
Withdrawal times have been established for ormetoprim and sulfadimethoxine for medicated feed (see the Dosage Forms section).

Canada—
Withdrawal times have been established for ormetoprim and sulfadimethoxine for medicated feed; pyrimethamine and sulfaquinoxaline oral solution; sulfadiazine and trimethoprim boluses, oral paste, oral powder, and oral suspension; and sulfadoxine and trimethoprim injection (see the Dosage Forms section).

CHEMISTRY

Chemical group:
Ormetoprim, pyrimethamine, and trimethoprim—Diaminopyrimidines.
Sulfadiazine, sulfadimethoxine, sulfadoxine, sulfamethoxazole, and sulfaquinoxaline—Sulfonamides.

Chemical name:
Ormetoprim—2,4-Pyrimidinediamine, 5-{[(4,5-dimethoxy-2-methylphenyl) methyl]-} [R-1].
Pyrimethamine—2,4-Pyrimidinediamine, 5-(4-chlorophenyl)-6-ethyl- [R-1].
Sulfadiazine—Benzenesulfonamide, 4-amino-N-(2,6-dimethoxy-4-pyrimidinyl)- [R-1].
Sulfadimethoxine—Benzenesulfonamide, 4-amino-N-(2,6-dimethoxy-4-pyrimidinyl)- [R-1].
Sulfadoxine—Benzenesulfonamide, 4-amino-N-(5,6-dimethoxy-4-pyrimidinyl)- [R-1].
Sulfamethoxazole—Benzenesulfonamide, 4-amino-N-(5-methyl-3-isoxazolyl)- [R-1].
Sulfaquinoxaline—N1,2-Quinoxalinylsulfanilamide [R-1].
Trimethoprim—2,4-Pyrimidinediamine, 5-{[3,4,5-trimethoxyphenyl) methyl]-} [R-1].

Molecular formula:
Ormetoprim—C10H16N4O2 [R-1].
Pyrimethamine—C12H15ClN4 [R-1].
Sulfadiazine—C10H10N2O2S [R-1].
Sulfadimethoxine—C12H14N2O4S [R-1].
Sulfadoxine—C12H14N4O4S [R-1].
Sulfamethoxazole—C10H11N2O3S [R-1].
Sulfaquinoxaline—C14H13N4O3S [R-1].
Trimethoprim—C14H14N2O3 [R-1].

Molecular weight:
Ormetoprim—274, 32 [R-1].
Pyrimethamine—274, 32 [R-1].
Sulfadiazine—250, 28 [R-1].
Sulfadimethoxine—310, 34 [R-1].
Sulfadoxine—310, 33 [R-1].
Sulfamethoxazole—253, 28 [R-1].
Sulfaquinoxaline—300, 34 [R-1].
Trimethoprim—290, 32 [R-1].
**Description:**

Ormetoprim—White powder.

Pyrimethamine USP—White, odorless, crystalline powder.

Sulfadiazine USP—White or slightly yellow powder. Odorless and stable in air, but slowly darkens on exposure to light.

Sulfadoxine USP—Practically white, crystalline powder.

Sulfadiazine USP—Practically insoluble in water; freely soluble in dilute solutions of sodium hydroxide; sparingly soluble in alcohol and in acetone; slightly soluble in ether.

Sulfadoximidine—White or slightly yellow powder. Odorless or nearly odorless and stable in air, but slowly darkens on exposure to light.

Sulfadoxine—6.3

Sulfadiazine—6.4

Sulfadimethoxine—6.2

**Solubility:**

Pyrimethamine USP—Practically insoluble in water; slightly soluble in acetone, in alcohol, and in chloroform.

Sulfadiazine USP—Practically insoluble in water; freely soluble in dilute mineral acids, in solutions of potassium and sodium hydroxides, and in ammonia TS; sparingly soluble in alcohol and in acetone; slightly soluble in human serum at 37 °C.

Sulfadoximidine—Soluble in 2 N sodium hydroxide; sparingly soluble in 2 N hydrochloric acid; slightly soluble in alcohol, in ether, in chloroform, and in hexane; practically insoluble in water.

Sulfadiazine—Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in ether. Soluble in solutions of alkali hydroxides and in dilute mineral acids.

Sulfadoximidine—Practically insoluble in water, in ether, and in chloroform; freely soluble in acetone and in dilute solutions of sodium hydroxide; sparingly soluble in alcohol.

Sulfadoximidine—Practically insoluble in water; very slightly soluble in alcohol; practically insoluble in ether; freely soluble in aqueous solutions of alkali.

Trimepranil USP—Very slightly soluble in water; soluble in benzyl alcohol; sparingly soluble in chloroform and in methanol; slightly soluble in alcohol and in acetone; practically insoluble in ether and in carbon tetrachloride.

**PHARMACOLOGY/PHARMACOKINETICS**

Note: Unless otherwise noted, pharmacokinetic values are based on administration of a single intravenous dose and concurrent administration of a diaminopyrimidine and a sulfonamide.

When sulfamethoxazole and trimethoprim are administered concurrently to horses, the pharmacokinetics of each drug appears to be unaffected by the presence of the other.

**Mechanism of action/effect:**

Sulfonamides—The sulfonamides are bacteriostatic antimicrobials that interfere with the biosynthesis of folic acid in bacterial cells; they compete with para-aminobenzoic acid (PABA) for incorporation into dihydrofolate acid. By replacing the PABA molecule in dihydrofolic acid, they prevent formation of folic acid required for nucleic acid synthesis and multiplication of the bacterial cell. Sulfonamides are effective only in cells that must produce their own folic acid; mammalian cells do not synthesize folic acid, but get it from outside sources.

Diaminopyrimidines—Ormetoprim and trimethoprim are bacteriostatic antimicrobials that block a step in folate production just subsequent to that affected by the sulfonamides. Bacterial production of tetrahydrofolic acid from dihydrofolic is interrupted by the diaminopyrimidines as it reversibly binds and inhibits dihydrofolic reductase. Because the conversion of dihydrofolic acid to tetrahydrofolic acid is blocked, folate cannot be produced. Pyrimethamine causes the same inhibition of dihydrofolic reductase in protozoa.

Like bacteria and protozoa, animal cells also reduce folic acid to tetrahydrofolic acid; however, bacterial and protozoal dihydrofolic reductase is significantly more tightly bound by trimethoprim than is human dihydrofolic reductase.

Potentiated sulfonamides—Because the diaminopyrimidines exert their effect on folate biosynthesis at a step immediately subsequent to the one at which the sulfonamides act, the combination of a sulfonamide and diaminopyrimidine produces a synergistic effect that deprives the cell of essential nucleic acids and proteins. The potentiated sulfonamide combination produces an antimicrobial effect that is bacteriostatic and sometimes bactericidal against certain bacteria under optimum conditions.

The minimal effective ratio of sulfonamide to diaminopyrimidine in the target tissue is 20 to 1 for synergism. At equimolar quantities, other ratios are equally effective, depending on the strain of organism and the minimum inhibitory concentration (MIC) for each drug. Therefore, 16 to 1, 10 to 1, and other ratios may be effective, but combinations are formulated to achieve at least 20 to 1 in vivo.

**Absorption:** Oral—

Ormetoprim and sulfadimethoxine:

Calves, 6 weeks of age—The bioavailability of oral ormetoprim is very poor in ruminating calves; the bioavailability of oral sulfadimethoxine in calves is slow but complete and unaffected by ruminant status.

Dogs—Ormetoprim and sulfadimethoxine are rapidly and well absorbed after oral administration.

Horses—Oral absorption of ormetoprim and sulfadimethoxine is variable. Sulfadimethoxine appears to be more efficiently absorbed than ormetoprim.

Sulfadimethoxine administered alone: Bioavailability—

Catfish, channel: 40 mg/kg dose—Free base: 31%.

Sodium salt: 34%.

Trout, rainbow:

42 mg/kg dose—Free base: 34%.

Sodium salt: 63%.

Sulfadiazine and trimethoprim:

Calves, 6 weeks of age—The bioavailability of oral trimethoprim is greatly reduced in ruminating calves as compared to preruminating calves. Therapeutic serum concentrations (> 0.1 mcg/mL) were not
achieved with oral administration of 25 mg of sulfadiazine and 5 mg of trimethoprim in combination to ruminating calves. The bioavailability of oral sulfadiazine in calves is slow but complete and unaffected by rumen status.

Dogs—Sulfadiazine and trimethoprim are rapidly and well absorbed following oral administration. However, absorption can be variable among dogs and between different doses given to the same dog.

Horses—The absorption of trimethoprim is delayed when a horse has free access to feed. Initial serum concentrations will be lower in a fed horse than in a fasted horse; however, the effect is greatly decreased by the third day of treatment.

Pigs—Bioavailability: Dose of 40 mg of sulfadiazine and 4 mg of trimethoprim per kg—Fasted or fed:

Sulfadiazine—85 to 89%
Trimethoprim—90 to 92%

Sheep—Absorption of sulfadiazine in sheep is comparable to that in dogs; however, trimethoprim is not as well absorbed orally in sheep as in dogs.

Sulfamethoxazole and trimethoprim: Bioavailability—Quail: Dose of 50 mg of sulfamethoxazole and 10 mg of trimethoprim per kg of body weight—

Sulfamethoxazole: 81%
Trimethoprim: 41%

Distribution: Potentiated sulfonamides are rapidly and widely distributed throughout body tissues. In general, the diaminopyrimidine concentration in plasma peaks early and is quickly found in high concentrations in tissues; therefore, concentrations are generally higher in the tissues than in the serum. The sulfonamide component generally is found at higher concentrations in plasma for a much longer time and tissue distribution is slower. Initial concentrations of sulfonamides in tissues are generally lower than those in plasma.

Calves, preruminating—Sulfadiazine and trimethoprim are distributed well into cerebrospinal fluid (CSF) and synovial fluid.

Dogs—Potentiated sulfonamides are rapidly and widely distributed in the tissues. Trimethoprim and sulfadiazine are distributed into the aqueous and vitreous humors of the eye at concentrations that are 30 to 50% of serum concentrations. Trimethoprim is distributed into prostatic fluid at concentrations that are up to three times the serum concentration and are higher when trimethoprim is administered concurrently with sulfadiazine or sulfamethoxazole. Sulfadiazine and sulfamethoxazole are distributed into prostatic fluid at about 10% of the concurrent serum concentration.

Horses—Distribution of potentiated sulfonamides has been broadly investigated in the horse. Ormetoprim and sulfadimethoxine, sulfaflazine and trimethoprim, and sulfadimethoxine and trimethoprim are all well distributed into peritoneal fluid, CSF, synovial fluid, and urine. Ormetoprim and sulfadimethoxine also have been shown to be well distributed into the endometrium. Inflammation in the meninges or synovium does not significantly affect distribution into the respective fluids.

Ormetoprim and sulfadimethoxine: Equine endometrial tissue and synovial and peritoneal fluid concentrations of ormetoprim were similar to concurrent serum concentrations and concentrations of sulfadimethoxine in those fluids were 25 to 30% of serum concentration.

Sulfadimethoxine and trimethoprim: After 4-day dosing in mares, trimethoprim was measured in CSF at 50% of serum concentrations, but sulfadimethoxine was measured at 2.7% of serum concentrations.

Sulfamethoxazole and trimethoprim: A single dose of 36 mg of sulfamethoxazole and 7.5 mg of trimethoprim per kg of body weight, administered intravenously to mares, reached concentrations in serum sufficient to exceed the minimum inhibitory concentrations (MICs) of common bacterial and protozoal pathogens. After repeated doses, sulfamethoxazole, unlike trimethoprim, accumulated in the CSF.

Fish—Sulfadimethoxine administered alone:

In channel catfish, sulfadimethoxine is distributed into the muscle at the highest concentration immediately after administration, but within 48 to 96 hours the highest concentrations are in the bile. At any point in time there can be wide variation in tissue residues among fish. In rainbow trout, sulfadimethoxine is distributed at the highest concentrations into the bile, followed by the intestine, liver, blood, skin, kidney, spleen, gill, muscle, and fat.

Volume of distribution (Vd): Ormetoprim and sulfadimethoxine—Horses:

Ormetoprim:
Area: 1.7 Liters per kg (L/kg).
Steady state: 1.2 L/kg.
Sulfadimethoxine:
Area: 0.28 L/kg.
Steady state: 0.27 L/kg.

Sulfadiazine and trimethoprim—Calves: Area—

Sulfadiazine:
1 day of age—0.72 L/kg
1 week of age—0.66 L/kg
6 weeks of age—0.58 L/kg
Ruminating—0.85 L/kg
Trimethoprim:
1 day of age—1.69 L/kg
1 week of age—2.2 to 2.5 L/kg
6 weeks of age—2.27 L/kg
Ruminating—1.97 L/kg
Horses: Steady state—

Sulfadiazine: 0.58 L/kg
Trimethoprim: 1.68 L/kg

Pigs: Steady state—

Sulfadiazine: 0.54 L/kg
Trimethoprim: 1.8 L/kg

Sulfadimethoxine administered alone—Steady state:

Catfish, channel—0.66 L/kg
Trout, rainbow—0.42 to 0.5 L/kg

Sulfadoxine and trimethoprim—

Cows: Apparent—
Sulfadoxine: 0.37 L/kg
Trimethoprim: 1.14 L/kg

Goats: Apparent—
Sulfadoxine: 0.27 L/kg
Trimethoprim: 1.2 L/kg

Horses: Apparent—
Sulfadoxine: 0.39 L/kg
Sulfadoxine and trimethoprim —

**Foals:**
Sulfadoxoxazole — Area and steady state: 0.73 L/kg
Trimethoprim — Area and steady state: 2.2 L/kg

**Horses:**
Sulfadoxoxazole —
Area: 0.36 L/kg
Steady state: 0.33 L/kg; 0.5 L/kg
Trimethoprim —
Area: 2.27 L/kg
Steady state: 1.62 L/kg; 2.79 L/kg

**Quail:**
Sulfadoxoxazole — Area: 0.48 L/kg
Trimethoprim — Area: 3.9 L/kg

**Protein binding:** In general, the binding of sulfonamides to proteins is concentration-dependent and, in general, trimethoprim protein binding is independent of plasma concentration. There appears to be no interference in protein binding between sulfadoxine and trimethoprim; this may also be true for other potentiated sulfonamides.

Sulfadiazine —
Cattle: Moderate (50%) (concentration not specified)

Sulfadimethoxine —
Cats: High (87.5%) (50 mcg/ml plasma concentration)
Catfish: channel — Low (18%), not concentration-dependent
Chickens: Average binding over a range of concentrations — Moderate (40%), at serum concentrations of 2 to 10 mcg/ml
Dogs: High (>75%), at plasma concentrations of 50 to 150 mcg/ml
Goats: Very high (94%), at plasma concentration of 100 micromole/l
Trout, rainbow: Low (17%), not concentration-dependent

Sulfadoxine —
Horses: High (72%), at serum concentration of 50 mcg/ml
Moderate (40%), at serum concentration of 150 mcg/ml
Low (14%), at serum concentration of 450 mcg/ml
Cows: High (65 to 80%), at serum concentration of 100 mcg/ml or below
Moderate (44 to 51%), at serum concentration of 150 mcg/ml or more
Trimethoprim —
Cows: Moderate (57%)
Goats: Moderate (48%)
Horses: Moderate (50%)
Pigs: Moderate (33 to 54%)

**Biotransformation:**
Sulfonamides — Sulfonamides are metabolized primarily in the liver, but metabolism also occurs in other tissues. Biotransformation occurs by acetylation, glucuronide conjugation, and aromatic hydroxylation in many species. The types of metabolites formed and the amount of each varies depending on the specific sulfonamide administered; the species, age, diet, and environment of the animal; the presence of disease; and, with the exception of pigs and ruminants, the gender of the animal. N-acetyl metabolites have no antimicrobial activity and hydroxymetabolites have 2.5 to 39.5% of the activity of the parent compound. Metabolites may compete with the parent drug for involvement in folic acid synthesis. They have little detrimental effect on the bacterial cell, so their presence could decrease the activity of the remaining parent drug.

Sulfadiazine —
Calves: Sulfadiazine is excreted primarily as unchanged drug in the urine; the percentage of unchanged drug excreted increases from 1 day of age to 42 days of age, changing from 22 to 50%.

Sulfadimethoxine —
Catfish: channel — Metabolized primarily by the liver; acetylation is the major pathway.

Dogs — Sulfadimethoxine is not acetylated in the dog as it is in other species, and it is excreted primarily as unchanged drug.

Salmon — Metabolism occurs primarily in the liver.

Diaminopyrimidines — Trimethoprim: In many species, including cows, goats, and pigs, trimethoprim is extensively metabolized.

**Half-life:**
Absorption — Horses: Oral — Sulfadiazine and trimethoprim: Dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight (mg/kg)
Sulfadiazine: 0.35 hour
Trimethoprim: 0.44 hour

Distribution — Horses: Oral — Sulfadiazine and trimethoprim: Dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight
Sulfadiazine: 0.27 hour
Trimethoprim: 0.15 hour

Elimination —
Ormetoprim and sulfadimethoxine: Horses — Ormetoprim: 1.7 hours
Sulfadimethoxine: 7.9 hours

Sulfadiazine and trimethoprim: Calves —
1 day of age:
Sulfadiazine: 5.7 hours
Trimethoprim: 8.4 hours
1 week of age:
Sulfadiazine: 4.4 hours
Trimethoprim: 2.1 hours
6 weeks of age:
Sulfadiazine: 3.6 hours
Trimethoprim: 0.9 hour

Calves, ruminating —
Sulfadiazine: 3.25 hours
Trimethoprim: 1 hour
3.44 hours

Horses —
Sulfadiazine: 2.7 hours
Trimethoprim: 2 to 3 hours

Sulfadoxine and trimethoprim: Calves, lactating —
Sulfadiazine: Alpha phase (up to 4 hours postadministration) — 0.9 hour
Beta phase (between 4 and 48 hours postadministration) — 10.8 hours
Sulfamethoxazole and trimethoprim—Oral:

Calves—
1 week of age: 11.9 mcg of sulfadiazine per mL at 12 hours and 0.41 mcg of trimethoprim per mL at 3 hours (dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg)\(^{[R-81]}\).
6 weeks of age:
    Milk-fed—17.3 mcg of sulfadiazine per mL at 3 hours and 0.43 mcg of trimethoprim per mL at 1.5 hours (dose of 25 mg sulfadiazine and 5 mg of trimethoprim per kg of body weight)\(^{[R-81]}\).
    Grain and fiber-fed—14.9 mcg of sulfadiazine per mL at 8 hours and < 0.1 mcg of trimethoprim per mL (below test limit) for entire trial (dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight)\(^{[R-81]}\).

Dogs—
12.4 mcg of sulfadiazine per mL at 4 hours and 1.7 mcg of trimethoprim per mL at 1 hour (dose of 20 mg of sulfadiazine and 4 mg of trimethoprim per kg of body weight)\(^{[R-49]}\).
30.1 mcg of sulfadiazine per mL\(^{[R-19]}\) and 1.52 mcg of trimethoprim per mL\(^{[R-2; 19]}\) at 3 hours (dose of 25 mg of sulfadiazine and 5 mcg of trimethoprim per kg of body weight).
After 2 days of dosing every 12 hours: 67.4 mcg of sulfadiazine per mL and 2.98 mcg of trimethoprim per mL at 2 hours\(^{[R-46]}\) (dose of 25 mg of sulfadiazine and 5 mcg of trimethoprim per kg).
After 4 days of dosing every 24 hours: 84.7 mcg of sulfadiazine at 3 hours and 2.55 mcg of trimethoprim per mL at 2 hours\(^{[R-46]}\) (dose of 25 mg of sulfadiazine and 5 mcg of trimethoprim per kg).

Horses—
Fasted: 9 to 13 mcg of sulfadiazine per mL at 3 hours and 1 to 1.5 mcg of trimethoprim per mL at 1 to 2 hours (dose of 25 to 29 mg of sulfadiazine and 5 to 6 mg of trimethoprim per kg of body weight)\(^{[R-27; 29]}\).
Fed: 10 mcg of sulfadiazine per mL and 0.5 mcg of trimethoprim per mL at 6 hours (dose of 29.2 mcg of sulfadiazine and 5.8 mg of trimethoprim per kg of body weight)\(^{[R-27]}\).

Pigs—
Fasted: 32 mcg of sulfadiazine per mL at 4.3 hours and 1.9 mcg of trimethoprim per mL at 2.1 hours (oral dose of 40 mg of sulfadiazine and 8 mg of trimethoprim per kg of body weight)\(^{[R-91]}\).
Fed: 25 mcg of sulfadiazine per mL at 3.2 hours and 1.5 mcg of trimethoprim per mL at 3.4 hours (oral dose of 40 mg of sulfadiazine and 8 mg of trimethoprim per kg of body weight)\(^{[R-91]}\).

Salmon—20.3 mcg of sulfadiazine per mL at 24 hours and 3.25 mcg of trimethoprim per mL at 12 hours (oral dose of 83.3 mg of sulfadiazine and 16.7 mg of trimethoprim per kg of body weight of fish at 8 °C)\(^{[R-63]}\).

Sulfamethoxazole and trimethoprim—Cattle: Intramuscular administration—30.3 mcg of sulfadiazine per mL at 2 hours and 0.7 mg of trimethoprim per mL at 0.75 to 1 hour (dose of 13.3 mcg of sulfadiazine and 2.7 mg of trimethoprim per kg of body weight)\(^{[R-85]}\).

Sulfamethoxazole and trimethoprim—Horses: Oral administration—0.26 mcg/mL of trimethoprim at 0.75 hour and 13.7 mcg/mL of sulfamethoxazole at 1.5 hours (dose of 12.5 mg of sulfamethoxazole and 2.5 mg of trimethoprim per kg of body weight)\(^{[R-91]}\).

Duration of action: Duration of action may be estimated by the length of time target serum concentrations are maintained; however, duration of action for the potentiated sulfonamides is difficult to estimate from target serum concentrations\(^{[R-78]}\) because of the rapid movement of the
Sulfonamides—Renal excretion is the primary route of elimination for sulfonamides. Elimination:

Sulfadiazine: Administered alone—

- Calves: Sulfadiazine serum concentrations exceeded 9.5 mcg/mL from 12 minutes to 10 hours postinjection and trimethoprim serum concentrations exceeded 0.5 mcg/mL from 15 minutes to 2 hours (intramuscular dose of 13.3 mg of sulfadiazine and 2.7 mg of trimethoprim per kg of body weight) postinjection. 

- Horses: Sulfadiazine: 0.42 mL/min/kg

Sulfadimethoxine: 0.4 mL/min/kg

- Calves, ruminating—
  - Sulfadiazine: 3.15 mL/min/kg
  - Trimethoprim: 6.6 mL/min/kg

- Horses—
  - Sulfadiazine: 1.92 mL/min/kg
  - Trimethoprim: 8.49 mL/min/kg

Pigs—

- Sulfadiazine: 2.3 mL/min/kg
- Trimethoprim: 9.1 mL/min/kg

Sulfamethoxazole and trimethoprim:

- Horses: Two-thirds of the total dose is eliminated in the urine as parent drug, tubular excretion of unchanged drug and metabolites, most nonenteric sulfonamides and it occurs by glomerular filtration of the urine increases the fraction of the dose that is eliminated in the urine.

Species sensitivity

Dogs: An idiosyncratic sulfonamide toxicosis can occur in any breed of dog, but this reaction has been reported more frequently in the Doberman Pinscher than in other breeds. This specific type of drug reaction includes blood dyscrasias, nonseptic polyarthritis, and skin rash. See also the Side Adverse Effects section in this monograph.

Horses: Trimethoprim with sulfadiazine or with sulfadoxine infused into the uterus of horses can cause endometrial inflammation, straining, and expulsion of the medication. Conception rates may be lowered. Because there is good distribution of these medications when administered by systemic routes, intrauterine administration is not recommended.

CROSS-SENSITIVITY AND/OR RELATED PROBLEMS

Patients allergic to one sulfonamide may be allergic to other sulfonamides also.

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PREGNANCY/REPRODUCTION

Sulfonamides and diaminopyrimidines cross the placenta in pregnant animals and some teratogenic effects have been seen with very high doses given to pregnant mice and rats. Ormetoprim and sulfadimethoxine: Dogs—Safety in breeding or pregnant animals has not been established.

Sulfadiazine and trimethoprim:

Dogs—The recommended dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight administered during pregnancy had no apparent effect on offspring.

Horses—Safety in pregnant animals has not been established.

With administration of recommended doses, no changes in spermato genesis in stallions were apparent.

LACTATION

Sulfonamides are distributed into milk, with 0.5 to 2% of the total dose found in the milk. For example, the milk-to-plasma concentration ratio for sulfadiazine and sulfadoxine was measured to be 0.5 in cows. Trimethoprim is distributed into milk. Trimethoprim concentrations in milk were found to be 1.3 to 3.5 times the plasma concentration measured at the same time in goats. The concentration of trimethoprim in the milk of cows is 1 to 3 times higher than in plasma and the concentration of trimethoprim in the milk of pigs is 1.3 to 3.5 times higher than in plasma.

DRUG INTERACTIONS AND/OR RELATED PROBLEMS

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):

Note: Combinations containing the following medication, depending on the amount present, may also interact with this medication.

Detomidine

(a trimethoprim and sulfonamide combination administered to a detomidine-anesthetized horse can lead to arrhythmias, hypotension, and death; it is suspected that the antimicrobial potentiates the cardiac changes reported with detomidine).

HUMAN DRUG INTERACTIONS

In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans and are included in the human monographs Sulfonamides (Systemic) and Trimethoprim (Systemic) in USP DI Volume I; these drug interactions are intended for informational purposes only and may or may not be applicable to the use of sulfonamides in the treatment of animals:

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Anticoagulants, coumarin- or indandione-derivative, or Anticoagulants, oral

Antidiabetic agents, oral

(these medications may be displaced from protein binding sites and/or their metabolism may be inhibited by some sulfonamides, resulting in increased or prolonged effects and/or toxicity; dosage adjustments may be necessary during and after sulfonamide therapy)

Bone marrow depressants

(concurrent use of bone marrow depressants with sulfonamides or aminopyrimidines may increase the leukopenic and/or thrombocytopenic effects; if concurrent use is required, close observation for myelotoxic effects should be considered)

Cyclosporine

(concurrent use with sulfonamides or trimethoprim may increase the metabolism of cyclosporine, resulting in decreased plasma concentrations and potential transplant rejection, and additive nephrotoxicity; plasma cyclosporine concentrations and renal function should be monitored)

Dapsone

(concurrent use with trimethoprim will usually increase the plasma concentrations of both dapsone and trimethoprim, possibly due to an inhibition in dapsone metabolism, and/or competition for renal secretion between the two medications; increased serum dapsone concentrations may increase the number and severity of side effects, especially methemoglobinemia)

Folates, other

(concurrent use with trimethoprim or use of trimethoprim between courses of other folic acid antagonists is not recommended because of the possibility of an increased risk of megaloblastic anemia)

Hemolytics, other

(concurrent use with sulfonamides may increase the potential for toxic side effects)

Hepatotoxic medications, other

(concurrent use with sulfonamides may result in an increased incidence of hepatotoxicity; patients, especially those on prolonged administration or those with a history of liver disease, should be carefully monitored)

Methenamine

(in acid urine, methenamine breaks down into formaldehyde, which may form an insoluble precipitate with certain sulfonamides, especially those that are less soluble in urine, and may also increase the danger of crystalluria; concurrent use is not recommended)

Methotrexate or Phenylbutazone or Sulfapyrazone

(the effects of methotrexate may be potentiated during concurrent use with sulfonamides because of displacement from plasma protein binding sites; phenylbutazone and sulfapyrazone may displace sulfonamides from plasma protein binding sites, increasing sulfonamide concentrations)

Phenytoin

(trimethoprim may inhibit the hepatic metabolism of phenytoin, increasing the half-life of phenytoin by up to 50% and decreasing its clearance by 30%)

Procarbazine

(concurrent use with trimethoprim may increase the plasma concentration of both procarbazine and its metabolite NAPA by decreasing their renal clearance)

Rifampin

(concurrent use may significantly increase the elimination and shorten the elimination half-life of trimethoprim)

Warfarin

(trimethoprim may potentiate the anticoagulant activity of warfarin by inhibiting its metabolism)

LABORATORY VALUE ALTERATIONS

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):
With diagnostic test results:
Thyrotropin stimulation tests or total serum thyroxine (T4)
(thyroid function tests may be lowered in dogs with administration of sulfamethoxazole and trimethoprim combination at high doses [25 mg of sulfamethoxazole and 5 mg of trimethoprim per kg of body weight every 12 hours for 6 weeks] or ormetoprim and sulfadimethoxine [8 weeks of medication with the labeled dose or with three to five times the labeled dose]; the T4 and thyrotropin stimulation tests, but not T3, may be significantly reduced; this effect was not shown with labeled doses of sulfadiazine and trimethoprim)

With physiology/laboratory test values:
Cholesterol, serum
(cholesterol concentrations can be elevated with administration of sulfonamides, including ormetoprim and sulfadimethoxine combination; however, this effect is reversible)

HUMAN LABORATORY VALUE ALTERATIONS
In addition to the above laboratory value alterations reported in animals, the following laboratory value alterations have been reported in humans, and are included in the human monographs Sulfonamides (Systemic) and Trimethoprim (Systemic) in USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of sulfonamides in the treatment of animals:

With diagnostic test results:

Benedict’s test
(sulfonamides may produce a false-positive Benedict’s test for urine glucose)

Creatinine determinations
(sulfamethoxazole or trimethoprim may interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in creatinine values that are approximately 10% higher than actual values)

Sulfosalicylic acid test
(sulfonamides may produce a false-positive sulfosalicylic acid test for urine protein)

Urine urobilinogen test strip (e.g., Urobilistix)
(sulfonamides may interfere with the Urobilistix test for urinary urobilinogen)

With physiology/laboratory test values:

Alanine aminotransferase (ALT [SGPT]), serum, and aspartate aminotransferase (AST [SGOT]), serum
(values may be increased)

Bilirubin, serum, and blood urea nitrogen (BUN) and creatinine, serum
(concentrations may be increased)

MEDICAL CONSIDERATIONS/CONTRAINDICATIONS
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist:

» Blood dyscrasias (slight to moderate reduction in hematopoietic activity has been reported with long-term high dosing of potentiated sulfonamides)

» Hypersensitivity to diaminopyrimidines or sulfonamides (animals that have had a previous reaction may be much more likely to react on subsequent administration)

Risk-benefit should be considered when the following medical problems exist:

Hepatic function impairment (delayed biotransformation may increase the risk of adverse effects)
Renal function impairment (delayed elimination could cause accumulation of sulfonamide and metabolites, increasing the risk of adverse effects)

Urolithiasis
(sulfonamides can crystallize in the renal system under certain conditions)

PATIENT MONITORING
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

Complete blood count (CBC), including platelet count
(some animals have had reductions in hematopoietic activity when administered potentiated sulfonamides; periodic CBC and platelet counts are recommended if it is necessary to administer long-term treatment with potentiated sulfonamides)

Culture and susceptibility, in vitro, and minimum inhibitory concentration (MIC)
(in vitro cultures and MIC test should be done on samples collected prior to potentiated sulfonamide administration to determine pathogen susceptibility)

Schirmer’s tear test
(periodic Schirmer’s tear tests during potentiated sulfonamide therapy in dogs may be warranted to monitor for early keratoconjunctivitis sicca)

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THESE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
For all species

Crystallization in the urinary tract (hypersensitivity, specifically anaphylaxis)

Note: Crystallization of sulfonamides is theoretically possible with administration of potentiated sulfonamides; however, the lower doses of sulfonamide used in the potentiated sulfonamide combination makes crystallization less likely to occur than with sulfonamide administered alone. Sulfonamides can crystallize in the kidneys or urine in animals with aciduria, with high doses of sulfonamide, or with dehydration. The amount of drug in the acetylated metabolite form also can affect solubility. Because dogs do not produce acetylated metabolites, they may be less susceptible to this adverse effect. Crystallization also can be minimized in susceptible animals by maintaining a high urine flow and, if necessary, alkalinating the urine.
Dogs

Anemia, hemolytic\(^{[R-5; 19]}\); anemia, nonregenerative\(^{[R-23; 51]}\); anorexia\(^{[R-5; 19]}\); cutaneous drug eruption, including erythema multiforme, perforating folliculitis, and pustular dermatitis\(^{[R-54; 60]}\); diarrhea\(^{[R-5; 19]}\); facial swelling\(^{[R-5; 19]}\); fever\(^{[R-5; 19]}\); hepatitis\(^{[R-5; 19; 52; 54]}\); hypothyroidism\(^{[R-21; 61; 62]}\); idiosyncratic toxicosis\(^{[R-5-53; 54; 57-60]}\) (blood dyscrasias, including anemia, leukopenia, or thrombocytopenia; fever; focal retinitis; lymphadenopathy; nonseptic polyarthritis; polymyositis; skin rash); keratoconjunctivitis sicca\(^{[R-5; 19; 55; 56]}\); idiosyncratic disorders\(^{[R-19]}\) (agression, ataxia, behavioral changes, hyperexcitability, seizures); polyarthrits\(^{[R-5; 19]}\); polydipsia/polyuria\(^{[R-6; 19]}\); thrombocytopenia—case one reported without other blood lines affected\(^{[R-116]}\); urticaria\(^{[R-5; 19]}\); vomiting\(^{[R-5; 19]}\).

Note: Idiosyncratic toxicosis can occur 8 to 20 days after starting treatment and is believed to be caused by either an immune-mediated syndrome or by an idiosyncratic reaction in dogs, perhaps due to toxic metabolites of the sulfonamide. Of 22 reported cases compiled in one study, 7 were Doberman Pinschers and it has been theorized that they are more susceptible than other breeds to this toxicosis\(^{[R-5-53; 54]}\). A large majority of the animals in which idiosyncratic toxicosis occurs have had a previous exposure to a sulfonamide\(^{[R-54]}\). When sulfonamide therapy is discontinued, recovery generally occurs within 2 to 5 days\(^{[R-5-53; 56]}\).

Keratoconjunctivitis sicca is considered a possible side/adverse effect in any dog administered sulfonamides; it can occur at any time after therapy is initiated. The most frequent reports have been with sulfasalazine or trimethoprim and sulfonamide combination\(^{[R-55; 56]}\), perhaps because these medications are most commonly used for long-term therapy in dogs. As many as 15% (5 out of 33 in one study) of dogs treated with sulfadiazine and trimethoprim may develop keratoconjunctivitis sicca\(^{[R-124]}\). While increased risk has not been linked to higher dose or longer treatment, dogs weighing less than 12 kg may be at increased risk\(^{[R-124]}\). Lacrimation may return to normal after discontinuation of sulfonamide treatment. The nonregenerative anemias seen in response to long-term administration of sulfadiazine and trimethoprim combination are, in some cases, believed to be related to folate reduction with long-term, high-dose administration (60 to 120 mg/kg a day for many weeks)\(^{[R-23; 50]}\), of potentiated sulfonamides\(^{[R-23; 50]}\); these anemias generally respond well to withdrawal of the medication\(^{[R-23; 50]}\). In the event an animal does not respond to medication withdrawal, folic acid or folic acid supplementation may be necessary\(^{[R-137; 138]}\).

Iatrogenic hypothyroidism may occur and thyroid function test results may be lowered with administration of sulfamethoxazole and trimethoprim combination at high doses (2.5 mg of sulfamethoxazole and 5 mg of trimethoprim per kg every 12 hours for 6 weeks)\(^{[R-6; 2]}\) or ormetoprim and sulfadimethoxine\(^{[R-21]}\) (8-week medication with the labeled dose or with three to five times the labeled dose). Results of the T\(_4\) and thyrotropin stimulation tests, but not T\(_3\), may show significant reduction\(^{[R-6; 41]}\); this effect was not shown with labeled doses of sulfadiazine and trimethoprim (12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg every 12 hours for 4 weeks)\(^{[R-6; 2]}\).

**Horses**

Diarrhea, transient—approximately 3% of horses treated in one study\(^{[R-5; 119]}\); hypersensitivity reactions (anorexia; decreased hematopoiesis\(^{[R-3]}\); loose stool; or muscle tremors)—with intravenous administration of potentiated sulfonamides\(^{[R-25; 26; 35]}\)

**Pigs**

Thyroid hyperplasia—in gilts, sows and piglets; believed to be in response to the sulfadimethoxine component of ormetoprim and sulfadimethoxine combination\(^{[R-92]}\)

For sulfaquinoxaline

**Chickens and dogs**

Hemorrhagic syndrome (anorexia, epistaxis, hemoysis, lethargy, pale mucous membranes, death)\(^{[R-100; 112; 113; 121; 122]}\)

Note: Hemorrhagic syndrome has been reported in chickens and dogs but may occur in other species. It is most often reported with the addition of sulfaquinoxaline to feed for chickens, but in dogs, reports follow administration of products labeled for poultry but administrated to dogs in the water supply\(^{[R-112; 113; 121; 122]}\). Sulfafloxazoline is a vitamin K antagonist that inhibits vitamin K epoxide and vitamin K quinone reductase and causes an effect similar to that of coumarin anticoagulants.\(^{[R-100]}\) Rapid hypoprothrombinemia occurs in dogs and an additional adverse effect of sulfoxazoline on specific cell types may explain why supplementation of chicken feeds with vitamin K has not always prevented the syndrome in chickens.\(^{[R-100; 112]}\) Rapid discontinuation of medication and initiation of therapy with vitamin K\(_1\) may reverse the effects.

**THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME**

Incidence more frequent

**Cats**

Salivation—with uncoated tablets or broken tablets\(^{[R-111]}\); thyroid function changes—with prolonged dosages\(^{[R-111]}\); vomiting, transient—up to 1 hour after administration of sulfadiazine and trimethoprim combination\(^{[R-23]}\)

**Cattle, horses, or pigs**

Local pain and swelling—with intramuscular injection of sulfonamide and trimethoprim\(^{[R-9; 13; 14]}\)

**Pigs**

Irritant reactions—with intramuscular injections\(^{[R-14]}\); vomiting—with oral surgical injection of sulfadiazine and trimethoprim combination\(^{[R-10]}\)

**HUMAN SIDE/ADVERSE EFFECTS**\(^{[R-149]}\)

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans and are included in the human monographs Sulfonamides (Systemic) and Trimethoprim (Systemic) in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of potentiated sulfonamides in the treatment of animals:

For sulfonamides—

Incidence more frequent

Central nervous system (CNS) effects; gastrointestinal disturbances; hypersensitivity; photosensitivity

Incidence less frequent

Blood dyscrasias; hepatitis; Lyell’s syndrome (difficulty in swallowing; redness, blistering, peeling, or loosening of skin); Stevens-Johnson syndrome (aching joints and muscles; redness, blistering, peeling, or loosening of skin; unusual tiredness or weakness)

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Recommended treatment consists of the following:

**TREATMENT OF OVERDOSE**

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

- **For ormetoprim and sulfadimethoxine**
  - Dogs (53 mg ormetoprim and 267 mg sulfadimethoxine per kg of body weight dose or 160 mg ormetoprim per kg administered alone)
  - **Convulsions; hyperglycemia, mild**

**ORAL DOSAGE FORMS ONLY**

Horses: The oral administration of 25 to 100 mg of sulfadiazine and 5 to 20 mg of trimethoprim per kg of body weight a day for 5 days does not cause the increase in coliform bacteria and *Clostridium perfringens* type A associated with induced colitis. Healthy horses do not appear to develop watery stools within this dosage range. At the highest dose, a slight decrease in total count is noted in healthy horses. Having free access to feed does not significantly affect the horse’s ability to absorb sulfadiazine during administration of oral sulfadiazine and trimethoprim combination. The absorption of trimethoprim is delayed so initial serum concentrations will be lower in a fed horse than in a fasted horse; however, this effect is greatly decreased by the third day of treatment.

**FOR TREATMENT OF ADVERSE EFFECTS**

Recommended treatment consists of the following:

- **For anaphylaxis**
  - Parenteral epinephrine.
  - Oxygen administration and respiratory support.

**ORMETOPRIM AND SULFADIMETHOXINE**

**ORAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**ORMETOPRIM AND SULFADIMETHOXINE FOR MEDICATED FEED**

**Usual dose:**

- Coccidiosis (prophylaxis) — *Chickens* and *partridges*, chukar: Oral. 68.1 grams of ormetoprim and 113.5 grams of sulfadimethoxine per ton of feed, fed as the only ration.
Potentiated Sulfonamides Veterinary—Systemic

Strength(s) usually available[^R-150];

U.S.—
Veterinary-labeled product(s):
50 grams of ormetoprim and 250 grams of sulfadimethoxine per kg of premix (OTC) [Romet 30 (catfish and salmonids)].
150 grams of ormetoprim and 250 grams of sulfadimethoxine per kg of premix (OTC) [Rofenaid 40 (chickens, ducks, partridges, and turkeys)].

Canada—
Veterinary-labeled product(s):
50 grams of ormetoprim and 250 grams of sulfadimethoxine per kg of premix (Rx) [Romet-30 (salmonids)].

Withdrawal times:
U.S.[^R-6; 7]—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens, ducks, partridges, turkeys</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Product labeling with the above withdrawal times states that this combination is not for use in birds producing eggs for food or for chickens over 16 weeks of age.[^R-6].

U.S.[^R-6; 7].

Species | Withdrawal time |
<table>
<thead>
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<tr>
<td>Catfish, trout</td>
<td>1</td>
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<tr>
<td>Salmon, trout</td>
<td>42</td>
</tr>
</tbody>
</table>

Canada[^R-16].

Species | Withdrawal time |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon, trout</td>
<td>42</td>
</tr>
</tbody>
</table>

Note: Product labeling with the above withdrawal time states that it applies to a dose of 15 mg per kg of body weight a day when the water temperature is ≥ 10 °C.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.

Additional information: Canadian labeling states that the product should not be used when the water temperature is below 10 °C.[^R-16].

USP requirements: Not in USP.

Rometprim and sulfadimethoxine tablets

Usual dose:
Skin and soft tissue infections[^1] or urinary tract infections[^1].

Dogs—Oral, 9.2 mg of ormetoprim and 45.8 mg of sulfadimethoxine per kg of body weight as an initial dose, followed by 4.6 mg of ormetoprim and 22.9 mg of trimethoprim per kg of body weight every twenty-four hours[^R-5]. Administration for more than twenty-one days is not recommended[^R-5].

Note: Dogs—Although the efficacy has not been established, a dose of 11 mg of ormetoprim and 55 mg of sulfadimethoxine a day has been used in the treatment of enteric coccidiosis[^1] in dogs. This therapy may reduce shedding of oocysts and relieve symptoms[^R-116].

Strength(s) usually available[^R-150];

U.S.[^R-5].

Veterinary-labeled product(s):
20 mg of ormetoprim and 100 mg of sulfadimethoxine (Rx) [Primor 120].
40 mg of ormetoprim and 200 mg of sulfadimethoxine (Rx) [Primor 240].
100 mg of ormetoprim and 500 mg of sulfadimethoxine (Rx) [Primor 600].
200 mg of ormetoprim and 1000 mg of sulfadimethoxine (Rx) [Primor 1200].

Canada—
Veterinary-labeled product(s):
Not commercially available.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.
USP requirements: Not in USP.

1Not included in Canadian product labeling or product not commercially available in Canada

PYRIMETHAMINE AND SULFAQUINOXALINE

ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

PYRIMETHAMINE AND SULFAQUINOXALINE ORAL SOLUTION

Usual dose: [Coccidiosis (prophylaxis and treatment)]—Chickens and turkeys: Oral, 14.7 mg of pyrimethamine and 48.8 mg of sulfaquinonoxaline per liter of water, administered as the only source of drinking water for two days. Treatment is stopped for three days and then repeated as necessary to control infection. For existing infection, treatment should be repeated until symptoms of disease have disappeared.

Strength(s) usually available:

U.S.—Veterinary-labeled product(s): Not commercially available.

Canada¹—Veterinary-labeled product(s): 9.8 grams of pyrimethamine and 32.5 grams of sulfaquinonoxaline per liter of solution (OTC) [Quinnoxine-S; Sulfadiazine-S].

Withdrawal times:

Canada¹—

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens, turkeys</td>
<td>4</td>
</tr>
</tbody>
</table>

Packaging and storage: Store below 23 °C (73 °F), unless otherwise specified by the manufacturer. Protect from freezing.

USP requirements: Not in USP.

SULFADIAZINE AND TRIMETHOPRIM

ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

SULFADIAZINE AND TRIMETHOPRIM ORAL PASTE

Usual dose:

Respiratory tract infections;
Skin and soft tissue infections;
Strangles;
Urogenital infections¹; or
[Perioperative infections]—Horses: Oral, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours.

Note: Based on pharmacokinetic studies, disease models of infectious arthritis, and the relatively short half-life of trimethoprim in the horse, an [oral dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twelve hours has been used to treat susceptible infections in horses¹], including equine infectious arthritis¹, in which case the dose is administered for three to six weeks.

The administration of oral sulfadiazine and trimethoprim combination while a horse has free access to feed does not significantly affect the absorption of the sulfadiazine; however, the absorption of trimethoprim is delayed so that initial serum concentrations will be lower in a fed horse than in a fasted horse. This effect is greatly decreased by the third day of treatment. For horses being treated for less severe, susceptible infections, allowing free access to food is recommended to decrease the risk of diarrhea.

Strength(s) usually available:

U.S.—Veterinary-labeled product(s):

333 mg of sulfadiazine and 67 mg of trimethoprim per gram of paste (Rx) [Tribrissen 400 Oral Paste].

Canada¹—Veterinary-labeled product(s):

Not commercially available.

Withdrawal times:

U.S.—Sulfadiazine and trimethoprim oral paste is not labeled for use in food-producing animals, including horses intended for food production. See Sulfadiazine and Trimethoprim Tablets for more information.

Packaging and storage: Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.

USP requirements: Not in USP.
SULFADIAZINE AND TRIMETHOPRIM TABLETS

Usual dose:

Gastrointestinal tract infections 1:

Respiratory tract infections 1:

Skin and soft tissue infections 1[2, 46]: Dogs and [cats]: Oral, 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg of body weight every twelve hours[3, 11; 19] or, less commonly, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours.

Withdrawal times:

Note: Only intact tablets should be administered to cats, to avoid excessive salivation caused by contact of the medication with oral mucosa[23].

Urinary tract infections 1—Dogs: Oral, 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg of body weight every twelve hours or, less commonly, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours[11].

Note: For [bacterial prostatitis in dogs, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twelve hours for two to four weeks 1 is recommended[25; 47; 48], based on pharmacokinetic data.

Product labeling states that administration for more than fourteen days is not recommended[2, 11; 19].

Note: Although the efficacy has not been established, doses up to [37.5 to 50 mg of sulfadiazine and 7.5 to 10 mg of trimethoprim per kg of body weight every twelve hours for three to six months have been used in the treatment of nocardiosis 1 in cats and dogs[23; 110; 132].

For organisms susceptible to both sulfadiazine and trimethoprim, once-daily dosing is likely to be efficacious for cats and dogs. However, for organisms that may be resistant to one of the antimicrobials, twice-daily dosing as above is recommended. For infections for which susceptibility is unknown or when life-threatening infections are present, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twelve hours has been used, based on current information about the pharmacokinetics of this medication in the dog[23].

Note: [Calves, nonruminating] 1—Until recently, Canadian sulfadiazine and trimethoprim boluses were labeled for use in the treatment of bacterial pneumonia in calves[12]. Although there are no sulfadiazine and trimethoprim products labeled for use in calves in the United States or Canada at this time, oral sulfadiazine and trimethoprim products might be used in the treatment of susceptible infections, such as pneumonia, in calves.

Tablets are not recommended for use in ruminating animals because of poor bioavailability 1[81] and subsequent lack of efficacy as calves progress to the ruminant state[81]. In ruminating calves, therapeutic serum concentrations of trimethoprim have not been reached with oral administration[81]. Increased rate of elimination and decreased absorption of the medication as calves mature lead to a decrease in resulting serum antibiotic concentration that is measurable at 6 weeks of age in milk-fed calves and becomes so pronounced with onset of rumination that this medication cannot be administered effectively[79; 81; 143].

According to some researchers[24; 81; 143], many pathogens important in calfhood diseases, including Escherichia coli, Salmonella species, and Haemophilus species, have minimum inhibitory concentrations (MICs) that range from 3 to 10 mcg per mL (mcg/mL) for sulfonamides and 0.1 to 0.5 mcg/mL for trimethoprim. Researchers have suggested that, in calves less than 1 week of age, oral...
administration of 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg of body weight every 24 hours would be appropriate in the treatment of infections caused by these organisms\textsuperscript{R-81}. They note that in animals older than 1 week of age, an oral dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight, administered every 12 hours, has been necessary to maintain therapeutic concentrations\textsuperscript{R-81}. However, the National Committee for Clinical Laboratory Standards (NCCLS) lists the breakpoints as ≤ 38/2 mcg/mL for sulfonamide and trimethoprim, respectively\textsuperscript{R-141}. It is possible for an organism to be classified as sensitive yet have MICs above the plasma concentration achieved by the above dosages\textsuperscript{R-145}. Based on pharmacokinetic calculations, an oral dosage of 37.5 mg of sulfadiazine and 7.5 mg of trimethoprim per kg of body weight every 12 hours in calves older than 1 week of age but younger than 6 weeks of age may be needed to consistently maintain concentrations greater than or equal to the NCCLS breakpoints, but the safety and efficacy of such a dose has not been tested in calves\textsuperscript{R-144; 145}.

**Strength(s) usually available\textsuperscript{R-150};**

**U.S.—**

Veterinary-labeled product(s):
- 25 mg of sulfadiazine and 5 mg of trimethoprim (Rx) [Tribrissen 30].
- 100 mg of sulfadiazine and 20 mg of trimethoprim (Rx) [Tribrissen 120].
- 400 mg of sulfadiazine and 80 mg of trimethoprim (Rx) [Tribrissen 480].
- 800 mg of sulfadiazine and 160 mg of trimethoprim (Rx) [Tribrissen 960].

Canada—

Veterinary-labeled product(s):
- Not commercially available.

**Withdrawal times:**

U.S. and Canada—Sulfadiazine and trimethoprim tablets are not labeled for use in food-producing animals.

There is no established withdrawal time for calves in the U.S. and, in Canada, where a sulfadiazine and trimethoprim bolus was once available, there is no longer any product labeled for use in calves. If a sulfadiazine and trimethoprim combination product available in the U.S. is administered to 1-week-old calves at a dose of 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim every twelve hours, there is some evidence to suggest that a meat withdrawal time of 10 days, the discontinued Canadian product label withdrawal time, would be sufficient to avoid residues that would violate U.S. standards\textsuperscript{R-12; 79; 80; 81; 140; 142}. Estimates for a withdrawal time for dosages larger than 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim every twelve hours are not available. It should be considered that substitution of one oral dosage form for another may result in differences in pharmacokinetic results. Available residue studies\textsuperscript{R-140} and pharmacokinetic\textsuperscript{R-81} studies for oral products were performed in calves using boluses and tablets, respectively.

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.

**USP requirements:** Not in USP.

\textsuperscript{1}Not included in Canadian product labeling or product not commercially available in Canada.

**PARENTERAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**SULFADIAZINE AND TRIMETHOPRIM INJECTION**

**Usual dose:**

Respiratory tract infections; or

Skin and soft tissue infections—

[Cats] and [dogs]: Subcutaneous, 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg of body weight every twelve hours or, less commonly, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours\textsuperscript{R-8}. Horses: Intramuscular or intravenous, 20 mg of sulfadiazine and 4 mg of trimethoprin per kg of body weight every twenty-four hours\textsuperscript{R-9}.

Strangles; or

Urogenital tract infections\textsuperscript{1}—Horses: Intramuscular or intravenous, 20 mg of sulfadiazine and 4 mg of trimethoprim per kg of body weight every twenty-four hours\textsuperscript{R-9}.

[Gastrointestinal tract infections]—Cats and dogs: Subcutaneous, 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg of body weight every twelve hours or, less commonly, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours\textsuperscript{R-8}.

Note: Although Canadian labeling recommends intramuscular or intravenous administration of sulfadiazine and trimethoprim combination and there are few reports in the literature of adverse reactions to intravenous administration of this combination, some sources recommend caution when administering these medications intravenously to horses\textsuperscript{R-25}.

Product labeling states that administration for more than fourteen days in cats and dogs and more than seven days in horses is not recommended\textsuperscript{R-8; 9}.

**Strength(s) usually available\textsuperscript{R-150};**

**U.S.—**

Veterinary-labeled product(s):
- 400 mg of sulfadiazine and 80 mg of trimethoprim per mL (Rx) [Tribrissen 48% (horses)].

Canada—

Veterinary-labeled product(s):
- 200 mg of sulfadiazine and 40 mg of trimethoprim per mL (Rx) [Tribrissen 24% (cats and dogs)].
- 400 mg of sulfadiazine and 80 mg of trimethoprim per mL (Rx) [Tribrissen 48% (horses)].

**Withdrawal times:**

U.S. and Canada—Products are not labeled for use in horses to be used for food production\textsuperscript{R-9}.

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.

**USP requirements:** Not in USP.

\textsuperscript{1}Not included in Canadian product labeling or product not commercially available in Canada.
SULFADOXINE AND TRIMETHOPRIM

PARENTERAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

SULFADOXINE AND TRIMETHOPRIM INJECTION

Usual dose:
[Bacterial enteritis];
[Bacterial pneumonia]; or
[Colibacillosis]—Cattle and pigs: Intramuscular or slow intravenous, 13.3 mg of sulfadoxine and 2.7 mg of trimethoprim per kg of body weight, every twenty-four hours for five days.[R-11–15]

Note: [Cattle]—Based on pharmacokinetic studies, a dose of 13.3 mg of sulfadoxine and 2.7 mg of trimethoprim per kg of body weight every twelve hours may be necessary to treat infections in cattle caused by organisms that are less than very sensitive to sulfadoxine and trimethoprim.[R-85].

[Bacterial arthritis];
[Mastitis]; or
[Metritis]—Pigs: Intramuscular or slow intravenous, 13.3 mg of sulfadoxine and 2.7 mg of trimethoprim per kg of body weight every twenty-four hours for five days.[R-11–15].

[Pododermatitis]; or
[Sepsisemia]—Cattle: Intramuscular or slow intravenous, 13.3 mg of sulfadoxine and 2.7 mg of trimethoprim per kg of body weight, every twenty-four hours for four days.[R-11–15].

Strength(s) usually available[R-150]:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
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<tbody>
<tr>
<td></td>
<td>Meat (days)</td>
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<td>Cattle</td>
<td>10</td>
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<tr>
<td>Pigs</td>
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Withdrawal times:

Canadian—Veterinary-labeled product(s): 200 mg of sulfadoxine and 40 mg of trimethoprim per mL (Rx) [Bimotrim; Borgal; Potensulf; Trimidox; Trivetrin].

USP requirements: Preserve in tight, light-resistant containers. Contains the labeled amounts, within ±10%. Meets the requirements for identification, pH (5.0–6.5), Chromatographic purity, and Alcohol content (not more than 0.5%).[R-117].

SULFADOXINE AND TRIMETHOPRIM ORAL SUSPENSION USP

Usual dose:
Note: [Dogs]—Although the safety and efficacy have not been established, an oral dose of 25 mg of sulfamethoxazole and 5 mg of trimethoprim per kg of body weight every twelve hours for two to four weeks has been used in the treatment of bacterial prostatitis in dogs, based on pharmacokinetic data.[R-47; 48].

[Horses]—Although the safety and efficacy have not been established, an oral dose of 25 mg of sulfamethoxazole and 5 mg of trimethoprim per kg of body weight every twelve hours has been used in the treatment of bacterial infections, based on pharmacokinetic studies.[R-111].

Strength(s) usually available:

U.S.—Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):[R-119]
40 mg of sulfamethoxazole and 8 mg of trimethoprim per mL (Rx) [Bactrim Pediatric; Cotrim Pediatric; Septra Grape Suspension; Septra Suspension; Sulafuram Pediatric; Sulfafrim Suspension; Generik].

Canada—Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
40 mg of sulfamethoxazole and 8 mg of trimethoprim per mL (Rx) [Apo-Sulfatrim; Bactrim; Novo-Trimel; Nu-Cotrimox; Septra].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Store in a tight, light-resistant container. Protect from freezing.

USP requirements: Preserve in tight, light-resistant containers. Contains the labeled amounts, within ±10%. Meets the requirements for identification, pH (5.0–6.5), Chromatographic purity, and Alcohol content (not more than 0.5%).[R-117].

SULFAMETHOXAZOLE AND TRIMETHOPRIM TABLETS USP

Usual dose: See Sulfamethoxazole and Trimethoprim Oral Suspension USP.

Strength(s) usually available:

U.S.—Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):[R-119]
400 mg of sulfamethoxazole and 80 mg of trimethoprim (Rx) [Bactrim; Cotrim; Septra; Sulfram; Sulfram S/S].

800 mg of sulfamethoxazole and 160 mg of trimethoprim (Rx) [Bactrim DS; Cofatrim Forte; Cotrim DS; Septra DS; Sulfram DS].

Canada—Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
100 mg of sulfamethoxazole and 20 mg of trimethoprim (Rx) [Apo-Sulfatrim].

SULFAMETHOXAZOLE AND TRIMETHOPRIM

ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.
400 mg of sulfamethoxazole and 80 mg of trimethoprim (Rx) [Apotex—Canada; Bactrim DS; Novo-Triumeq; Septra DS].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Store in a well-closed, light-resistant container.

USP requirements: Preserve in well-closed, light-resistant containers. Contain the labeled amounts, within ±7%. Meet the requirements for Identification, Dissolution (70% of each active ingredient in 60 minutes in 0.1 N hydrochloric acid in Apparatus 2 at 75 rpm), and Uniformity of dosage units.\(^1\)

\(^1\)Not included in Canadian product labeling or product not commercially available in Canada.

PARENTERAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

SULFAMETHOXAZOLE AND TRIMETHOPRIM INJECTION USP

Usual dose:

Note: [Foals] and [horses]—Although the efficacy and safety have not been established, a slow intravenous dose of 12.5 mg of sulfamethoxazole and 2.5 mg of trimethoprim per kg of body weight every twelve hours has been used in the treatment of susceptible bacterial and protozoal infections in foals and horses, based on pharmacokinetic data.\(^{R-31; 32}\). However, to reach effective concentrations in the cerebrospinal fluid (CSF) for bacterial and protozoal infections, higher doses are required; distribution studies show that an intravenous dose of 36 mg of sulfamethoxazole and 7.5 mg of trimethoprim per kg of body weight will produce CSF concentrations sufficient to treat susceptible bacterial and protozoal infections.\(^{R-31; 33}\)

Intravenous doses should be administered slowly.

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

- Not commercially available.

Human-labeled product(s):\(^{R-119}\)

- 80 mg of sulfamethoxazole and 16 mg of trimethoprim per mL (Rx) [Bactrim IV; Septra IV].

Canada—

Veterinary-labeled product(s):

- Not commercially available.

Human-labeled product(s):

- 80 mg of sulfamethoxazole and 16 mg of trimethoprim per mL (Rx) [Septra].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Store in a light-resistant container. Should not be refrigerated.

Preparation of dosage form: The contents of each vial (5 mL) must be diluted to 75 to 125 mL with 5% dextrose injection prior to administration by intravenous infusion. The resulting solution should be administered by intravenous infusion over a sixty- to ninety-minute period.

Stability: After initial dilution with 75 or 125 mL of 5% dextrose injection, infusion should be administered within two or six hours, respectively. The solution should not be used if it is cloudy or contains a precipitate. The solution should not be mixed with other medications or solutions.

USP requirements: Preserve in single-dose, light-resistant containers, preferably of Type I glass. May be packaged in 50-mL, multiple-dose containers. A sterile solution of Sulfamethoxazole and Trimethoprim in Water for Injections, which, when diluted with Dextrose Injection, is suitable for intravenous infusion. Label it to indicate that it is to be diluted with 5% Dextrose Injection prior to administration. Contains the labeled amounts, within ±10%. Meets the requirements for Identification, Pyrogen, pH (9.5–10.5), Particulate matter, and Related compounds, and for Injections.\(^{R-117}\)

\(^{R-117}\)Not included in Canadian product labeling or product not commercially available in Canada.

REFERENCES

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8. Sulfadiazine and trimethoprim product information (Tribrissen 24% Injection, Schering-Plough—Canada). Downloaded from Schering-Plough Animal Health Product Label Retrieval Service on 2/21/03.
9. Sulfadiazine and trimethoprim product information (Tribrissen 48% Injection, Schering-Plough—Canada). Downloaded from Schering-Plough Animal Health Product Label Retrieval Service on 2/21/03.
10. Sulfadiazine and trimethoprim package insert (Tribrissen Piglet Suspension, Mallinckrodt—Canada), Rec 6/1/95.
11. Sulfadiazine and trimethoprim package insert (Tribrissen Tablets, Mallinckrodt—Canada), Rec 6/1/95 [discontinued product].
12. Sulfadiazine and trimethoprim package insert (Tribrissen Boluses, Mallinckrodt—Canada), Rec 6/1/95 [discontinued product].
13. Sulfadoxine and trimethoprim product information (Trivantrin Injection, Schering-Plough—Canada). Downloaded from Schering-Plough Animal Health Product Label Retrieval Service on 2/21/03.
15. Sulfadoxine and trimethoprim package insert (Trimidox, Sanofi—Canada), Rec 5/19/95.

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123. Panel comment on Sulfonamides (Veterinary-Systemic). 6/96.
144. Panel comment, 10/97.
145. Panel comment, 10/97.
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PYRIMETHAMINE Veterinary—Systemic

A commonly used brand name for a human-labeled product is Daraprim. Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:
Antiprotozoal (systemic).

INDICATIONS
Note: In other USP DI monographs, bracketed information in the Indications section refers to uses that are not included in U.S. product labeling, and superscript 1 refers to uses that are not included in Canadian product labeling. However, since pyrimethamine is not specifically approved for veterinary use, there is no product labeling identifying approved indications.

GENERAL CONSIDERATIONS
Pyrimethamine is a folic acid antagonist[11], active against protozoal dihydrofolate reductase. It is considered most effective against pathogenic protozoa when administered in combination with a sulfonamide[11; 16; 20].

The ready availability of combination products containing trimethoprim and sulfadiazine or trimethoprim and sulfamethoxazole may have contributed to the frequency of their concurrent administration with pyrimethamine. While trimethoprim does not increase the efficacy of therapy against protozoa[10], it is suspected to increase the incidence of side effects due to folate reduction[1; 21]. Whenever possible, pyrimethamine should be administered in combination with a sulfonamide alone in the treatment of susceptible infections.

The development of resistant organisms has been stimulated in in vitro experiments, and cross-resistance by these cultures to other dihydrofolate inhibitors has been shown. However, when pyrimethamine was combined with a sulfonamide in the treatment of pyrimethamine-resistant Neospora cultures, the combination was completely effective[11].

In the case of equine protozoal myeloencephalitis, resistance may occur within an individual horse if inadequate treatment is administered; however, transmission of resistance to the Sarcocystis neurona population outside the individual is not considered a problem because the horse is an aberrant host and does not shed infectious organisms[21].

ACCEPTED
[Equine protozoal myeloencephalitis (treatment)]1—Horses: Pyrimethamine is used in combination with a sulfonamide, such as sulfadiazine or sulfamethoxazole[8; 9], in the treatment of protozoal myeloencephalitis. Pyrimethamine reversibly binds to and inhibits the enzyme dihydrofolate reductase in protozoa. This inhibition prevents the production of tetrahydrofolic acid from dihydrofolate and thereby prevents the metabolism of folate[6]. Like protozoa, mammalian cells reduce folic acid to tetrahydrofolic acid; however, the therapeutic action of pyrimethamine relies on a greater selectivity for protozoal dihydrofolate reductase than for the mammalian enzyme[11]. Pyrimethamine is generally administered in conjunction with a sulfonamide to take advantage of the sequential inhibition of enzymatic steps in folate synthesis provided by the combination.

[Toxoplasmosis (treatment)]1—Cats: Although the efficacy and safety have not been established, pyrimethamine is used in combination with sulfadiazine in the treatment of toxoplasmosis in cats[18–20]. Side effects associated with the administration of pyrimethamine and sulfadiazine have led clinicians to search for other treatments. However, this therapy may have some value in the treatment of infection with nonencysted organisms in cats that can tolerate the medications.

REGULATORY CONSIDERATIONS
U.S. and Canada—Pyrimethamine is not labeled for use in animals, including food-producing animals; therefore, there are no established withdrawal times.

CHEMISTRY
Chemical group: A diaminopyrimidine; structurally related to trimethoprim[6].

Chemical name: 2,4-Pyrimidinediamine, 5-(4-chlorophenyl)-6-ethyl[2].

Molecular formula: C12H13ClN4[2].

Molecular weight: 248.71[2].

Description: Pyrimethamine USP—White, odorless, crystalline powder[1].

pKa: 7.34[5].

Solubility: Pyrimethamine USP—Practically insoluble in water; slightly soluble in acetone, in alcohol, and in chloroform[3].

PHARMACOLOGY/PHARMACOKINETICS
Mechanism of action/effect: Pyrimethamine reversibly binds to and inhibits the enzyme dihydrofolate reductase in protozoa. This inhibition prevents the production of tetrahydrofolic acid from dihydrofolate and thereby prevents the metabolism of folate[6]. Like protozoa, mammalian cells reduce folic acid to tetrahydrofolic acid; however, the therapeutic action of pyrimethamine relies on a greater selectivity for protozoal dihydrofolate reductase than for the mammalian enzyme[11]. Pyrimethamine is generally administered in conjunction with a sulfonamide to take advantage of the sequential inhibition of enzymatic steps in folate synthesis provided by the combination.

Absorption: Oral—Human beings: Pyrimethamine is well absorbed orally[1].

Bioavailability: Oral—Horses: Average, 56% (range, 39 to 78%)[5].

Distribution: Rapidly and extensively distributed after intravenous administration[5].

Horses—Cerebrospinal fluid (CSF) concentrations reached 25 to 50% of the serum concentrations but did not appear to accumulate in horses administered daily oral doses of 1 mg per kg of body weight (mg/kg) for 10 days[6].

Pigs—Distribution occurs in two phases after a 10 mg/kg intravenous dose: the fast phase has a half-life of 0.11 hour, and the slow phase has a half-life of 1.6 hours[10].
**Pyrimethamine Veterinary—Systemic**

**Rats**—Mean CSF concentration was 27% of the plasma concentration during the first 48 hours after a single oral dose of 2.9 mg/kg (1 mg per rat).  

**Volume of distribution**—Intravenous administration:  
- **Horses**—Steady-state: 1.52 liters per kg (L/kg).  
- **Pigs**—Area: 12.1 ± 2 L/kg.

**Protein binding:**  
- **Dogs**—High (85%).  
- **Human beings**—High (87%).  
- **Mice**—High (78%).  
- **Pigs**—High (85%), independent of serum concentration.  
- **Rats**—High (78%).

**Biotransformation:** Less than 5% of administered doses are excreted as unchanged drug in the urine in pigs and rats; five hours after administration of radiolabeled pyrimethamine to a rat, less than 50% of radioactivity in the blood was intact parent drug. Therefore, it is believed that pyrimethamine is extensively metabolized, although metabolites have not been identified in animals. In human beings, pyrimethamine is believed to be heptatically metabolized.

**Half-life:** Elimination—Intravenous administration:  
- **Horses**—12 ± 3.7 hours.  
- **Pigs**—13.3 ± 4.9 hours.

**Concentrations:**  
- **Peak serum concentration**—Oral administration: **Horses**—Single dose: 0.18 ± 0.03 mcg per mL of serum (mcg/mL) with administration of 1 mg/kg.  
  Multiple doses: 0.32 ± 0.11 mcg/mL after the 5th dose and 0.26 ± 0.07 mcg/mL after the 10th dose of 10 daily doses of 1 mg/kg.  
  **Time to peak concentration**—Oral administration: **Horses**—Single dose: 2.9 ± 2.1 hours after administration of 1 mg/kg.  
  Multiple doses: 2.2 hours after the 5th dose and 2.7 hours after the 10th dose of 10 daily doses of 1 mg/kg.  
  **Serum concentrations, other**—Oral administration: **Horses**—Single dose: 0.09 mcg/mL 24 hours after administration of 1 mg/kg.  
  Multiple doses: Plasma steady state was reached at the 5th day of 10 daily doses of 1 mg/kg; at that time the serum concentrations fluctuated approximately 65% over each 24-hour period, with the peak at approximately 0.32 mcg/mL.

**Elimination:** **Pigs**—Only about 3% of an intravenous dose of pyrimethamine is excreted in the urine as unchanged drug, although up to 90% of the dose is eliminated in that time.

**Total clearance—**  
- **Horses**: 1.6 ± 0.32 mL per minute per kg (mL/min/kg).  
- **Pigs**: 0.68 ± 0.16 mL/min/kg.

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**PREGNANCY/REPRODUCTION**

Reproduction: **Rats**—The fertility index of rats treated with pyrimethamine is lowered only by the highest doses administered. This suggests a toxic effect on the whole animal or the conceptus.

Pregnancy:  
- **Hamsters**—Single doses of 20 mg per pregnant hamster caused malformation or death in less than 10% of fetuses.
- **Horses**—In a group of horses treated with oral pyrimethamine at 1 mg per kg of body weight (mg/kg) a day, sulfadiazine at 16.7 mg/kg every twelve hours, and trimethoprim at 3.3 mg/kg every twelve hours, the three horses that were pregnant during therapy aborted during the second or third month of treatment. Each of the aborted fetuses was in the fifth month of gestation. It is not certain which of the medications might have caused the abortions. The horses' diets had not been supplemented with folate at the time of the abortions.

The administration of oral folic acid to pregnant mares being treated for equine protozoal myeloencephalitis may not protect the fetus from the effects of folate deficiency. Reports have been made of mares delivering foals with congenital defects after oral administration during pregnancy of pyrimethamine, 0.5 to 1 mg/kg a day, with sulfadiazine, 25 mg/kg a day; or sulfamethoxazole, 12.5 mg/kg day, and trimethoprim, 2.5 mg/kg. Two of the three reported mares had been treated in the last 3 months of gestation and one for 2 years before foaling. These mares had also been supplemented with oral folic acid, 40 mg as a total daily dose, and vitamin E, 8000 Units as a total daily dose, during the period of antibiotic treatment. Each of three mares on this dosage regimen produced a foal with renal hypoplasia or nephrosis and bone marrow aplasia or hypoplasia. In both mares and foals, serum folate concentrations were below the laboratory reference range and in two foals, folic was less than 30% of the minimum reference range. The risk of congenital defects should be considered when treating pregnant mares with pyrimethamine and sulfonamide.

**Miniature pigs**—A high incidence of malformations (70%), such as cleft palate, club foot, and micrognathia, was seen in offspring when pregnant sows were administered pyrimethamine, 3.6 mg/kg a day, from days 11 to 35 of gestation; however, no abnormalities were noted in the offspring of sows administered 0.9 to 1.8 mg/kg a day during the same period of gestation. Two of the three reported mares had been treated in the last 3 months of gestation and one for 2 years before foaling. These mares had also been supplemented with oral folic acid, 40 mg as a total daily dose, and vitamin E, 8000 Units as a total daily dose, during the period of antibiotic treatment. Each of three mares on this dosage regimen produced a foal with renal hypoplasia or nephrosis and bone marrow aplasia or hypoplasia. In both mares and foals, serum folate concentrations were below the laboratory reference range and in two foals, folic was less than 30% of the minimum reference range. The risk of congenital defects should be considered when treating pregnant mares with pyrimethamine and sulfonamide.

**LACTATION**

Pyrimethamine is distributed into human milk. Distribution into milk in lactating animals has not been determined.

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**PRECAUTIONS TO CONSIDER**

**CARCINOGENICITY**

**Mice**—A significant increase in the number of lung tumors per mouse has been reported with doses of 25 mg per kg of body weight (mg/kg), administered intraperitoneally.  

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DRUG INTERACTIONS AND/OR RELATED PROBLEMS
The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (« = major clinical significance):

Note: Drug interactions relating specifically to the use of pyrimethamine in animals are rarely reported in veterinary literature. Human drug interactions have been reported and are included in the following section.

HUMAN DRUG INTERACTIONS AND/OR RELATED PROBLEMS[R-27]
The following drug interactions have been reported in humans, and are included in the human monograph Pyrimethamine (Systemic) in USP DI Volume I; these drug interactions are intended for informational purposes only and may or may not be applicable to the use of pyrimethamine in the treatment of animals:

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Bone marrow depressants
(concurrent use of pyrimethamine with bone marrow depressants may increase the leukopenic and/or thrombocytopenic effects; if concurrent use is required, the possibility of increased myelotoxic effects should be considered, especially when pyrimethamine is used in large doses, such as those required in the treatment of toxoplasmosis)

Folate antagonists, other
(concurrent use of other folate antagonists with pyrimethamine or use of pyrimethamine between courses of other folate antagonists is not recommended because of the possible development of megaloblastic anemia)

MEDICAL CONSIDERATIONS/CONTRAINDICATIONS
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (« = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist:

» Anemia or
Bone marrow suppression
(pyrimethamine may cause folate deficiency, resulting in megaloblastic anemia and blood dyscrasias, including agranulocytosis and thrombocytopenia[R-19; 21; 26])

» Hepatic function impairment, severe
(in human beings, pyrimethamine is metabolized in the liver)

Risk-benefit should be considered when the following medical problem exists:

Pregnancy
(the risk of teratogenesis should be considered in planning treatment with pyrimethamine[R-18; 21])

PATIENT MONITORING
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; « = major clinical significance):

Complete blood counts (CBCs)[R-19; 21; 23] and Platelet counts
(should be performed on a regular basis, particularly with long-term or high-dose therapy; periodic packed cell volume evaluation is recommended in horses being treated for equine protozoal myeloencephalitis to monitor for anemia[R-29])

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

Note: It is assumed that animals have the same tendency as people to develop signs of folate deficiency with long-term use or high doses of folic acid antagonists such as pyrimethamine. Signs of folate deficiency have been reported frequently in the human literature and include agranulocytosis, megaloblastic anemia, and thrombocytopenia[R-16]. Similar signs have been noted in cats, dogs, and horses[R-19; 21; 26]. It should be considered that signs of folate deficiency may occur in any species administered pyrimethamine. When administering pyrimethamine with a sulfonamide, the risk of sulfonamide-related side effects should be considered. See the Sulfonamides (Veterinary—Systemic) monograph for further information.

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
Cats
Leukopenia—seen with a dose of 1 mg per kg of body weight (mg/ kg) a day for 6 days[R-19]

Horses
Anemia[R-21]; congenital defects in offspring (bone marrow aplasia or hypoplasia; renal nephrosis or hypoplasia; skin lesions)[R-15]; diarrhea[R-21]; leukopenia[R-21]

HUMAN SIDE/ADVERSE EFFECTS[R-17]
In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Pyrimethamine (Systemic) in USP DI Volume I; these side/adverse effects are intended for informational purposes only, and may or may not be applicable to the use of pyrimethamine in the treatment of animals:

Incidence less frequent
Agranulocytosis, leukopenia, or thrombocytopenia; atrophic glossitis; gastrointestinal disturbances (anorexia, diarrhea, nausea, and vomiting)

Incidence rare
Erythema multiforme and/or Stevens-Johnson syndrome; hypersensitivity

OVERDOSE
For more information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.
CLINICAL EFFECTS OF OVERDOSE
The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

**Dogs**—with a dose of 5 to 10 mg per kg of body weight (mg/kg) a day for 10 to 21 days\[^{R-26}\].

**Chronic effects**
- Anorexia and/or decreased appetite; ataxia; bone marrow suppression, including leukopenia and reticuloctopenia; dehydration; gastrointestinal toxicity (diarrhea, occasionally bloody; vomiting); weakness; weight loss

Note: Bone marrow suppression has been demonstrated by biopsy in a few dogs receiving extremely high doses of pyrimethamine (6 mg/kg a day for 10 to 15 days)\[^{R-26}\]. Three of eight dogs treated had bone marrow suppression, particularly of the erythroid elements\[^{R-26}\]. In dogs, vomiting was reported to be common within 2 to 5 hours of administration of 7.5 to 10 mg/kg, but vomiting was seen only occasionally in dogs receiving 5 mg/kg a day for 10 to 21 days\[^{R-26}\]. Intestinal lesions, including inflammation, mucoid degeneration, shortened villi and mucosal atrophy, are visible on histopathologic examination after administration of 6.2 mg/kg a day for 10 days to dogs\[^{R-26}\]. Respiratory depression and circulatory collapse, as well as neurotoxicity leading to seizures, have been reported in people receiving total doses of 250 to 300 mg of pyrimethamine\[^{R-1}\]. These specific signs have not been reported in animals; however, one of four dogs administered 5 mg/kg a day died on the 17th day of therapy; the specific cause of death was not reported\[^{R-26}\].

TREATMENT OF OVERDOSE\[^{R-1}\]
- Gastric lavage.
- Control of central nervous system stimulation by administration of benzodiazepines or short-acting barbiturates, if necessary.
- Respiratory assistance, if necessary.
- Administration of folic acid or folinic acid supplementation to prevent signs of folic deficiency caused by pyrimethamine and sulfonamide is sometimes not effective in preventing congenital defects in foals caused by folic deficiency\[^{R-15}\]. Fresh grass has more than twice the total folacin concentration of hay\[^{R-12}\], and serum folate concentrations tend to be much higher in pastured horses than in permanently stalled horses or horses in training\[^{R-33}; 14\]. It has been recommended that horses be maintained on feeds containing high folacin concentrations during pyrimethamine therapy\[^{R-29}\]. Rather than supplementing horses with folic acid, some clinicians recommend monitoring the packed-cell volume to detect developing anemias.
- Some clinicians have used the in vitro minimum inhibitory concentration (MIC) of pyrimethamine considered necessary to inhibit Toxoplasma gondii\[^{R-5}; 21\] or the MIC of pyrimethamine necessary to inhibit Neospora caninum\[^{R-11}\] as guidelines for target cerebrospinal fluid concentrations for control of the Sarcocystis species responsible for equine protozoal myeloencephalitis.\[^{R-5}\]

Diet/Nutrition
Horses: Pyrimethamine should be administered 1 hour prior to feeding hay\[^{R-9}\].

Human beings: Information from human product labeling includes the statement that anorexia and vomiting induced by pyrimethamine may be minimized by administering it with food\[^{R-1}\].

ORAL DOSAGE FORMS
Note: In other USP DI monographs, bracketed information in the Dosage Forms section refers to categories of use and/or indications that are not included in U.S. product labeling, and superscript 1 refers to categories of use and/or indications that are not included in Canadian product labeling. However, since pyrimethamine is not specifically approved for veterinary use, there is no product labeling identifying approved indications.

PYRIMETHAMINE TABLETS USP
Usual dose:
- [Equine protozoal myeloencephalitis]\[^{1}\]—Horses: Oral, 1 mg per kg of body weight every twenty-four hours\[^{R-9}\] in combination with 16.7 mg of sulfadiazine or sulfamethoxazole per kg of body weight every twelve hours\[^{R-5}; 8; 9; 21\] has been used. The average duration of treatment necessary to clear the organism may be as long as 130 days.
or more\[^{[21]}\]. Testing cerebrospinal fluid for \emph{Sarcocystis neurona} antibodies may help determine when to discontinue treatment\[^{[21]}\].

Note: The above dose is based on clinical case reports with successful outcomes that also included the concurrent administration of 3.3 mg of trimethoprim per kg of body weight. However, the administration of pyrimethamine concurrently with trimethoprim generally is not recommended. To decrease the risk of toxicity, the administration of pyrimethamine with sulfadiazine alone is preferred, but there are no specific reports of the efficacy of this combination.

\[\text{Neospora caninum} \text{ infection}\]  — \textit{Dogs:} Although the efficacy and safety have not been established, an oral dose of 1 mg of pyrimethamine per kg of body weight every twenty-four hours\[^{[14]}\] in combination with 12.5 mg of sulfadiazine per kg of body weight every twelve hours\[^{[14]}\] for four weeks has been used.

Note: The above dose is based on clinical case reports with successful outcomes that also included the concurrent administration of 2.5 mg of trimethoprim per kg of body weight. However, the administration of pyrimethamine concurrently with trimethoprim generally is not recommended. To decrease the risk of toxicity, the administration of pyrimethamine with sulfadiazine alone is preferred, but there are no reports of the efficacy of this combination.

\[\text{Toxoplasmosis}\]  — \textit{Cats:} Although the efficacy and safety have not been established, an oral dose of 1 mg of pyrimethamine per kg of body weight every twenty-four hours\[^{[18]}\] in combination with 25 mg of sulfadiazine per kg of body weight every twelve hours\[^{[18]}\] for fourteen to twenty-eight days has been used.

Note: The above dose was extrapolated from studies evaluating the efficacy of pyrimethamine and sulfadiazine in ending or reducing shedding of oocysts\[^{[18]}\] as well as preventing tissue infection\[^{[19]}\]. Because pyrimethamine is only available in 25-mg tablets, some clinicians will arrange for capsules to be formulated in smaller strengths for easier administration of the unpalatable medication to cats. Consultation with an experienced pharmacist is recommended.

**Strength(s) usually available:**

\textbf{U.S.} —

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s)\[^{[1]}\];

25 mg (Rx) \textit{Daraprim (scored)}.

\textbf{Canada} —

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

25 mg (Rx) \textit{Daraprim (scored)}.

**Withdrawal times:**

U.S. and Canada—Pyrimethamine is not labeled for use in animals, including food-producing animals; therefore, there are no established withdrawal times.

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

**Auxiliary labeling:**

- Keep out of the reach of children\[^{[1]}\].

**Caution:** Potential danger of accidental overdose\[^{[1]}\].

**USP requirements:**

Preserve in tight, light-resistant containers. Contain the labeled amount, within ± 7%. Meet the requirements for Identification, Dissolution (75% in 45 minutes in 0.01 N hydrochloric acid in Apparatus 2 at 50 rpm), and Uniformity of dosage units\[^{[1]}\].

Developed: 07/01/98

Interim revision: 10/14/99; 9/30/02; 03/28/03

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RIFAMPIN Veterinary—Systemic

Some commonly used brand names for human-labeled products are: Rifadin; Rifadin IV; Rimactane; and Rofact.

CATEGORY:
Antibacterial (systemic).

INDICATIONS

Note: In other USP DI monographs, bracketed information in the Indications section refers to uses that are not included in U.S. product labeling, and superscript 1 refers to uses that are not included in Canadian product labeling. However, since rifampin is not specifically approved for veterinary use, there is no product labeling identifying approved indications.

GENERAL CONSIDERATIONS

Rifampin is a broad-spectrum antibiotic, with activity against many gram-positive and some gram-negative aerobic bacteria as well as facultative anaerobic organisms. However, for clinical purposes, rifampin generally should not be considered broad-spectrum until proven so in each case. Most gram-negative bacteria should be considered resistant or to have unpredictable susceptibilities until susceptibility data are available. Because many infections involve more than one species of bacterium and because resistance can develop quickly, rifampin is most often administered in combination with other antimicrobial agents.

Rifampin is considered especially active in the treatment of staphylococcal infections and in the eradication of pathogens located in difficult to reach target areas, such as inside phagocytic cells. The ability of rifampin to reach intracellular bacteria can make it difficult to predict in vivo therapy results based on in vitro sensitivity tests.

Rifampin has been shown to have in vitro activity against equine Corynebacterium pseudotuberculosis, Rhodococcus equi, Staphylococcus species, Streptococcus equi, S. equisimilis, and S. zooepidemicus isolates. Susceptibility has been variable for the equine gram-negative nonenteric bacteria. It has shown moderate activity against Actinobacillus suis, A. equuli, Bordetella bronchiseptica, and Pasteurella species isolates. Equine isolates of Pseudomonas aeruginosa, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Proteus species, and Salmonella species were found to be resistant.

Strains of the porcine pathogen Actinobacillus pleuropneumoniae, isolated in Spain, were found to be susceptible to rifampin in vitro at a concentration of 1 mcg/mL or less. Rifampin had also activity against Pasteurella multocida species isolated from pigs with pneumonia in Spain. Some strains of Mycobacterium paratuberculosis were found to be sensitive to rifampin in vitro. Anaerobes found to be susceptible in vitro include 132 strains of Bacteroides species and 25 strains of Fusobacterium species isolated from goats in Spain; with blood concentrations of 2 mcg/mL, only 18% of strains were resistant. Although in vitro tests showed rifampin to be active against Clostridium perfringens type A isolates, when higher concentrations of pathogens per milliliter were tested, the antimicrobial was not very effective and in vivo efficacy against induced infections in mice was only weakly significant. Resistance to rifampin can develop quickly; therefore, it is most often used in combination with other antimicrobials. Resistant mutants may be concentration-sensitive and contain RNA polymerases with one of a variety of sensitivities to rifampin. Resistance may occur as a single-step mutation of the DNA-dependent RNA polymerase; therefore, initial susceptibility can rapidly diminish as small populations of resistant cells soon outnumber susceptible cells. This effect is diminished when combination antibiotic treatment is administered.

One case of the development of resistant Rhodococcus equi in a foal treated with erythromycin and rifampin has been reported. Cross-resistance to other antibiotics or transfer of resistance to other local microorganisms has not been reported.

ACCEPTED

[Pneumonia, Rhodococcus equi (treatment adjunct)]

Foals: Rifampin is used in combination with erythromycin in the treatment of pneumonia caused by Rhodococcus (Corynebacterium) equi in foals. Although the lung appears to be most vulnerable to Rhodococcus equi infection, in some cases susceptible foals have been found to have abdominal or subcutaneous abscesses, bacterial endocarditis, diskospondylitis, gastrointestinal infections, osteomyelitis, or septicemia. In many, but not all, of these cases the foal has a concomitant pneumonia. R. equi are susceptible in vitro to erythromycin alone, and erythromycin alone has been effective in the treatment of this infection. However, no studies have been performed to compare the efficacy of erythromycin alone with the combination of erythromycin and rifampin in foals. The in vitro evidence of synergistic activity for the combination of erythromycin and rifampin against R. equi and the volume of case reports supporting the efficacy of the combination make treatment with a combination of erythromycin and rifampin more commonly recommended for this indication than erythromycin alone.

ACCEPTANCE NOT ESTABLISHED

[Infections, bacterial (treatment)]—Although the safety and efficacy have not been established, rifampin is used in combination with other antimicrobials in the treatment of susceptible bacterial infections, and in particular, staphylococcal infections in animals. Rifampin is particularly suited for the treatment of organisms that are resistant to other therapies by nature of their intracellular location. Because the pharmacokinetics of rifampin have been well-studied in horses and minimal side effects have been reported in foals, the treatment of these infections in horses may be more well-defined than for other species. The use of rifampin in other animals could be based on available pharmacokinetic data for calves, dogs, foals, rabbits, and sheep, knowledge of bacterial susceptibility; case reports describing treatment of infections in a cat, a deer, and a dog; and also efficacy studies that have been performed in rats. However, there is
limited knowledge about the safety of rifampin use in species other than horses.

[Brucellosis (treatment)]: Dogs: Although the safety and efficacy have not been established, rifampin in combination with doxycycline has been recommended in the treatment of brucellosis in dogs. This recommendation is based on demonstrated efficacy in the treatment of human brucellosis and evidence of possible canine pathogen susceptibility to rifampin. There are no controlled studies in dogs.

[Paratuberculosis (treatment)]: Cattle, goats, and sheep: For use in animals not to be used in food production—Although the safety and efficacy have not been established, rifampin has been administered in conjunction with isoniazid in the alleviation of signs associated with paratuberculosis. The addition of an aminoglycoside to the regimen has also been used in the initial weeks of severe infection. The use of rifampin is based on in vitro culture and sensitivity results, and on case reports of clinical improvement for extended periods of time. However, internal lesions and fecal shedding of the organism are rarely controlled. It should be noted that semen from bulls with paratuberculosis have been found to contain M. paratuberculosis even after freezing and processing. Placental infection of a fetus also can occur in infected cows. It is not known if rifampin and isoniazid therapy can prevent transmission in semen or transplacentally. The cost of rifampin therapy, as well as the inability to completely clear infection and prevent spread of disease, limits treatment only to valuable quarantined animals.

[Potomac horse fever (treatment)]: Horses: Although the efficacy is not established, rifampin is used in combination with erythromycin in the treatment of Potomac horse fever (equineehrlichial coli) . It is as effective as oxytetracycline in the resolution of clinical signs, with the exception that rifampin and erythromycin will not reduce fever as quickly as oxytetracycline, taking up to 12 hours longer to return the body temperature to normal. Rifampin and erythromycin have the advantage of being available in oral dosage forms.

UNACCEPTED

[Mycobacterial infections (treatment)]: Current therapeutic regimens for mycobacterial infections cannot guarantee that an animal is no longer contagious during treatment. Treatment of Mycobacterium tuberculosis, Mycobacterium bovis, and other mycobacterial species transmissible to human beings is nearly always considered inappropriate. The treatment of tuberculosis in cattle is not permitted in Canada or the U.S. The treatment of mycobacterial infections that do not cause human tuberculosis, such as atypical mycobacterial infections in cats, may be acceptable although there is insufficient evidence of efficacy at this time.

REGULATORY CONSIDERATIONS

U.S. and Canada—Rifampin is not labeled in the United States or Canada for use in animals, including food-producing animals. There are no established withdrawal times. The treatment of tuberculosis in cattle is not permitted in Canada or the U.S.

CHEMISTRY

Source: Semisynthetic derivative of rifamycin B, a natural fermentation product of Nocardia (Streptomycyes) mediterranei.

Chemical group: Macrocyclic antibiotic.

Chemical name: Rifamycin,3-[(4-methyl-1-piperazinyl)imino]methyl]-

Molecular formula: C₄₃H₇₇N₄O₂₂

Molecular weight: 822.94

Description: Rifampin USP—Red-brown, crystalline powder.

pKa: 7.0

Solubility: Rifampin USP—Very slightly soluble in water; freely soluble in chloroform; soluble in ethyl acetate and in methanol.

PHARMACOLOGY/PHARMACOKINETICS

Mechanism of action/effect: Rifampin inhibits DNA-dependent RNA polymerase; however, at therapeutic doses, it inhibits the enzyme in bacteria, while not affecting mammalian polymerase. Rifampin is bactericidal and is active against extracellular organisms as well as against susceptible intracellular organisms, including intracellular organisms. Rifampin can enter neutrophils and macrophages to kill intracellular bacteria, while not interfering with phagocytosis.

Rifampin appears to penetrate the outer membrane of gram-positive bacteria more easily than that of gram-negative bacteria. This is reflected in the significantly lower minimum inhibitory concentrations (MIC) required for gram-positive bacteria (0.01 mcg per mL of serum) compared with gram-negative bacteria (8 to 32 mcg per mL).

Absorption: Rifampin is rapidly absorbed after oral administration to people, calves, dogs, and horses, although bioavailability is not high in horses and sheep. Administration with food can prolong the time to peak serum concentration in adult horses and people.

Adult sheep appear to have prolonged absorption, possibly because of prolonged movement through the rumen.

Bioavailability—Oral:

Horses—48.8%, with a single dose of 10 mg per kg of body weight (mg/kg).

39.5%, with a single dose of 10 mg/kg, administered in the feed.

Note: An unpublished study of horses receiving a dose of 5 mg/kg found a bioavailability of 68% when rifampin was administered 1 hour before feeding and 26% when it was administered 1 hour after feeding. Because rifampin is most often administered with feed, recommended dosages compensate for the decreased absorption.

Sheep—36.6 ± 3.2%, with a dose of 10 mg/kg, as an oral drench.

3 to 32%, with a dose of 20 mg/kg, in gel capsules.

14 to 122%, with a dose of 50 mg/kg, in a gel capsule.

Note: The study performed using gel capsules of rifampin in sheep found that absorption was incomplete and still continuing by the end of the study, producing extremely variable results.

Absorption was also relatively low and variable with the oral
Rifampin is highly lipid-soluble and is widely distributed in tissues\[^{R-4, 6}\]. Antimicrobial concentrations are approached in all tissue compartments throughout the body, including milk\[^{R-22}\], bone\[^{R-54}\], cerebrospinal fluid\[^{R-18}\], exudates, ascitic fluid, and soft tissues\[^{R-4}\]. Rifampin crosses the blood-brain barrier\[^{R-6; 18}\] and, in rabbits, the cerebrospinal fluid to plasma concentration ratio ranged from 0.52 to 1.17, from 30 minutes to 12 hours after an oral dose of 10 mg/kg\[^{R-18}\]. Rifampin can penetrate phagocytic cells to kill susceptible intracellular bacteria\[^{R-6; 7; 20}\]. In many species, as has been documented in dogs and human beings, feces, saliva, sweat, tears, and urine may be discolored red-orange by rifampin and its metabolites\[^{R-4}\].

**Volume of distribution**

**Horses:** 0.93 ± 0.29 liter per kg (L/kg)\[^{R-7}\]; 0.63 ± 0.06 L/kg\[^{R-11}\].

**Sheep:** Steady state—0.76 L/kg\[^{R-4}\].

**Sheep—Nonlactating:** 2.9 hours\[^{R-19}\]; 4.56 hours\[^{R-21}\].

**Sheep—Lactating:** 3.3 hours\[^{R-22}\].

**Distribution**

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**Protein binding**

**Horses—High (78%),** with serum concentrations of 2 to 20 micrograms per milliliter (mcg/mL)\[^{R-6}\].

**Human beings—High (80%)**\[^{R-4}\].

**Sheep—High (84%)**\[^{R-22}\].

**Biotransformation**

The biotransformation and elimination of rifampin in animals is not well defined. Induction of hepatic enzymes occurs in response to administration of rifampin in many species\[^{R-17; 25; 26}\], but major metabolites of the parent drug in most animals have not yet been trace\[^{R-6; 21}\]. In human studies, it was found that the primary metabolite of rifampin is 25-desacetylrifampin, which is bioactive\[^{R-4}\]. Human desacetylrifampin is more profusely secreted in the bile compared with rifampin, but is less concentrated in the serum than the parent drug\[^{R-4}\]. And while rifampin undergoes extensive human enterohepatic recycling, desacetylrifampin is poorly absorbed and therefore is not recycled\[^{R-6}\].

**Horses—Desacetylrifampin** was not detected in serum samples after an intravenous dose of 10 mg/kg or oral doses of 10 mg/kg every 12 hours for seven doses\[^{R-6}\]. The metabolite was measured in urine, but the parent compound was much more predominant\[^{R-6}\], however, only 6.82% of the total dose was recovered in the urine as either rifampin or desacetylrifampin\[^{R-6}\].

**Rats—Desacetylrifampin** is formed in extremely low quantities in rats\[^{R-25}\].

**Sheep—Desacetylrifampin** was not found in serum samples from sheep administered either intravenous or oral rifampin\[^{R-21}\]. Rifampin and metabolites have not been measured in sheep urine.

Rifampin can induce hepatic enzymes, including increasing its own hepatic biotransformation with multiple doses\[^{R-17; 25}\]. Induction has been shown to occur in many species, including dogs\[^{R-27}\], horses\[^{R-17}\], pigs\[^{R-10}\], and rabbits\[^{R-28; 29}\]. The dose needed to induce an increase in hepatic enzymes varies among species. Rats administered 50 mg/kg intraperitoneally every 12 hours for 6 days did not show induction of liver microsomal enzyme activity against substances tested\[^{R-26}\], but mice administered the same dose showed significant induction of the hepatic mixed-function oxidase system and enzymatic activity\[^{R-26}\]. In horses, enzyme induction has generally not been seen with less than 5 days of therapy, but once there is an increase in hepatic enzyme activity, the increase may last for more than 2 weeks after discontinuation of treatment\[^{R-17}\]. However; several factors may modify the therapeutic levels of rifampin, such as the variability in its absorption in horses when given alone, and the possible change in pharmacokinetics due to interactions with other medications that often are administered with rifampin; data are insufficient for determining whether the increased elimination of rifampin due to hepatic enzyme induction during prolonged dosing may be corrected for by a dose modification.

**Half-life**

**Absorption**

**Intramuscular administration:** **Horses—6.7 ± 1.5 hours,** with a dose of 10 mg/kg\[^{R-13}\].

**Oral, with food:** **Horses—**

4.2 ± 1.2 hours, with a dose of 10 mg/kg\[^{R-13}\].

2.6 ± 1.3 hours, with a dose of 25 mg/kg\[^{R-11}\].

**Distribution—Intravenous:** **Horses—13.8 ± 5.2 minutes,** with a dose of 10 mg/kg\[^{R-13}\].

**Elimination**

**Intravenous:**

**Horses—8.1 hours**\[^{R-6}\]; 7.3 hours\[^{R-7}\]; 6 hours\[^{R-11}\].

**Sheep—**

Nonlactating: 2.9 hours\[^{R-19}\]; 4.56 hours\[^{R-21}\].

Lactating: 3.3 hours\[^{R-22}\].

**Intramuscular (terminal elimination)—**

**Horses:** 7.3 hours, with a dose of 10 mg/kg\[^{R-11}\].

**Sheep:** 11 hours, with a dose of 20 mg/kg\[^{R-22}\].

**Oral (terminal elimination)—**

**Single dose:**

**Dogs—8 hours,** with a dose of 10 mg/kg\[^{R-4; 65}\].

**Foals—**

1 week of age: 25.4 ± 1.2 hours, with a dose of 10 mg/kg\[^{R-14}\].

10 weeks of age: 7.9 ± 1.5 hours, with a dose of 10 mg/kg\[^{R-14}\].

**Horses—13.3 hours,** with a dose of 10 mg/kg\[^{R-6}\].

**Sheep—6.42 hours,** with a dose of 20 mg/kg\[^{R-21}\].

**Multiple doses:** **Horses—**7.99 hours, after the seventh dose of 10 mg/kg, administered every 12 hours\[^{R-6}\].

Note: Multiple doses result in lower peak serum concentrations and a decreased half-life, because of autoinduction of hepatic enzymes\[^{R-4}\].

**Concentrations**

**Time to peak concentration—**

**Intramuscular administration:**

**Horses—4.2 ± 0.2 hours,** with a dose of 10 mg/kg\[^{R-13}\].

**Sheep—3 hours,** with a dose of 20 mg/kg\[^{R-22}\].

**Oral:**

**Calves, 2 to 3 weeks of age—**4 to 8 hours,** with a dose of 10 mg/kg\[^{R-19}\].
Dogs—2 to 4 hours, with a dose of 10 mg/kg \[^{[R-4; 65]}\].

Foals. 6 to 8 weeks of age—4 hours, with a dose of 10 mg/kg \[^{[R-16]}\].

Horses—
3 hours \[^{[R-6]}\]; 1.6 ± 0.5 hours \[^{[R-14]}\], with a single dose of 10 mg/kg.
3.7 ± 1.2 hours \[^{[R-11]}\]; 3.5 ± 1.7 hours \[^{[R-14]}\], with a single dose of 10 mg/kg, administered with food \[^{[R-11]}\].

2.5 hours, with an intragastric dose of 20 mg/kg of oral suspension \[^{[R-7]}\].

3.5 hours, with a dose of 25 mg/kg, administered with food \[^{[R-11]}\].

Sheep—4 to 8 hours \[^{[R-19]}\]; 8 to 24 hours \[^{[R-21]}\].

Peak serum concentration—Autoinduction of hepatic enzymes can cause multiple doses of rifampin to result in lower peak serum concentrations than expected, if based on single dose measurements \[^{[R-4; 19]}\].

Intramuscular:

Horses—4 ± 0.3 mcg/mL, with a dose of 10 mg/kg \[^{[R-13]}\].

Sheep—Approximately 8 mcg/mL (from graph), with a dose of 20 mg/kg \[^{[R-22]}\].

Oral:

Cows, 2 to 3 weeks of age—11.7 to 24.6 mcg/mL, with a dose of 10 mg/kg \[^{[R-19]}\].

Dogs—40 mcg/mL, with a dose of 10 mg/kg \[^{[R-4; 65]}\].

Foals, 6 to 8 weeks of age—6.7 mcg/mL, with a dose of 10 mg/kg \[^{[R-16]}\].

Horses—
3.9 mcg/mL \[^{[R-6]}\]; 4.5 ± 1.1 mcg/mL \[^{[R-14]}\], with a dose of 10 mg/kg.
2.9 ± 0.4 mcg/mL \[^{[R-13]}\]; 3.3 ± 2.9 mcg/mL \[^{[R-14]}\], with a dose of 10 mg/kg, administered with food.
13.3 ± 2.7 mcg/mL, with intragastric administration of 20 mg/kg of oral suspension \[^{[R-7]}\].

9.8 ± 1.9 mcg/mL, with a dose of 25 mg/kg, administered with food \[^{[R-13]}\].

Sheep—

0.6 to 2.4 mcg/mL, with a dose of 10 mg/kg \[^{[R-19]}\].

3.27 ± 1.43, with a dose of 20 mg/kg \[^{[R-21]}\].

Other concentrations—

Cerebrospinal fluid: Rabbits—1.3 to 1.6 mcg/mL from 30 minutes to 12 hours after an oral dose of 10 mg/kg \[^{[R-18]}\].

Serum:

Dogs—9 to 10 mcg/mL, 24 hours after an oral dose of 10 mg/kg \[^{[R-65]}\].

Horses—
6.86 ± 1.69 mcg/mL, 12 hours after an intragastric dose of 20 mg/kg of oral suspension \[^{[R-7]}\].

3.83 ± 0.87 mcg/mL, 24 hours after an intragastric dose of 20 mg/kg of oral suspension \[^{[R-7]}\].

Rabbits—Ranged from 1.8 to 2.5 mcg/mL from 30 minutes to 12 hours after an oral dose of 10 mg/kg \[^{[R-18]}\].

Sheep—0.97 ± 0.61 mcg/mL, 24 hours after an oral dose of 20 mg/kg in a gelatin capsule \[^{[R-21]}\].

Duration of action: The National Committee for Clinical Laboratory Standards (NCCLS) in the United States lists minimum inhibitory concentration (MIC) breakpoints for animal isolates and rifampin as ≤ 1 mcg/mL for susceptible organisms and ≥ 4 mcg/mL for resistant organisms \[^{[R-8]}\].

Dogs: Serum concentration was 9 to 10 mcg/mL 24 hours after a single oral dose of 10 mg/kg \[^{[R-65]}\].

Horses: Serum concentrations greater than 2 mcg/mL were reached 45 minutes after intragastric rifampin administration of 20 mg/kg and concentrations were maintained at greater than 3 mcg/mL for at least 24 hours.

Elimination: Horses: Only 6.82% of the intravenous dose of 10 mg/kg was recovered in the urine as rifampin or desacetylrifampin, an active metabolite \[^{[R-6]}\]. It is not known if the rifampin not recovered is predominately sequestered in the tissue or perhaps excreted in bile primarily as desacetylrifampin, a more polar and more easily bile-excreted compound \[^{[R-6]}\].

Total clearance—

Horses: 1.14 mL/min/kg \[^{[R-6]}\], 1.34 mL/min/kg \[^{[R-13]}\].

Sheep: 1.16 ± 0.21 mL/min/kg \[^{[R-21]}\], 5.17 mL/min/kg \[^{[R-19]}\].

PRECAUTIONS TO CONSIDER

SPECIES SENSITIVITY

Dogs: There is very little information about the effects of rifampin in small animals; however, there is anecdotal information warning that up to 20% or more of dogs receiving 5 to 10 mg per kg of body weight (mg/kg) a day will develop increases in hepatic enzymes that may lead to clinical hepatitis \[^{[R-4]}\]. Because one study found peak serum concentrations in dogs that were four times that of horses after a standard dose of 10 mg/kg, it has been suggested that the incidence of side effects in dogs may be due to overdosage \[^{[R-4; 65]}\]. Some clinicians have noted lethargy, bilirubinemia, and bilirubinuria in dogs administered rifampin, but there is no information on incidence of adverse effects, dosage administered, pretreatment liver evaluation, or other factors \[^{[R-57]}\].

TUMORGENICITY

Studies in female mice of a strain known to be particularly susceptible to the spontaneous development of hepatomas have shown that rifampin, given in doses of 2 to 10 times the maximum human dose (20 mg per kg of body weight, up to 600 mg every 12 hours) for 1 year, causes a significant increase in the development of hepatomas. However, studies in male mice of the same strain, in other strains of male or female mice, and in rats have not shown that rifampin is tumorigenic \[^{[R-2]}\].

PREGNANCY/REPRODUCTION

Mice and rats: Oral doses of 150 to 250 mg/kg during pregnancy produced dose-dependent teratogenic effects in offspring, including cleft palate in the mouse and spina bifida in the rat \[^{[R-2]}\].

Human information: Rifampin has caused postnatal hemorrhage in the mother and infant when administered during the last weeks of pregnancy \[^{[R-2]}\]. Treatment with vitamin K may be indicated \[^{[R-2]}\].

LACTATION

Sheep: Rifampin is well-distributed into milk, with a milk to serum concentration ratio of 0.9 to 1.28 in sheep given an intramuscular dose of 10 mg/kg \[^{[R-22]}\].
DRUG INTERACTIONS AND/OR RELATED PROBLEMS

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (• = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Drugs metabolized by hepatic microsomal enzymes, including:
- Ciprofloxacin[R-29] or
- Corticosteroid[R-4] or
- Digitalis glycosides[R-4] or
- Itraconazole[R-30] or
- Ketoconazole[R-4] or
- Phenobarbital[R-5] or
- Phenylbutazone[R-17] or
- Warfarin[R-17]

(rifampin causes induction of hepatic enzymes in dogs[R-27], mice[R-26], horses[R-5-17], pigs[R-30], and rabbits[R-28, 29], potentially increasing metabolism[R-4] and thereby decreasing serum concentrations[R-4] of the above medications; there is some selectivity in enzyme induction so that not every drug that is oxidized by the system is affected[R-29]; in guinea pigs and rats, hepatic metabolism does not appear to be significantly induced by commonly administered dosages of rifampin[R-26-27] but can be by extremely high doses[R-25]; phenobarbital will also increase the metabolism of rifampin by enzyme induction[R-17])

HUMAN DRUG INTERACTIONS AND/OR RELATED PROBLEMS[R-79]

In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monograph Rifampin (Systemic) in USP DI Volume I: these drug interactions are intended for informational purposes only and may or may not be applicable to the use of rifampin in the treatment of animals:

- Aminophylline or
- Oxtiphrylline or
- Theophylline

(rifampin may increase metabolism of theophylline, oxtiphrylline, and aminophylline by induction of hepatic microsomal enzymes, resulting in increased theophylline clearance)

- Anesthetics, hydrocarbon inhalation, except isoflurane (chronic use of hepatic enzyme–inducing agents prior to anesthesia, except isoflurane, may increase anesthetic metabolism, leading to increased risk of hepatotoxicity)

- Anticoagulants, coumarin- or indandione-derivative (concurrent use with rifampin may enhance the metabolism of these anticoagulants by induction of hepatic microsomal enzymes, resulting in a considerable decrease in the activity and effectiveness of the anticoagulants; prothrombin time determinations may be required as frequently as once a day; dosage adjustments of anticoagulants may be required before and after rifampin therapy)

- Azole antifungals (concurrent use may increase the metabolism of the azole antifungals, lowering their plasma concentrations; depending on the clinical situation, the dose of an azole antifungal may need to be increased during concurrent use with rifampin)

Barbiturates
(concurrent use with rifampin may enhance the metabolism of hexobarbital by induction of hepatic microsomal enzymes, resulting in lower serum concentrations; there are conflicting data on rifampin’s effect on phenobarbital; dosage adjustment may be required)

Beta-adrenergic blocking agents, systemic
(concurrent use of metoprolol or propranolol with rifampin has resulted in reduced plasma concentrations of these two beta-adrenergic blocking agents due to enhanced metabolism of hepatic microsomal enzymes by rifampin; although not documented, other beta-adrenergic blocking agents may also interact with rifampin)

Bone marrow depressants
(concurrent use of bone marrow depressants with rifampin may increase the leukopenic and/or thrombocytopenic effects; if concurrent use is required, close observation for myelotoxic effects should be considered)

Chloramphenicol
(concurrent use with rifampin may enhance the metabolism of chloramphenicol by induction of hepatic microsomal enzymes, resulting in significantly lower serum chloramphenicol concentrations; dosage adjustment may be necessary)

Clofazimine
(concurrent use with rifampin has resulted in reduced absorption of rifampin, delaying its time to peak concentration, and increasing its half-life)

Corticosteroids, glucocorticoid and mineralocorticoid
(concurrent use with rifampin may enhance the metabolism of corticosteroids by induction of hepatic microsomal enzymes, resulting in a considerable decrease in corticosteroid plasma concentrations; dosage adjustment may be required; rifampin has also counteracted endogenous cortisol and produced acute adrenal insufficiency in patients with Addison’s disease)

Cyclosporine
(rifampin may enhance metabolism of cyclosporine by induction of hepatic microsomal enzymes and intestinal cytochrome P450 enzymes; dosage adjustment may be required)

Dapsone
(concurrent use with rifampin may decrease the effect of dapsone because of increased metabolism resulting from stimulation of hepatic microsomal enzyme activity; dapsone concentrations may be decreased by half; dapsone dosage adjustments are not required during concurrent therapy with rifampin for leprosy)

Diazepam
(concurrent use with rifampin may enhance the elimination of diazepam, resulting in decreased plasma concentrations; whether this effect applies to other benzodiazepines has not been determined; dosage adjustment may be necessary)

Disopyramide or Mexiletine or Propafenone or Quinidine or Tocainide
(concurrent use with rifampin may enhance the metabolism of these antiarrhythmics by induction of hepatic microsomal enzymes, resulting in significantly lower serum antiarrhythmic concentrations; serum antiarrhythmic concentrations should be monitored and dosage adjustment may be necessary)
Estramustine or
Estrogens
(concurrent use of estramustine or estrogens with rifampin may result in significantly reduced estrogenic effect because of stimulation of estrogen metabolism or reduction in enterohepatic circulation of estrogens)

Hepatotoxic medications, other
(concurrent use of rifampin and other hepatotoxic medications may increase the potential for hepatotoxicity; patients should be monitored closely for signs of hepatotoxicity)

Human immunodeficiency virus (HIV) protease inhibitors, such as
Amprenavir or
Indinavir or
Nelfinavir or
Ritonavir or
Saquinavir
(rifampin accelerates the metabolism of protease inhibitors through induction of hepatic P450 cytochrome oxidases, resulting in subtherapeutic levels of the protease inhibitors; in addition, protease inhibitors retard the metabolism of rifampin, resulting in increased serum levels of rifampin and the likelihood of increased drug toxicity; concurrent use of HIV protease inhibitors with rifampin is only recommended under specific circumstances as outlined by the Centers for Disease Control and Prevention [CDC])

Isoniazid
(concurrent use of isoniazid with rifampin may increase the risk of hepatotoxicity, especially in patients with preexisting hepatic function impairment and/or in fast acetylators of isoniazid; patients should be monitored closely for signs of hepatotoxicity during the first 3 months of therapy)

Phenytoin
(concurrent use with rifampin may stimulate the hepatic metabolism of phenytoin, increasing its elimination and thus counteracting its anticonvulsant effects; careful monitoring of serum hydantoin concentrations and dosage adjustments may be necessary before and after rifampin therapy)

Probenecid
(may compete with rifampin for hepatic uptake when used concurrently, resulting in increased and more prolonged rifampin serum concentrations and/or toxicity; however, the effect on rifampin serum concentrations is inconsistent, and concurrent use of probenecid to increase rifampin serum concentrations is not recommended)

Trimethoprim
(concurrent use with rifampin may significantly increase the elimination and shorten the elimination half-life of trimethoprim)

Verapamil, oral
(rifampin has been found to accelerate the metabolism of oral doses of verapamil, resulting in a significant decrease in serum verapamil concentration, and thereby reversing its cardiovascular effects; concurrent use of intravenous verapamil with rifampin was found to have only minor effects on verapamil’s clearance and no significant effect on cardiovascular effects)

LABORATORY VALUE ALTERATIONS
The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (* = major clinical significance):

With diagnostic test results
Indocyanine green and
Sulfobromophthalein sodium excretion test (BSP)
(in rats, plasma clearances of indocyanine green and sulfobromophthalein sodium were increasingly and significantly delayed after 200 mg per kg of body weight a day was administered for 1 to 7 days;{R-25}; the impact of recommended doses, such as 20 mg/kg a day, on these excretion tests has not been measured)

With physiology/laboratory test values
Alkaline phosphatase{R-47}
(in the dog, mild increases in serum alkaline phosphatase levels are common and are not considered significant unless accompanied by elevations in other hepatic enzymes{R-4; 54})

HUMAN LABORATORY VALUE ALTERATIONS{R-79}
The following laboratory value alterations have been reported in humans, and are included in the human monograph Rifampin (Systemic) in the USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of rifampin in the treatment of animals:

With diagnostic test results
Coombs’ (antiglobulin) tests, direct (may become positive rarely during rifampin therapy)
Dexamethasone suppression test
(rifampin may prevent the inhibitory action of a standard dexamethasone dose administered for the overnight suppression test, rendering the test abnormal; it is recommended that rifampin therapy be discontinued 15 days before administering the dexamethasone suppression test)
Folate determinations, serum and
Vitamin B12 determinations, serum and
(therapeutic concentrations of rifampin may interfere with standard microbiological assays for serum folate and vitamin B12; alternate methods must be considered when determining serum folate and vitamin B12 concentrations in patients taking rifampin)
Sulfobromophthalein (BSP) uptake and excretion
(hepatic uptake and excretion of BSP in liver function tests may be delayed by rifampin, resulting in BSP retention; the BSP test should be performed prior to the daily dose of rifampin to avoid false-positive test results)
Urinalyses based on spectrometry or color reaction
(rifampin may interfere with urinalyses that are based on spectrometry or color reaction due to rifampin’s reddish-orange to reddish-brown discoloration of urine)

With physiology/laboratory test values
Alanine aminotransferase (ALT [SGPT]) and
Alkaline phosphatase and
Aspartate aminotransferase (AST [SGOT])
(values may be increased)
Bilirubin, serum and
Blood urea nitrogen (BUN) and
Uric acid, serum
(concentrations may be increased)

MEDICAL CONSIDERATIONS/CONTRAINDICATIONS
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons
In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph "Rifampin (Systemic) in USP DI Volume I": these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of rifampin in the treatment of animals:

**Risk-benefit should be considered when the following medical problem exists:**

- Hepatic function impairment, severe
- (in dogs, hepatic function impairment may predispose to major side effects, and the risk should be carefully considered\(^{[R-64]}\); in any species, dosage adjustments may be necessary with hepatic dysfunction and avoiding use of rifampin should be considered\(^{[R-4; 65]}\)

**PATIENT MONITORING**
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; \(\ast\) = major clinical significance):

- Hepatic enzyme tests
  (particularly in dogs, hepatic enzymes should be monitored during rifampin therapy)

**SIDE/ADVERSE EFFECTS**
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

**THOSE INDICATING NEED FOR MEDICAL ATTENTION**

- **Incidence more frequent**
  - **Diarrhea, self-limiting**\(^{[R-13; 14]}\)—often occurs in the first week of therapy and resolves without treatment\(^{[R-14]}\)
  - **Horses**
    - **Hepatotoxicity**\(^{[R-4]}\)
      - With intravenous administration (dimethylsulfoxide vehicle)
        - **Allergic reactions, specifically anaphylactoid reactions**\(^{[R-17]}\)
        - **central nervous system depression, generalized**\(^{[R-11]}\)
        - **decreased appetite**\(^{[R-11]}\)
        - **signs of distress** (apprehension, pawing with foofect, shifting of weight-bearing from one side to another)\(^{[R-13]}\)
        - **sudden defecation**\(^{[R-14]}\)
        - **weakness or unsteadiness**\(^{[R-6]}\)
  - **Foods**
    - **Incidence unknown**
  - **Dogs**
    - **Hepatotoxicity**\(^{[R-4]}\)

**THESE INDICATING NEED FOR MEDICAL ATTENTION only if they continue or are bothersome**

- **Incidence more frequent**
  - **Horses**
    - **Sweating, mild to moderate**—may occur with parenteral administration, more prominent with intravenous administration\(^{[R-13; 14]}\)

**HUMAN SIDE/ADVERSE EFFECTS**\(^{[R-79]}\)

**OVERDOSE**

For more information in the case of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the manufacturer.

The lethal dose for 50% of test animals (LD\(_{50}\)) is approximately 885 mg per kg of body weight (mg/kg) in the mouse, 1720 mg/kg in the rat, and 2120 mg/kg in the rabbit\(^{[R-2]}\).

**CLINICAL EFFECTS OF OVERDOSE**

In human beings, overdose can cause mental changes, nausea and vomiting, angioedema, generalized pruritus, and red-orange discoloration of the mucous membranes, sclera, and skin\(^{[R-63]}\). Signs of overdose specific to animals are not known.

**TREATMENT OF OVERDOSE**

From the human therapeutic literature\(^{[R-2; 63]}\):

To decrease absorption—

- Evacuating stomach contents using ipecac syrup or gastric lavage.
- Administering an activated charcoal slurry to help adsorb residual rifampin in the gastrointestinal tract.
- Supportive therapy.

**CLIENT CONSULTATION**

Notify your veterinarian of any medications your animal is already receiving before treatment or any medications that may be initiated during treatment with rifampin because drug interactions can occur\(^{[R-4]}\). It is important to be sure that the animal receives the full course of treatment prescribed. However, if new signs occur, such as decreased appetite, depression, diarrhea, or jaundice\(^{[R-13; 14; 34]}\), contact your veterinarian.

Reddish-orange to reddish-brown discoloration of urine, stools, saliva, sputum, sweat, and tears may occur as a typical effect of the medication, but is not harmful\(^{[R-63; 64]}\).
VETERINARY DOSING INFORMATION

The National Committee for Clinical Laboratory Standards (NCCLS) in the United States lists minimum inhibitory concentration (MIC) breakpoints of animal isolates for rifampin as ≤ 1 mcg/mL for susceptible organisms and ≥ 4 mcg/mL for resistant organisms. Organisms testing between these values are considered intermediate and may or may not be inhibited.

Specifically for *Rhodococcus equi*, one study of nine strains found minimum inhibitory concentrations (MICs) for rifampin to be 0.0078 to 0.0625 mcg/mL. In another study, a MIC of less than or equal to 0.25 mcg/mL was found for 18 *Rhodococcus equi* isolates; 83% of these isolates had an MIC of 0.0625 or less.

Other equine organisms have also been found to have MICs of less than 0.25 mcg/mL, including coagulase-positive *Staphylococcus* species (MIC of 0.0625 or less), *Streptococcus zooepidemicus* (MIC of 0.0625 or less), *S. equi* (MIC of 0.0625 or less), *S. equisimilis* (MIC of 0.125 or less), and *Corynebacterium pseudotuberculosis* (MIC of 0.0156 or less). Gram-negative organisms have been found to be variably susceptible or resistant. The MICs of 19 *Actinobacillus* isolates from horses ranged from 1 to 4 mcg/mL.

The possibility of mixed infections involving both gram-positive and gram-negative organisms should be considered in some situations, such as young horses with respiratory tract infections. Because nonenteric gram-negative organisms can have variable susceptibility, susceptibility data should be used to determine the appropriate therapy. The possibility of mixed infections and the rapid rise of resistance to rifampin make combination therapy the most logical recourse in many cases.

Rifampin has been shown in *in vitro* tests to have synergistic activity with erythromycin or trimethoprim and to have an additive effect with ampicillin or penicillin. However, rifampin’s activity in *in vitro* tests can be antagonistic to those of other antimicrobials, such as gentamicin; it is not certain how this interaction might affect *in vivo* activity.

FOR ORAL DOSAGE FORMS ONLY

Administration with food reduces the rate of absorption and prolongs the time to peak concentration in adult horses.

ORAL DOSAGE FORMS

Note: In other USP DI monographs, bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling, and superscript 1 refers to categories of use and/or indications that are not included in Canadian product labeling. However, since rifampin is not specifically approved for veterinary use, there is no product labeling identifying approved indications.

rifampin capsules usp

Usual dose:

[Pneumonia, *Rhodococcus equi*] — Horses: Oral, 5 mg per kg of body weight every twelve hours in combination with 25 mg of erythromycin estolate or erythromycin ethylsuccinate per kg of body weight every six to eight hours. Therapy may be continued for four to nine weeks or until radiographs and complete blood counts are normal.

[Potomac horse fever] — Horses: Oral, 10 mg per kg of body weight every twelve hours in combination with 25 mg of erythromycin estolate or erythromycin ethylsuccinate per kg of body weight every twelve hours.

Note: [Horses] — Although the safety and efficacy of rifampin have not been established, an oral dose of 10 mg rifampin per kg of body weight every twelve hours has been used in the treatment of susceptible bacterial infections, such as *staphylococcal* infections in horses, based on pharmacokinetic data. It is usually administered in combination with another antimicrobial, such as erythromycin or penicillin.

[Cattle], [goats], and [sheep] — For use in animals not to be used in food production: Although the safety and efficacy of rifampin have not been established, an oral dose of 20 mg per kg of body weight every twenty-four hours has been used in the treatment of susceptible *bacterial infections* in cattle and sheep, based on pharmacokinetic data. For the treatment of paratuberculosis in cattle, goats, and sheep, an oral dose of 20 mg per kg of body weight every twenty-four hours, administered in conjunction with 20 mg of oral isoniazid per kg of body weight every twenty-four hours, has been used to control signs, based on case reports and the pharmacokinetics known; however, clinical improvement only occurs for a short period of time and does not prevent spread of the infection to other animals.

[Dogs] — If rifampin is administered to dogs, dosing of rifampin should generally be kept below 10 mg per kg of body weight a day, based on limited pharmacokinetic data and reports of hepatic toxicity in dogs.

A single oral dose of 10 mg per kg appears to produce much higher serum concentrations than the same dose administered to other species, with a possibly increased risk of toxicity. The best dose for maximum safety and efficacy has not been established.

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

150 mg (Rx) [Rifadin®]; 300 mg (Rx) [Rifadin®; Rimactane®; Rofact®].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

150 mg (Rx) [Rifadin®; Rimactane®; Rofact®]; 300 mg (Rx) [Rifadin®; Rimactane®; Rofact®].

Withdrawal times:

U.S. and Canada — The use of rifampin in food-producing animals has not been approved by the Food and Drug Administration or the Canadian Health Protection Branch; therefore, there are no established withdrawal times.

The issue of whether rifampin should be used in food animals is complicated by its link to hepatic tumors in one strain of female mice (see Tumorgenicity under Precautions in this monograph). The significance of this link is not known, but any residue of a known carcinogen in animal products for human consumption is considered a violation of the Food, Drug, and Cosmetic Act. As such, the USP Veterinary Medicine Advisory Panel has concluded that rifampin should not be administered to animals intended for production of products for human consumption.

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Packaging and storage: Store below 40 °C (104 °F), in a tight container, unless otherwise specified by the manufacturer. Protect from light.

Preparation of dosage form: Human product labeling suggests the preparation of an extemporaneous oral 1% w/v suspension with prepared syrups when necessary.

USP requirements: Preserve in tight, light-resistant containers, protected from excessive heat. Contain the labeled amount, within ±10%. Meet the requirements for Identification, Dissolution (75% in 45 minutes in 0.1 N hydrochloric acid in Apparatus 1 at 100 rpm), Uniformity of dosage units, and Loss on drying (not more than 3.0%).

PARENTERAL DOSAGE FORMS
Note: In other USP DI monographs, bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling, and superscript refers to categories of use and/or indications that are not included in Canadian product labeling. However, since rifampin is not specifically approved for veterinary use, there is no product labeling identifying approved indications.

RIFAMPIN FOR INJECTION USP
Note: Although parenteral pharmacokinetic studies have been performed in horses and sheep, rifampin is generally administered by the oral route in animals. See Rifampin Capsules USP; however, also note that oral dosing for horses is adjusted for poor bioavailability. Use of oral dosing for parenteral administration of rifampin could result in overdosage. Parenteral rifampin should be administered only by the intravenous route, not intramuscularly or subcutaneously.

Strength(s) usually available:
U.S. — Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
600 mg (Rx) [Rifadin IV]
Canada — Veterinary-labeled product(s):
Not commercially available.
Human-labeled product(s):
Not commercially available.

Withdrawal times:
U.S. and Canada — The use of rifampin in food-producing animals has not been approved by the Food and Drug Administration or the Canadian Health Protection Branch; therefore, there are no established withdrawal times.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by the manufacturer. Protect from light.

Preparation of dosage form: Human product labeling recommends that 600 mg of rifampin powder be reconstituted with 10 mL of sterile water for injection to produce a 60 mg per mL (mg/mL) solution.

Prior to intravenous infusion, the amount calculated for administration is added to 500 mL or, in some cases, 100 mL of infusion medium and mixed well before administration. Dextrose 5% for Injection is recommended for infusion medium, but sterile saline may also be used with a slight reduction in stability.

Stability: The reconstituted 60 mg/mL solution is stable for 24 hours at room temperature. Once mixed with infusion medium to produce a 100 mL or 500 mL solution, the product should be administered within 4 hours; precipitation of rifampin may occur after this time.

USP requirements: Preserve in Containers for Sterile Solids. Contains the labeled amount, within −10% to +15%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH (7.8–8.8, in a solution containing 60 mg of rifampin per mL), Water (not more than 1.0%), and Particulate matter.

Developed: 11/05/99
Interim revision: 09/30/02: 03/28/03

REFERENCES


**GENERAL CONSIDERATIONS**

Spectinomycin is an antibiotic that is active against a variety of aerobic gram-negative and gram-positive organisms as well as *Mycoplasma* species. Spectinomycin is used clinically, primarily for its activity against gram-negative organisms; some gram-positive organisms may also be susceptible to this agent. It has in vitro and in vivo activity against *Mannheimia* (*Pasteurella* haemolytica), *Pasteurella multocida*, and *Haemophilus somnus*. Anaerobic organisms are generally resistant. As an aminocyclitol antibiotic, spectinomycin is structurally and functionally similar to the aminoglycoside antibiotics, which are also aminocyclitols. Spectinomycin lacks the toxic effects of the aminoglycoside antibiotics; however, its use is limited by the ready development of bacterial resistance.

**ACCEPTED**

Air sacculitis (treatment)—Turkey poults, 1- to 3-day-old: Spectinomycin hydrochloride injection is indicated to aid in the control of air sacculitis associated with *Mycoplasma meleagrisitis* sensitive to spectinomycin.

Chronic respiratory disease (CRD) (prophylaxis)—Chickens, broiler: Spectinomycin powder for oral solution is indicated to aid in the prevention of mortality due to CRD associated with susceptible *Mycoplasma gallisepticum*.

Chronic respiratory disease (CRD) (treatment)—Turkey poults, 1- to 3-day-old: Spectinomycin hydrochloride injection is indicated to aid in the control of CRD associated with *Escherichia coli*.

Chicks, broiler: Spectinomycin powder for oral solution is indicated to aid in the control of mortality due to CRD associated with susceptible *Mycoplasma gallisepticum*.

Colibacillosis (treatment)—Chicks, newly hatched: Spectinomycin hydrochloride injection is indicated in the control of mortality and to lessen the severity of infections caused by *Salmonella typhimurium*.

Paratyphoid (treatment)—Chicks, newly hatched: Spectinomycin hydrochloride injection is indicated in the control of mortality and to lessen the severity of infections caused by *Salmonella typhimurium*.

Pneumonia, bacterial (treatment)—Cattle: Spectinomycin sulfate injection is indicated in the treatment of pneumonia (bovine respiratory disease) associated with *M. haemolytica*, *P. multocida*, and *H. somnus* in cattle.

*Salmonella infantis* infection (treatment)—Chicks, newly hatched: Spectinomycin hydrochloride injection is indicated in the control of mortality and to lessen severity of infections caused by *S. infantis*; however, *S. infantis* is not considered to be a major pathogen in the poultry industry.

Synovitis (prophylaxis)—Chickens, broiler: Spectinomycin powder for oral solution is indicated to aid in the prevention of mortality associated with infectious synovitis due to susceptible *Mycoplasma synoviae*.

Synovitis (treatment)—Chickens, broiler: Spectinomycin powder for oral solution is indicated to aid in the control of mortality associated with infectious synovitis due to susceptible *M. synoviae*.

Chicks, newly hatched: Spectinomycin hydrochloride injection is indicated in the control of mortality and to lessen severity of infections caused by susceptible *M. synoviae*.

[Fowl cholera (treatment)]—Turkeys: Spectinomycin hydrochloride injection is indicated to reduce mortality due to fowl cholera caused by sensitive strains of *Pasteurella multocida*.

**ACCEPTANCE NOT ESTABLISHED**

Colibacillosis (treatment)—[Ducklings]: There are insufficient data to establish the safety and efficacy of spectinomycin in the treatment of colibacillosis in ducklings; however, in one study, subcutaneous administration of spectinomycin reduced the mortality and improved weight gain in 1-day-old ducklings experimentally infected with *E. coli*.

Infections, bacterial (treatment), including Respiratory tract infections (treatment)—[Pigs]: There are insufficient data to establish the safety and efficacy of spectinomycin injection in the treatment of respiratory infections and systemic infections due to susceptible organisms in pigs; however, the parenteral administration of spectinomycin to pigs has been used in clinical practice to treat these infections.

**REGULATORY CONSIDERATIONS**

U.S.—Spectinomycin oral solution is labeled for use in piglets younger than 4 weeks of age or weighing < 6.8 kg.

Spectinomycin injection is labeled for use only in newly hatched chicks and in 1- to 3-day-old turkey poults.

Spectinomycin is not labeled for use in birds producing eggs for human consumption.

Withdrawal times have been established for the use of spectinomycin in newly hatched chicks, broiler chickens. 1- to
3-day-old turkey pouls, piglets (see the Dosage Forms section).

Canada—
Spectinomycin is not labeled for use in birds producing eggs for human consumption.

Withdrawal times have been established for the use of spectinomycin in broiler chickens, piglets, and turkeys (see the Dosage Forms section).

CHEMISTRY
Source: Spectinomycin is a product of Streptomyces spectabilis.
Chemical group: Aminocyclitol.
Chemical name: Spectinomycin hydrochloride—C_{14}H_{24}N_{2}O_{7}.2HCl.
Molecular formula: C_{21}H_{31}N_{2}O_{8}HCl.
Solubility: Practically insoluble in water; soluble in chloroform.

CHEMISTRY

PHARMACOLOGY/PHARMACOKINETICS
Note: Unless otherwise noted, pharmacokinetic data in this section are based on single intravenous injection of spectinomycin.

Mechanism of action/Effect: Spectinomycin binds to the 30S ribosomal subunit of the microorganism and inhibits protein synthesis by preventing elongation of the polypeptide chain at the translation step.

Absorption: Spectinomycin is only slightly absorbed from the gastrointestinal tract; however, it is rapidly absorbed following intramuscular administration. In cattle, spectinomycin is completely bioavailable following intramuscular administration. Repeated administration in cattle does not appear to result in tissue concentrations higher than those achieved with a single dose.

Distribution: Twelve hours following intramuscular administration and 24 hours following oral administration, concentrations of spectinomycin are found in the following swine tissues in decreasing concentrations: kidney, liver, lung, muscle, and fat. An identical profile is seen in cattle 24 and 72 hours following intramuscular administration of spectinomycin. Tissue/serum ratios of spectinomycin usually do not exceed 0.25 to 0.5 and are much lower in brain, aqueous humor, and bone.

Volume of distribution (Vd/F):
- Cows—0.295 Liter per kg (L/kg).
- Ewes—0.307 L/kg.

Protein binding:
- Cows—Low (approximately 10%).

Biotransformation: Spectinomycin is not labeled for use in birds producing eggs for human consumption.

Peak serum concentration/Time to peak serum concentration:
- Calves, preruminating—20 mcg/mL, between 0.33 and 0.67 hours following an intramuscular dose of 10 mg/mL.
- Cows—Approximately 55 micrograms per mL (mcg/mL) at 1 hour following an intramuscular dose of 20 mg per kg of body weight (mg/kg).
- Pigs: 0.98 hour.

Elaboration: Following intramuscular administration—Spectinomycin is rapidly absorbed, then quickly eliminated from plasma and tissues. Because of this rapid excretion, drug accumulation is not observed following repeated administration. Renal impairment may cause accumulation of the active drug.

Following oral administration—Because spectinomycin is poorly absorbed from the gastrointestinal tract, it is excreted mostly in the feces.

PRECAUTIONS TO CONSIDER
LACTATION
Cows: In one experimental study, the milk-to-serum ratio of spectinomycin concentrations ranged from 0.44 to 1.12 in mastitic cows receiving one intramuscular dose of 20 mg per kg of body weight (mg/kg), followed by three intramuscular doses of 10 mg/kg at hourly intervals. Spectinomycin levels in milk from dairy cows receiving an intramuscular dose of 20 mg/kg two times a day for 3 consecutive days were below 0.2 mcg/mL at the fifth milking after the last injection. No residues of spectinomycin were detectable at the seventh milking.
SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown

All species

Anaphylactic reactions[R-25]; neuromuscular blockade[R-5]

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME
Incidence unknown

Cattle

Discoloration of tissue at the injection site;[R-25] swelling at the injection site, mild[R-25]

HUMAN SIDE/ADVERSE EFFECTS[R-15]
In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Spectinomycin (Systemic) in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of spectinomycin in the treatment of animals:

Incidence rare

Dizziness; gastrointestinal disturbance; hypersensitivity; pain at site of injection

OVERDOSE
For more information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

Cattle: When cattle were administered 150 mg per kg a day (10 times the labeled dose) for 5 days, the effects seen at the end of the treatment period included increased relative kidney weights[R-25]. Urinalysis was performed only on steers. Urinary pH was decreased and squamous and transitional cells were found in the urine[R-25].

CLINICAL EFFECTS OF OVERDOSE
Note: The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive (+ = major clinical significance):

Acute effects—

Turkey poults[R-1]

Ataxia[R-1]; coma[R-1]

Note: Clinical signs of ataxia and coma following a single, subcutaneous dose of 90 mg per poult were transient, resolving after 4 hours[R-1]; a single, subcutaneous injection of up to 50 mg per poult caused no detectable ill effects[R-1].

VETERINARY DOSING INFORMATION
SAFETY CONSIDERATIONS
Some individuals who handle spectinomycin develop serious reactions involving skin, nails, and eyes[R-1; 9]. Individuals who have experienced a rash or other evidence of allergic reaction should avoid further contact with spectinomycin[R-2].

ORAL DOSAGE FORMS
Note: The dosing and strengths of the dosage forms available are expressed in terms of spectinomycin base (not the hydrochloride salt).

SPECTINOMYCIN HYDROCHLORIDE ORAL SOLUTION
Usual dose: Enteritis, bacterial—Piglets, younger than 4 weeks of age: For piglets weighing < 4.5 kg—Oral, 50 mg (base) as a total dose per animal two times a day for three to five days[R-3; 4]. For piglets weighing 4.5 kg to 6.8 kg—Oral, 100 mg (base) as a total dose per animal two times a day for three to five days[R-3; 4]. Note: If improvement is not seen within forty-eight hours of initiating treatment, the diagnosis or choice of therapy should be reconsidered[R-3; 4].

Strength(s) usually available:

U.S.—For veterinary-labeled product(s): 50 mg (base) per mL (OTC) [AmTech Spectam Scour-Halt; Spectam Scour-Halt].

Canada—For veterinary-labeled product(s): 50 mg (base) per mL (OTC) [Spectam Oral Solution; Spectam Scour-Halt].

Withdrawal times:

U.S. and Canada[R-3; 4; 19]—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs</td>
<td>21 (days)</td>
</tr>
</tbody>
</table>

Note: The above withdrawal time applies when medication is administered at a total dose of 50 mg (base) two times a day for piglets weighing less than 4.5 kg or 100 mg (base) two times a day for piglets weighing 4.5 kg to 6.8 kg, for a maximum duration of five days[R-3; 4].

Packaging and storage: Store below 23 °C (73 °F). Do not freeze [R-3; 4].

Auxiliary labeling: When not in use, the plastic doser should be removed and the original cap replaced on bottle[R-3; 4]. The plastic doser should be rinsed with water after each use.

USP requirements: Not in USP[R-16].

SPECTINOMYCIN HYDROCHLORIDE POWDER FOR ORAL SOLUTION
Usual dose:
Chronic respiratory disease (prophylaxis and treatment)—Chickens, broiler: Oral, administered as the sole source of drinking water at a

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concentration of 0.5 mg (base) per mL (2 grams [base] per gallon) of water for the first three days of life and for one day following each vaccination\textsuperscript{[R-2; 16; 24]}. Synovitis (prophylaxis and treatment\textsuperscript{1})—Chickens, broiler: Oral, administered as the sole source of drinking water at a concentration of 0.26 mg (base) per mL (1 gram [base] per gallon) of water for the first three to five days of life\textsuperscript{[R-16; 24]}. Note: Canadian labeling lists a dose of 0.5 mg (base) per mL (2 grams [base] per gallon) of water for this indication\textsuperscript{[R-2; 24]}.

**Strength(s) usually available:**

**U.S.—**
Veterinary-labeled product(s):
- 500 mg (base) per gram of water-soluble powder (OTC) [Spectam Water Soluble].

**Canada—**
Veterinary-labeled product(s):
- 500 mg (base) per gram of water-soluble powder (OTC) [Spectam Soluble Powder].

**Withdrawal times:**

**U.S. and Canada\textsuperscript{[R-2; 16; 24]}**

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time (Meat) (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chickens</strong></td>
<td>5</td>
</tr>
</tbody>
</table>

Note: The above withdrawal time applies when medication is administered in the drinking water up to a maximum concentration of 0.5 mg (base) per mL for up to a maximum duration of 5 days\textsuperscript{[R-2; 16; 24]}. Products are not labeled for use in poultry laying eggs for human consumption\textsuperscript{[R-24]}. 

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Preparation of dosage form:** Water-soluble powder should be mixed with drinking water according to the manufacturer’s directions.

**USP requirements:** Not in USP\textsuperscript{[R-16]}.

\textsuperscript{1}Not included in Canadian product labeling or product not commercially available in Canada.

**PARENTERAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

The dosing and strengths of the dosage forms available are expressed in terms of spectinomycin base (not the hydrochloride or sulfate salt).

**SPECTINOMYCIN HYDROCHLORIDE INJECTION**

**Usual dose:**
- Air sacculitis (treatment\textsuperscript{1})—Turkey pouls, 1- to 3-day-old: Subcutaneous in cervical area, 10 mg (base) as a single, total dose per poult\textsuperscript{[R-17]}.
- Chronic respiratory disease (treatment\textsuperscript{1})—Turkey pouls, 1- to 3-day-old: Subcutaneous in cervical area, 5 mg (base) as a single, total dose per poult\textsuperscript{[R-17]}. Dilution with sterile physiologic saline is recommended to facilitate accurate dosing\textsuperscript{[R-17]}.
- Colibacillosis (treatment\textsuperscript{1});
- Paratyphoid (treatment\textsuperscript{1});
- Salmonella infantis infection (treatment\textsuperscript{1}); or
- Synovitis (treatment\textsuperscript{1})—Chicks, newly hatched: Subcutaneous in cervical area, 2.5 to 5 mg (base) as a single, total dose per chick\textsuperscript{[R-17]}. Dilution with sterile physiologic saline is recommended so that the total volume administered is 0.2 mL\textsuperscript{[R-17]}.
- [Fowl cholera (treatment)]—Turkeys: Subcutaneous in dorsal cervical area, 11 to 22 mg (base) per kg of body weight as a single injection. The entire flock should be treated as soon as symptoms of fowl cholera are observed\textsuperscript{[R-1]}.

**Withdrawal times:**

**U.S.**

<table>
<thead>
<tr>
<th>Withdrawal time (Meat) (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey pouls, 1- to 3-day-old</td>
</tr>
</tbody>
</table>

Note: The above withdrawal time applies when medication is administered up to a maximum dose of 5 mg per animal in chicks and 10 mg per animal in turkey pouls as a single injection\textsuperscript{[R-17]}.

**Canada**

<table>
<thead>
<tr>
<th>Withdrawal time (Meat) (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey pouls, 1- to 3-day-old</td>
</tr>
</tbody>
</table>

Note: The above withdrawal time applies when medication is administered up to a maximum dose of 5 mg per animal in chicks and 10 mg per animal in turkey pouls as a single injection\textsuperscript{[R-17]}.

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Note: The above withdrawal time applies when medication is administered up to a maximum dose of 22 mg per kg of body weight as a single injection.\(^{[R-1]}\)

**Preparation of dosage form:**
Dilution with sterile physiologic saline according to product labeling is recommended when administering total doses <5 mg and is appropriate when large flocks are being treated\(^{[R-17]}\). Aseptic technique must be employed and unused diluted solution should be discarded\(^{[R-17]}\).

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Protect from freezing\(^{[R-17]}\).

**Auxiliary labeling:** Injection site should be disinfected prior to injection and precautions should be taken to prevent contamination of the contents of the bottle\(^{[R-1; R-17]}\).

**USP requirements:** Not in USP\(^{[R-16]}\).

**SPECTINOMYCIN SULFATE INJECTION**

**Usual dose:** Pneumonia—Cattle: Subcutaneous, 10 to 15 mg (base) per kg of body weight every twenty-four hours for three to five days\(^{[R-25]}\).

Note: It is recommended that this medication be administered subcutaneously in the neck and that not more than 50 mL be given per site\(^{[R-25]}\).

**Strengths usually available**\(^{[R-21; R-22; R-25]}\):

**Veterinary-labeled product(s):**
- 100 mg (base) per mL (Rx) [Adspec Sterile Solution; Bovispec Sterile Solution].
- 100 mg (base) per mL (Rx) [Adspec Sterile Solution].

**Withdrawal times:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>11 (Meat)</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal time states that withdrawal times have not been established for preruminating calves or for lactating dairy cattle and that it should not be used in female dairy cattle 20 months of age or older or in calves to be processed for veal\(^{[R-25]}\).

Discoloration of tissue at the injection site may last more than 11 days, making it necessary to trim the site and surrounding tissue at slaughter\(^{[R-25]}\).

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>11 (Meat)</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal time states that it applies to a dosage of 10 mg per kg of body weight every twenty-four hours for three to five days.

**Package and storage:** Store at 20 to 25 °C (68 to 77 °F), unless otherwise specified by the manufacturer\(^{[R-25]}\). Protect from freezing.

**USP requirements:** Not in USP\(^{[R-16]}\).

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\(^{1}\)Not included in Canadian product labeling or product not commercially available in Canada.

Developed: 07/08/98

Interim revision: 10/15/99; 09/30/02; 04/05/03

**REFERENCES**

SULFONAMIDES Veterinary—Systemic

This monograph includes information on the following:
Sulfachlorpyridazine, Sulfadimethoxine, Sulfamethazine, Sulfanilamide, Sulfadiazine, Sulfaquinoxaline, Sulfathiazole.

Some commonly used brand names are:
For veterinary-labeled products—

- Albon Boluses [Sulfadimethoxine]
- Albon 12.5% Concentrated Solution [Sulfadimethoxine]
- Albon Injection 40% [Sulfadimethoxine]
- Albon Injection 40% [Sulfadimethoxine and Sulfathiazole]
- Albon Oral Suspension 5% [Sulfadimethoxine]
- Albon SR [Sulfadimethoxine]
- Albon Tablets [Sulfadimethoxine]
- AmTech Sulfadimethoxine Injection-40% [Sulfadimethoxine]
- AmTech Sulfadimethoxine Injection-40% [Sulfadimethoxine and Sulfathiazole]
- Di-Methox Injection-40% [Sulfadimethoxine]
- Di-Methox 12.5% Oral Solution [Sulfadimethoxine]
- Di-Methol Soluble Powder [Sulfadimethoxine]
- Optimed [Sulfaquinoxaline]
- Powder 21 [Sulfadimethoxine and Sulfathiazole]
- S-250 [Sulfadimethoxine]
- SDM Injection [Sulfadimetoxine]
- SDM Powder [Sulfadimethoxine]
- SDM Solution [Sulfadimethoxine]
- S-M-T [Sulfadimethoxine and Sulfathiazole]
- Sulfa 25% [Sulfadimethoxine]
- Sulfaalan Powder [Sulfadimethoxine and Sulfathiazole]

GENERAL CONSIDERATIONS
Sulfonamides are broad-spectrum antimicrobials inhibiting both gram-positive and gram-negative bacteria, as well as some protozoa, such as coccidia.

Resistance of animal pathogens to sulfonamides is widespread as a result of more than 50 years of therapeutic use and this limits their effectiveness; however, sulfonamides are still widely used in combination with other medications, as in the case of the potentiated sulfonamides. They are also utilized in herd management of disease and some individual animal applications. Cross-resistance between sulfonamides is considered complete.

ACCEPTED
Coccidiosis (treatment)—Resistence to sulfonamides by coccidia has been reported in several species, including cattle, chickens, and sheep. It also should be noted that sulfonamides aid in reducing the number of oocysts shed, but they may not alter the clinical course of a susceptible coccidial infection.

Calves and cattle: Sulfadimethoxine extended-release tablets are indicated in the treatment of Eimeria bovis and Eimeria zuernii. Sulfaquinoxaline is indicated in the control and treatment of susceptible E. bovis and E. zuernii.

Chickens: Sulfadimethoxine oral solution and powder for oral solution are indicated in the treatment of outbreaks of coccidiosis caused by susceptible coccidia. Sulfamethazine oral solution and powder for oral solution are indicated in the control of outbreaks of coccidiosis caused by susceptible Eimeria necatrix and Eimeria tenella. Sulfaquinoxaline is indicated in the control of outbreaks of coccidiosis caused by susceptible Eimeria acervulina, Eimeria brunetti, and E. tenella.

Dogs: Sulfadimethoxine injection, oral suspension, and tablets are indicated in the treatment of enteritis associated with coccidiosis caused by susceptible organisms.

Turkeys: Sulfadimethoxine oral solution and powder for oral solution are indicated in the treatment of outbreaks of coccidiosis caused by susceptible coccidia. Sulfamethazine oral solution and powder for oral solution are indicated in the control of susceptible Eimeria adenoides and Eimeria meleagrimitis. Sulfaquinoxaline is indicated in the control of outbreaks of susceptible E. adenoides and E. meleagrimitis.

Coryza, infectious (treatment)—Chickens: Sulfadimethoxine oral solution and powder for oral solution are indicated in the treatment of outbreaks of infectious coryza caused by susceptible Haemophilus gallinarum. Sulfamethazine oral solution and powder for oral solution are indicated in the control of infectious coryza caused by susceptible H. gallinarum.
Cystitis, bacterial (treatment)—Cats and dogs: Sulfadimethoxine injection\[^{1}\], oral suspension\[^{1}\], and tablets\[^{R-1; 6}\] are indicated in the treatment of cystitis caused by susceptible organisms; however, the potentiated sulfonamides and other antimicrobials have generally replaced sulfonamides administered alone.

Diphtheria (treatment)—Cattle: Sulfonamides are not directly effective against most obligate anaerobes\[^{R-86; 90; 93}\], but may affect aerobic organisms that create the microenvironment in which *Fusobacteria* thrive; therefore, sulfonamides may be useful in the treatment of diphtheria but are not recommended in advanced or serious infections. Sulfamethazine tablets\[^{R-11}\], oral solution\[^{R-2}\], injection\[^{R-3}\], powder for oral solution\[^{R-2; 4}\], and extended-release tablets\[^{R-5}\]; and sulfadimethoxine tablets, oral solution, powder for oral solution\[^{1}\], and extended-release tablets\[^{R-7; 9; 10; 12; 13}\] are indicated in the treatment of calf diphtheria caused by susceptible *Fusobacterium necrophorum*. [Sulfamethazine, sulfanilamide, and sulfathiazole combination is indicated as an aid in the treatment of diphtheria in calves\[^{R-97}\].]

Enteritis, bacterial (treatment)—The primary treatment for enteritis in many cases, including those involving colibacillosis in calves, is aggressive fluid replacement. Treatment of enteritis with antimicrobials should rely on a specific diagnosis and knowledge of pathogen susceptibility.

Calves, less than 1 month of age\[^{1}\]: Sulfachlorpyridazine injection and tablets are indicated in the treatment of diarrhea caused or complicated by *Escherichia coli*\[^{R-89}\].

Calves and cattle: Sulfamethazine tablets, oral solution, powder for oral solution\[^{1}\], and extended-release tablets\[^{R-7; 9; 10; 12; 13}\] and [sulfamethazine and sulfathiazole combination\[^{R-15; 15}\]] are indicated in the treatment of enteritis (colibacillosis, scours) caused by susceptible *E. coli*. [Sulfamethazine, sulfanilamide, and sulfathiazole combination\[^{R-97}\] is indicated as an aid in the treatment of enteritis caused by susceptible organisms.]

Dogs: Sulfadimethoxine injection\[^{R-3}\], oral suspension\[^{1}\], and tablets\[^{R-6}\] are indicated in the treatment of enteritis caused by susceptible *Salmonella* species.

Foals: Sulfamethazine tablets are indicated in the treatment of enteritis caused by susceptible *E. coli*\[^{R-13}\].

Pigs: Sulfachlorpyridazine powder for oral solution\[^{R-89}\], and sulfamethazine oral solution\[^{R-12}\] and powder for oral solution\[^{R-9}\] are indicated in the treatment of enteritis caused by susceptible *E. coli*. [Sulfamethazine and sulfathiazole combination is indicated as aid in the treatment of enteritis\[^{R-15; 15}\].]

[Sheep]: Sulfamethazine oral solution\[^{R-16}\] is indicated in the treatment of enteritis caused by susceptible organisms.

Fowl cholera (treatment)—

*Chickens*: Sulfadimethoxine oral solution\[^{R-21}\] and powder for oral solution\[^{R-4}\] are indicated in the treatment of acute fowl cholera caused by susceptible *Pasteurella multocida*. Sulfamethazine oral solution\[^{R-12}\] and powder for oral solution\[^{R-9}\], and sulfathiazole oral solution\[^{R-14}\] are indicated in the control of acute fowl cholera caused by susceptible *P. multocida*.

*Turkeys*: Sulfadimethoxine oral solution\[^{R-2}\] and powder for oral solution\[^{R-4}\] are indicated in the treatment of acute fowl cholera caused by susceptible *P. multocida*. Sulfathiazole oral solution\[^{R-14}\] is indicated in the control of acute fowl cholera caused by susceptible *P. multocida*.

Fowl typhoid (treatment)—*Chickens* and *turkeys*: Sulfaquinoxaline is indicated in the control of acute fowl typhoid caused by susceptible *Salmonella gallinarum*.\[^{R-14}\]

Pneumonia, bacterial (treatment)—

Calves: Sulfamethazine tablets\[^{R-13}\] and extended-release tablets\[^{R-7; 10; 11}\] are indicated in the treatment of pneumonia and bovine respiratory disease complex caused by susceptible *Pasteurella* species. However, *in vitro* studies have shown high levels of resistance to sulfamethazine by *Mannheimia (Pasteurella) haemolytica* and *P. multocida*\[^{R-23}\]; therefore, sulfamethazine generally has been replaced by antimicrobials known to be effective against the specific pathogens involved.

Cats and dogs: Sulfadimethoxine injection\[^{R-3}\], oral suspension\[^{1}\], and tablets\[^{R-6}\] are indicated in the treatment of bacterial pneumonia caused by susceptible organisms; however, sulfadimethoxine generally has been replaced by antimicrobials known to be effective against the specific pathogens involved.

Cattle: Sulfamethazine oral solution\[^{R-12}\], powder for oral solution\[^{R-9}\], and extended-release tablets\[^{R-10; 11}\]; and sulfadimethoxine tablets\[^{R-21}\], oral solution\[^{R-2}\], injection\[^{R-3}\], powder for oral solution\[^{R-4}\], and extended-release tablets\[^{R-5}\]; and [sulfamethazine and sulfathiazole combination\[^{R-15; 96}\]] are indicated in the treatment of bacterial pneumonia and bovine respiratory disease complex caused by susceptible organisms. [Sulfamethazine, sulfanilamide, and sulfathiazole combination is indicated as an aid in the treatment of pneumonia\[^{R-97}\].] However, *in vitro* studies have shown high levels of resistance to sulfamethazine by *M. haemolytica* and *P. multocida*\[^{R-23}\], and the sulfonamides generally have been replaced by antimicrobials known to be effective against the specific pathogens involved.

Foals: Sulfamethazine tablets\[^{R-11}\] are indicated in the treatment of pneumonia caused by susceptible *Pasteurella* species; however, sulfamethazine generally has been replaced by antimicrobials known to be effective against the specific pathogens involved.

Pigs: Sulfamethazine oral solution\[^{R-12}\] and powder for oral solution\[^{R-9}\] are indicated in the treatment of pneumonia caused by susceptible organisms; however, sulfamethazine generally has been replaced by antimicrobials known to be effective against the specific pathogens involved.

Pododermatitis, necrotic (treatment)—Cattle: Sulfonamides are not directly effective against most obligate anaerobes\[^{R-86; 90; 93}\], but may affect aerobic organisms that create the microenvironment in which *Fusobacteria* thrive; therefore, they may be useful in the treatment of pododermatitis but are not recommended in advanced or serious infections. Sulfadimethoxine tablets\[^{R-11}\], oral solution\[^{R-2}\], injection\[^{R-3}\], powder for oral solution\[^{R-4}\], and extended-release tablets\[^{R-5}\]; and sulfamethazine oral solution\[^{R-12}\], powder for oral solution\[^{R-9}\], and extended-release tablets\[^{R-10}\] are indicated in the treatment of pododermatitis caused by susceptible *Fusobacterium necrophorum*. [Sulfamethazine and sulfathiazole combination\[^{R-15; 96}\] are indicated as aids in the treatment of necrotic pododermatitis caused by susceptible *F. necrophorum*.]

Pulmonary disease (treatment)—*Chickens*: Sulfamethazine oral solution\[^{R-12}\] and powder for oral solution\[^{R-9}\] are indicated in the control of susceptible *Salmonella pullorum*. 

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Respiratory infections, bacterial (treatment)—
Cats and dogs: Sulfadimethoxine injection\(^{[R-3]}\), oral suspension, and tablets\(^{[R-6]}\) are indicated in the treatment of respiratory infections, such as bronchitis, caused by susceptible organisms.

Sheep: Sulfamethazine and sulfathiazole combination is indicated as an aid in the treatment of respiratory infections caused by susceptible organisms.\(^{[R-15]}\)

Pigs: Sulfamethazine and sulfathiazole combination is indicated as an aid in the treatment of respiratory infections caused by susceptible organisms.

Skull and soft tissue infections (treatment)—Cats and dogs: Sulfadimethoxine injection\(^1\), oral suspension\(^1\), and tablets\(^{[R-3; 6]}\) are indicated in the treatment of skin and soft tissue infections; however, sulfonamides are not effective in infections associated with purulent debris, such as abscesses.

**ACCEPTANCE NOT ESTABLISHED**

Cats, cattle, dogs, and sheep: Although product labeling in the U.S. and Canada includes the use of sulfonamides in the treatment of metritis in cats, dogs, and cattle, and pyometra\(^{[R-3; 6; 9; 10; 15; 16]}\) in cats and dogs, and Canadian labeling also includes the treatment of metritis in sheep, the efficacy of these uses is not established based on current knowledge. Sulfonamides are poorly distributed into the uterus and their activity may be decreased in the presence of purulent debris; sulfonamides therefore rarely are recommended in the treatment of metritis\(^{[R-103]}\).

Cattle and sheep: Although product labeling in the U.S. and Canada for cattle and in Canada for sheep includes use of sulfonamides in the treatment of mastitis\(^{[R-3; 6; 9; 10; 15; 16; 97]}\), the efficacy of this use is not established based on current knowledge. Many sulfonamides, including most of those labeled for treatment of mastitis, are poorly distributed into milk. Considering also the high incidence of pathogen resistance reported, sulfonamides rarely are recommended in the treatment of mastitis\(^{[R-103]}\).

Horses: Although product labeling in the U.S. and Canada includes the use of sulfonamides in the treatment of equine strangles (Streptococcus equi infection), the efficacy of this use is not established based on current knowledge. The activity of sulfonamides may be decreased in the presence of purulent debris; therefore, they rarely are recommended in the treatment of strangles\(^{[R-103; 107]}\).

\(^1\)Not included in Canadian product labeling or product not commercially available in Canada.

**REGULATORY CONSIDERATIONS**

U.S.—
The presence of sulfonamide residues in food for human consumption has been a concern in recent years. After a variety of efforts to control residues, the incidence of violative sulfonamide residues recently was reported to be as low as 1% in the U.S.\(^{[R-24]}\); however, because of a study linking moderate to high doses of sulfamethazine, directly or by a secondary mechanism, to the production of thyroid tumors in mice, concern about residues continues.\(^{[R-24; 51]}\)

The use of sulfonamides in lactating dairy cattle, other than those medications specifically approved for use, has been specified by the Food and Drug Administration as a high priority for regulatory attention\(^{[R-104]}\).

Withdrawal times have been established for sulfachlorpyridazine, sulfadmethoxine, sulfathiazole, and sulfaquinoxaline. See the Dosage Forms section.

Federal law restricts the use of some forms of sulfadimethoxine and sulfamethazine to use by or on the order of a licensed veterinarian. See the Dosage Forms section.

Canada—
Withdrawal times have been established for sulfamethazine, sulfadimethoxine and sulfathiazole combination; and sulfamethazine, sulfanilamide, and sulfathiazole combination. See the Dosage Forms section.

**CHEMISTRY**

**Chemical name:**
Sulfachlorpyridazine—\(N^1-(6\text{-Chloro-3-pyridazinyl})\text{sulfanilamide}\(^{[R-16]}\).
Sulfadimethoxine—Benzenesulfonamide, 4-amino-N-(2,6-dimethoxy-4-pyrimidinyl)-\(^{[R-36]}\).
Sulfamethazine—Benzenesulfonamide, 4-amino-N-(4,6-dimethyl-2-pyrimidinyl)-\(^{[R-16]}\).
Sulfanilamide—\(N\)-Aminobenzenesulfonamide\(^{[R-16]}\).
Sulfaquinoxaline—\(N^1\)-2-Quinoxalylsulfanilamide\(^{[R-16]}\).
Sulfathiazole—Benzenesulfonamide, 4-amino-N-2-thiazolyl\(^{[R-16]}\).

**Molecular formula:**
Sulfachlorpyridazine—\(C_{16}H_{13}ClN_4O_5S\(^{[R-16]}\).
Sulfadimethoxine—\(C_{12}H_{13}N_2O_5S\(^{[R-36]}\).
Sulfanilamide—\(C_6H_8N_2O_2S\(^{[R-36]}\).
Sulfamethazine—\(C_{12}H_{14}N_4O_2S\(^{[R-36]}\).
Sulfathiazole—\(C_9H_9N_3O_2S_2\(^{[R-36]}\).
Sulfadimethoxine—\(C_4H_6N_3O_5S_2\(^{[R-16]}\).
Sulfaquinoxaline—\(C_4H_13N_2O_4S\(^{[R-36]}\).
Sulfathiazole—\(C_8H_10N_3O_3S\(^{[R-36]}\).

**Molecular weight:**
Sulfachlorpyridazine—284.72 \(\text{g/mol}\)^{[R-16].}
Sulfadimethoxine—310.34 \(\text{g/mol}\)^{[R-36].}
Sulfamethazine—278.33 \(\text{g/mol}\)^{[R-36].}
Sulfanilamide—172.21 \(\text{g/mol}\)^{[R-36].}
Sulfaquinoxaline—300.14 \(\text{g/mol}\)^{[R-36].}
Sulfathiazole—255.32 \(\text{g/mol}\)^{[R-16].}

**Description:**
Sulfadimethoxine USP—Practically white, crystalline powder\(^{[R-56]}\).
Sulfamethazine USP—White to yellowish white powder, which may darken on exposure to light. Practically odorless\(^{[R-56]}\).
Sulfanilamide—White, odorless, crystalline powder\(^{[R-98]}\).
Sulfaquinoxaline—Yellow, odorless powder\(^{[R-94]}\).
Sulfathiazole USP—Fine, white or faintly yellowish white, practically odorless powder\(^{[R-56]}\).

**pKa:**
Sulfadimethoxine—6.15 \(^{[R-13; 35]}\).
Sulfamethazine—2.65, 7.4 \(^{[R-19]}\).
Sulfanilamide—10.5 \(^{[R-19; 46]}\).
Sulfaquinoxaline—5.5 \(^{[R-19]}\).
Sulfathiazole—7.1 \(^{[R-19]}\).

**Solubility:**
Sulfadimethoxine USP—Soluble in 2 \(\text{N}\) sodium hydroxide; sparingly soluble in 2 \(\text{N}\) hydrochloric acid; slightly soluble in alcohol, ether, in chloroform, and in hexane; practically insoluble in water\(^{[R-56]}\).
Sulfamethazine USP—Very slightly soluble in water and in ether; soluble in acetone; slightly soluble in alcohol\(^{[R-56]}\).
Sulfanilamide—Slightly soluble in water, in alcohol, in acetone, in glycerin, in propylene glycol, in hydrochloric acid, and in solutions of...
potassium and sodium hydroxide; practically insoluble in chloroform, in ether, and in petroleum ether{R-98}.
Sulfaquinoxaline—Practically insoluble in water; very slightly soluble in alcohol; practically insoluble in ether; freely soluble in aqueous solutions of alkali{R-94}.
Sulfathiazole USP—Very slightly soluble in water; soluble in acetone, in dilute mineral acids, in solutions of alkali hydroxides, and in 6 N ammonium hydroxide; slightly soluble in alcohol{R-56}.

PHARMACOLOGY/PHARMACOKINETICS

Note: Unless otherwise noted, pharmacokinetic values are based on a single intravenous administration of medication.

Mechanism of action: Bacteriostatic. Sulfonamides interfere with the biosynthesis of folic acid in bacterial cells; they compete with paraaminobenzoic acid (PABA) for incorporation in the folic acid molecule. By replacing the PABA molecule and preventing the folic acid formation required for DNA synthesis, the sulfonamides prevent multiplication of the bacterial cell. Susceptible organisms must synthesize their own folic acid; mammalian cells use preformed folic acid and, therefore, are not susceptible. Cells that produce excess PABA or environments with PABA, such as necrotic tissues, allow for resistance by competition with the sulfonamide{R-17; 18}.

Absorption: Most sulfonamides are well absorbed orally with the exception of the enteric sulfonamides, such as sulfaquinoxaline, which are minimally absorbed{R-19}. Delays in absorption may occur in adult ruminants or when sulfonamides are administered with food to monogastric animals{R-17; 20}.

Bioavailability: Oral—
Sulfadimethoxine:
Cattle—59% (107 mg per kg of body weight [mg/kg] dose){R-44}.
Dogs—48.8% (55 mg/kg dose){R-41}.
Sulfamethazine:
Pigs—86% (50 mg/kg dose){R-66}.
Ponies—84% (160 mg/kg dose){R-57}.

Distribution: Sulfonamides are widely distributed throughout the body.
They cross the placenta, and a few penetrate into the cerebrospinal fluid{R-20}. Sulfonamides may be distributed into milk; however, they vary greatly in their ability to do so. The process depends on several factors, including protein binding and pH values{R-102}.

Volume of distribution—
Sulfadimethoxine:
Goats—Area: 0.49 ± 0.095 L/kg{R-15}.
Pigs—Area:
Suckling (1 to 2 weeks)—0.483 ± 0.078 L/kg{R-45}.
Growing (11 to 2 weeks)—0.345 ± 0.016 L/kg{R-45}.
Rabbits—Steady state: 0.213 ± 0.007 L/kg{R-40}.
Sulfamethazine:
Buffalo—Area: 0.44 ± 0.17 L/kg{R-55}.
Cattle—Extrapolated: 0.35 L/kg{R-82}.
Goats—Area: 0.28 to 0.39 L/kg; 0.44 L/kg{R-15}.
Horses—Steady state: 0.63 ± 0.074 L/kg{R-57}.
Lambs—Area: 0.334 ± 0.031 L/kg{R-61}.

Pigs—Area: 0.5[6-66; 67], 0.77 ± 0.06 L/kg{R-70}.
Administered in conjunction with sulfathiazole: Area—1.01 ± 0.12 L/kg{R-70}.
Sheep—Area: 0.4 L/kg{R-62; 63}; 0.6 L/kg{R-58}.
Sulfanilamide: Goats—Area: 1.3 ± 0.13 L/kg{R-15}.
Sulfathiazole: Pigs—Area: 1.16 ± 0.16 L/kg{R-70}.

Protein binding: Binding can vary depending on serum concentration{R-43} and other factors.
Sulfachlorpyridazine—Cows: High (80 to 85%){R-14}.
Sulfadimethoxine—
Cats: High (87.5%){R-42}.
Chicken: Moderate (40%){R-43}.
Dogs: High (>75%){R-39}.
Goats: High (94%){R-15}.
Sulfamethazine—
Cows: When plasma concentration is less than 50 mcg per ml (mcg/ml)—High (79%){R-79}.
When plasma concentration is more than 50 mcg/ml—
Moderate (51%){R-79}.
Goats: High (86%){R-16}.
Horses: High (70%){R-17}.
Sheep: High (77%){R-58}.
Sulfanilamide—Cows: Low (<20%){R-14}.
Sulfathiazole—Cows: High (65 to 76%){R-14}.

Biotransformation: Sulfonamides are primarily metabolized in the liver but metabolism also occurs in other tissues. Biotransformation occurs mainly by acetylation, glucuronide conjugation, and aromatic hydroxylation in many species{R-17}. The types of metabolites formed and the amount of each varies depending on the specific sulfonamide administered; the species, age, diet, and environment of the animal; the presence of disease; and, with the exception of pigs and ruminants, even the sex of the animal{R-51; 54; 71; 79}. Dogs are considered to be unable to acetylate sulfonamides to any significant degree{R-108}.
N4-acetyl metabolites have no antimicrobial activity and hydroxymetabolites have 2.5 to 39.5% of the activity of the parent compound{R-17}. Metabolites may compete with the parent drug for involvement in folic acid synthesis but have little detrimental effect on the bacterial cell, and so could lower the activity of the remaining parent drug{R-37}.

In pigs, sulfamethazine is metabolized into N4-acethylsulfamethazine, desamino sulfamethazine and the N4-glucose conjugate of sulfamethazine{R-72}. In general, metabolites of sulfonamides are cleared more quickly than the parent drug{R-78}; however, the desamino sulfamethazine half-life of elimination can vary from 1 to 9 days, while sulfamethazine and other metabolites have a shorter half-life of 10 to 20 hours{R-71}. It has been theorized that diets containing nitrate, which is then reduced by bacteria to nitrite, will greatly increase the amount of sulfamethazine biotransformed to the desamino sulfamethazine metabolite and prolong tissue residues of metabolite{R-71}, but there is no conclusive evidence.

Half-life:
Absorption—Sulfadimethoxine: Dogs—Oral dose of 55 mg/kg: 1.9 hours{R-39}.

Elimination—
Sulfachlorpyridazine: Cows—1.2 hours{R-14}.
Sulfadimethoxine:
- Cats—10.2 hours\(^{[R-42]}\)
- Cattle—12.5 hours\(^{[R-18]}\)
- Dogs—13.1 hours\(^{[R-19]}\)
- Goats—8.6 hours\(^{[R-34]}\)
- Pigs—
  - Single dose: Suckling pig (1 to 2 weeks of age)—16.2 hours\(^{[R-45]}\)
  - Growing pig (11 to 12 weeks of age)—9.4 hours\(^{[R-45]}\)
  - After 5 days of once-daily intravenous dosing: 9.2 hours\(^{[R-40]}\)
- Rabbits—After 6 days of once-daily intravenous dosing: 5.2 hours\(^{[R-40]}\)
- Buffalo—5.5 hours\(^{[R-55]}\)
- Calves, 2 to 3 months of age—5.2 to 5.7 hours\(^{[R-78; 79]}\)
- Cattle—5 to 11.3 hours\(^{[R-14; 78; 79; 82]}\)
- Goats—2.4 to 4.1 hours\(^{[R-15; 82]}\), 8.5 to 9.6 hours\(^{[R-15; 82]}\)
- Horses—5.4 hours\(^{[R-37]}\), 11.4 hours\(^{[R-57]}\)
- Lambs—7.2 hours\(^{[R-61]}\)
- Pigs—9.8 hours\(^{[R-70]}\), 16.9 hours\(^{[R-66; 67]}\)
- Sheep—4.5 hours\(^{[R-58]}\), 9.5 to 10.8 hours\(^{[R-62; 63]}\)

Sulfanilamide:
- Cows—6.2 hours\(^{[R-34]}\)
- Goats—7.7 hours\(^{[R-34]}\)

Sulfathiazole:
- Cows—1.5 hours\(^{[R-34]}\)
- Pigs—9 hours\(^{[R-70]}\)
- Sheep—1.3 hours\(^{[R-84]}\)

Sulfamethazine:
- Oral (powder for oral solution): Calves, 8 months of age—9 hours\(^{[R-70]}\)
- Oral dose of 214.3 mg/kg a day (1848 mcg/L of water) administered in the only source of drinking water maintained a serum
concentration of at least 50 mcg/mL from 18 hours to at least 120 hours after start of treatment\(^{[R-76]}\)
- Oral dose of 142.9 mg/kg a day (1028 mg/L of water) administered in the only source of drinking water maintained a serum
concentration of at least 50 mcg/mL from 24 to 180 hours after the start of treatment\(^{[R-76]}\)
- Oral dose of 71.4 mg/kg a day (572 mg/L of water) administered in the only source of drinking water maintained a serum
concentration of at least 50 mcg/mL from only 72 to 96 hours after the start of treatment\(^{[R-76]}\)

Oral (extended-release tablets):
- Calves, 3 to 5 days of age: An oral dose of 396 mg/kg, administered as a single extended-release tablet, maintained a serum
concentration of at least 50 mcg/mL from 4 to 96 hours post-administration\(^{[R-80]}\)

Calves and cattle: An oral dose of 264 mg/kg maintained a serum
concentration greater than 50 mcg/mL from 12 to 48 or 72 hours
post-administration\(^{[R-81]}\)

Elimination: Renal excretion is the primary route of elimination for
most nonenteric sulfonamides and it occurs by glomerular filtration
of parent drug, tubular excretion of unchanged drug and metabolites,
and passive reabsorption of nonionized drug.\(^{[R-17; 20]}\) Alkalization of the urine increases the fraction of the dose that is eliminated in the
urine.\(^{[R-20]}\) In general, the metabolites of the parent drug are more
quickly eliminated by the kidney than the original sulfonamide
\(^{[R-78]}\), but the proportions of metabolites formed can vary,
depending on many factors.

Sulfonamides are also distributed in relatively small amounts into milk,
saliva, and into the gastrointestinal tract.\(^{[R-77; 79]}\)

Sulfadimethoxine—Cattle: 17.9% of an intravenous dose of 107 mg per kg of sulfadimethoxine is excreted into the urine unchanged and at least 58.4% is excreted as metabolites into urine.\(^{[R-44]}\) Only 6.3% of an oral dose of 107 mg of sulfadimethoxine per kg is excreted unchanged in the urine and 37.7% as metabolites in the
urine.\(^{[R-44]}\)

Total clearance:
- Cats—0.31 mL per minute per kg (mL/min/kg).\(^{[R-42]}\)
- Dogs—0.36 mL/min/kg.\(^{[R-19]}\)
- Goats—0.65 mL/min/kg.\(^{[R-15]}\)
- Pigs—
  - Suckling pig (1 to 2 weeks): 0.35 mL/min/kg.\(^{[R-45]}\)
  - Growing pig (11 to 12 weeks): 0.44 mL/min/kg.\(^{[R-45]}\)

Sulfamethazine—
- Cattle: 11 to 37% of a dose of sulfamethazine is excreted into the urine as parent drug.\(^{[R-78; 82]}\)
- Horses: Only 43% of the administered dose is eliminated in the urine and only 7.8% of it is in the form of parent drug.\(^{[R-17]}\)
- Pigs: 24.5% of a sulfamethazine dose is excreted in the urine as unchanged drug and 52.1% as measured metabolites.\(^{[R-67]}\)
- Sheep: 18% of a sulfamethazine dose is excreted into the urine as parent compound and 53% as metabolites.\(^{[R-64]}\)

Total clearance:
- Buffalo—0.93 mL/min/kg.\(^{[R-55]}\)
- Calves, 5 days of age—0.33 mL/min/kg.\(^{[R-79]}\)
- Calves, 2 to 3 months of age—0.57 mL/min/kg.\(^{[R-79]}\)
- Cows—0.73 mL/min/kg.\(^{[R-79]}\)
- Goats—0.55 to 0.65 mL/min/kg; 1.13 to 1.4 mL/min/kg.\(^{[R-35]}\)

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Horses—0.92 mL/min/kg
Pigs—0.35 mL/min/kg
Ponies—0.7 mL/min/kg
Sheep—1.6 mL/min/kg

Sulfathiazole—Total clearance: Pigs—1.5 mL/min/kg

**PRECAUTIONS TO CONSIDER**

**SPECIES SENSITIVITY**

**Dogs:** An idiosyncratic sulfonamide toxicity can occur in any breed of dog, but has been reported more frequently in the Doberman Pinscher than in other breeds. This specific type of drug reaction includes blood dyscrasias, nonseptic polyarthritis, and skin rash.

**CARCINOGENICITY**

For sulfamethazine—High doses have been shown to induce follicular cell hyperplasia of the thyroid gland and splenic changes in specific-pathogen-free mice. When the highest doses (4800 parts per million in the diet) were fed for 24 months, 26 to 33% of the mice developed thyroid gland adenomas. The applicability of these results to other species with recommended doses is unclear at this time.

**PREGNANCY/REPRODUCTION**

Sulfonamides cross the placenta in pregnant animals. Some teratogenic effects have been seen when very high doses were given to pregnant mice and rats.

**LACTATION**

Sulfonamides are distributed into milk; however, the sulfonamides that are clinically relevant to food-producing animals are distributed into milk in concentrations too low to be therapeutic but high enough to produce residues in production equipment. Sulfadiazine and sulfanilamide are more efficiently distributed into milk than most sulfonamides, but are not used in dairy cattle. For many sulfonamides, 0.5 to 2% of the total dose is found in the milk. Distribution into milk varies depending on the amount of non–protein-bound sulfonamide present in the blood and the amount of the nonionized and therefore liposoluble form of the medication present. Sulfonamides with higher pKa values produce a higher proportion of drug in the blood that is non-ionized, and if other factors, such as the rate of biotransformation, also support it, may be distributed more easily into milk. For lactating dairy cattle, concentration of the active parent compound of sulfamethazine, measured at a specific time in milk, is about 20% of the concentration in the blood.

**DRUG INTERACTIONS AND/OR RELATED PROBLEMS**

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (★ = major clinical significance):

**HUMAN DRUG INTERACTIONS**

The following drug interactions have been reported in humans, and are included in the human monograph Sulfonamides (Systemic) in USP DI Volume I: these drug interactions are intended for informational purposes only and may or may not be applicable to the use of sulfonamides in the treatment of animals:

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

- Anticoagulants, coumarin- or indandione-derivative, or
- Anticonvulsants, hydantoin, or
- Antidiabetic agents, oral
- Bone marrow depressants
- Cyclosporine
- Hemolytics, other
- Hepatotoxic medications, other
- Methotrexate or
- Phenylbutazone

**Note:** Drug interactions relating specifically to the use of sulfonamides in animals are rarely reported in veterinary literature. Human drug interactions have been reported and are included in the following section.
Penicillins
(since bacteriostatic drugs may interfere with the bactericidal effect of penicillins in the treatment of meningitis or in other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy)

LABORATORY VALUE ALTERATIONS
The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (« = major clinical significance):
Note: Laboratory value alterations relating specifically to the use of sulfonamides in animals are rarely reported in veterinary literature. Human laboratory value alterations have been reported and are included in the following section.

HUMAN LABORATORY VALUE ALTERATIONS{R-69}
The following laboratory value alterations have been reported in humans, and are included in the human monograph Sulfonamides (Systemic) in USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of sulfonamides in the treatment of animals:
With diagnostic test results
Benedict’s test
(sulfonamides may produce a false-positive Benedict’s test for urine glucose)
Jaffé alkaline picrate reaction assay
(sulfamethoxazole may interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of approximately 10% in the normal values for creatinine)
Sulfosalicylic acid test
(sulfonamides may produce a false-positive sulfosalicylic acid test for urine protein)
Urine urobilinogen test strip (e.g., Urobilistix)
(sulfonamides may interfere with the urine urobilinogen [Urobilistix] test for urinary urobilinogen)
With physiology/laboratory test values
Alanine aminotransferase (ALT [SGPT]), serum, and Aspartate aminotransferase (AST [SGOT]), serum, and Bilirubin, serum
(values may be increased)
Blood urea nitrogen (BUN) and Creatinine, serum
(concentrations may be increased)

MEDICAL CONSIDERATIONS/CONTRAINDICATIONS
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (« = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists:
* Hypersensitivity to sulfonamides
(animals that have had a previous reaction to sulfonamides may be much more likely to react on subsequent administration)
Risk-benefit should be considered when the following medical problems exist:
Hepatic function impairment
(systemically absorbed sulfonamides are metabolized by the liver; delayed biotransformation may increase the risk of adverse effects)
Renal function impairment
(systemically absorbed sulfonamides are renally excreted; delayed elimination could cause accumulation of sulfonamide and metabolites, increasing the risk of adverse effects)

PATIENT MONITORING
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; « = major clinical significance):
Culture and susceptibility, in vitro, and
Minimum inhibitory concentration (MIC)
(in vitro cultures and MIC test should be done on samples collected prior to sulfonamide administration to determine pathogen susceptibility)

SIDE/ADVERSE EFFECTS
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

THOSE INDICATING NEED FOR MEDICAL ATTENTION
Incidence unknown
All species
Crystalization in the urinary tract
Note: Crystalization of sulfonamides can occur in the kidneys or urine with high doses of sulfonamide or when an animal is dehydrated. Solubility in the urine is dependent on the concentration of drug in the urine, urinary pH (less soluble in an acidic pH), the patient’s hydration, and the amount of drug in the acetylated form. Because dogs do not produce acetylated metabolites, they may be less susceptible to this adverse effect{R-85}. It can be minimized in susceptible animals by maintaining a high urine flow and, if necessary, alkalinizing the urine.
Dogs
Cutaneous drug eruption{R-26}; hepatitis; hypothyroidism{R-100; 101}; idiosyncratic toxicosis{R-26}; 27) (blood dyscrasias, including anemia, leukopenia or thrombocytopenia; fever; focal retinitis; lymphadenopathy; nonseptic polyarthritis; polymyositis; skin rash); keratoconjunctivitis sicca{R-28–10}
Note: Iatrogenic hypothyroidism may occur and thyroid function test values may be lowered in dogs administered sulfonamides{R-100; 101}. Although studies have looked at this reaction with potentiated sulfonamides{R-100; 101}, sulfonamides administered alone have been reported to impair thyroid function{R-100}. With administration of sulfamethoxazole and trimethoprim combination at high doses or of ormetoprim and sulfadimethoxine, thyrotropin stimulation test values and serum thyroxine values have been significantly reduced{R-100}. Sulfadiazine and trimethoprim combination, administered at labeled doses (25 mg of sulfadiazine and 5 mg of trimethoprim per kg every 24 hours), has not affected thyroid test values in studies performed.
Idiosyncratic toxicosis can occur 8 to 20 days after initiation of treatment and is believed to be caused either by an immune-mediated syndrome or by an idiosyncratic reaction in dogs, perhaps due to toxic metabolites of the sulfonamide. Of 22 reported cases
In addition to the above side/adverse effects reported in animals, the HUMAN SIDE/ADVERSE EFFECTS are intended for informational purposes only and may or may not be applicable to the use of sulfonamides in the treatment of animals:

Incidence more frequent

Central nervous system effects; gastrointestinal disturbances; hypersensitivity; photosensitivity

Incidence less frequent

Blood dyscrasias; hepatitis; Lyell’s syndrome (difficulty in swallowing; redness, blistering, peeling, or loosening of skin); Stevens-Johnson syndrome (aching joints and muscles; redness, blistering, peeling, or loosening of skin; unusual tiredness or weakness)

Incidence rare

Central nervous system toxicity; Clostridium difficile colitis; crystalluria or hematuria; goiter or thyroid function disturbance; interstitial nephritis or tubular necrosis

Note: C. difficile colitis may occur up to several weeks after discontinuation of these medications. Fatalities have occurred, although rarely, due to severe reactions such as Stevens-Johnson syndrome, toxic epidermal necrosis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Therapy should be discontinued at the first appearance of skin rash or any serious side/adverse effects.

The multiorgan toxicity of sulfonamides is thought to be the result of the way sulfonamides are metabolized in certain patients. It is probably due to the inability of the body to detoxify reactive metabolites. Sulfonamides are metabolized primarily by acetylation. Patients can be divided into slow and fast acetylators. Slow acetylation of sulfonamides makes more of the medication available for metabolism by the oxidative pathways of the cytochrome P450 system. These pathways produce reactive toxic metabolites, such as hydroxylamine and nitroso compounds. The metabolites are normally detoxified by scavengers, such as glutathione. However, some populations, such as human immunodeficiency virus (HIV)–infected patients, have low concentrations of glutathione and these metabolites accumulate, producing toxicity. Patients who are slow acetylators have a higher incidence of sulfonamide hypersensitivity reactions, although severe toxicity has also been seen in fast acetylators. Acetylation status alone cannot fully explain sulfonamide toxicity since approximately 50% of North American blacks and whites are slow acetylators and severe reactions occur in less than 1% of patients treated with sulfonamides. However, decreased acetylation may increase the amount of sulfonamide metabolized to toxic metabolites.

OVERDOSE

For more information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

Toxicities secondary to acute overdose of sulfonamides are not typically reported. Side effects may be more likely to occur with high doses and long-term administration, but are seen at recommended doses as well.

CLIENT CONSULTATION

Dosage and length of treatment recommendations should be followed; high doses or long-term use can increase the risk of side effects. Animals should have a good water supply and should be monitored to ensure adequate water consumption during treatment.

VETERINARY DOSING INFORMATION

Residue avoidance: Management practices can affect depletion of residues in pigs. When pigs have environmental access to urine and manure from pigs treated with sulfamethazine, the residues are easily recycled and can cause these animals to have positive urine tests for sulfonamide and violative tissue residues. Hot or cold environmental temperatures do not appear to inactivate sulfamethazine in the environment.

FOR ORAL DOSAGE FORMS ONLY

Intestinal parasites, among other factors, can affect the pharmacokinetics of sulfamethazine in lambs and probably in other species also. In parasitized lambs given a single dose of 99 mg per kg of body weight (mg/kg), sulfamethazine’s half-life of elimination and time to peak concentration were doubled.
FOR TREATMENT OF ADVERSE EFFECTS
Recommended treatment consists of the following:
For anaphylaxis
• Parenteral epinephrine.
• Oxygen administration and respiratory support.

SULFACHLORPYRIDAZINE
SUMMARY OF DIFFERENCES
Pharmacology/pharmacokinetics: Intermediate duration of action.[R-19]

ORAL DOSAGE FORMS
SULFACHLORPYRIDAZINE POWDER FOR ORAL SOLUTION
Usual dose: Enteritis (diarrhea associated with E. coli)¹—
Calves, less than 1 month of age: Oral, 33 to 49.5 mg per kg of body weight every twelve hours.[R-89]
Pigs: Oral, 22 to 38.5 mg per kg of body weight, administered as a drench every twelve hours or 44 to 77 mg per kg of body weight a day administered in the only source of drinking water.[R-89]

Strength(s) usually available[R-92];
U.S.—
Veterinary-labeled product(s):
50 grams per bottle (OTC) [Vetisulid Powder].[R-89]
Canada—
Veterinary-labeled product(s):
Not commercially available.

Withdrawal times:[R-89]
U.S.—

<table>
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<tr>
<th>Species</th>
<th>Withdrawal time</th>
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<tbody>
<tr>
<td>Calves</td>
<td>7</td>
</tr>
<tr>
<td>Pigs</td>
<td>4</td>
</tr>
</tbody>
</table>

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.

SULFACHLORPYRIDAZINE TABLETS
Usual dose: Enteritis (diarrhea associated with Escherichia coli)¹—Calves, less than 1 month of age: Oral, 33 to 49.5 mg per kg of body weight every twelve hours.[R-88]

Strength(s) usually available[R-92];
U.S.—
Veterinary-labeled product(s):
2 grams (OTC) [Vetisulid Boluses],

Withdrawal times:[R-88]
U.S.—

<table>
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</thead>
<tbody>
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<td>Calves, ruminating</td>
<td>5</td>
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</table>

Note: Product labeling listing the above withdrawal time states that it applies when medication is administered for a maximum of five days. No withdrawal times have been established for use in preruminating calves.[R-88]

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.[R-87].

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.

1Not included in Canadian product labeling or product not commercially available in Canada.

PARENTERAL DOSAGE FORMS
SULFACHLORPYRIDAZINE INJECTION
Usual dose: Enteritis (diarrhea associated with E. coli)¹—Calves, less than 1 month of age: Intravenous, 33 to 49.5 mg per kg of body weight every twelve hours.[R-87]

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s):
200 mg per mL (OTC) [Vetisulid Injection],

Withdrawal times:
U.S.—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, ruminating</td>
<td>7</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal time states that it applies when medication is administered for a maximum of five days. No withdrawal times have been established for use in preruminating calves.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.[R-87].

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.

1Not included in Canadian product labeling or product not commercially available in Canada.
SULFADIMETHOXINE

SUMMARY OF DIFFERENCES
Pharmacology/pharmacokinetics: Intermediate to long duration of action.

ORAL DOSAGE FORMS

SULFADIMETHOXINE ORAL SOLUTION
Usual dose:
- Calf diphtheria:
- Pneumonia, bacterial:
- Necrotic pododermatitis—Calves and cattle: Oral, 55 mg per kg of body weight (2.4 to 3.75 grams per gallon of water) as an initial dose, followed by 27.5 mg per kg of body weight (1.2 to 1.8 grams per gallon of water) a day for four days.
- Coccidiosis:
- Fowl cholera:
- Infectious coryza outbreaks—Chickens, broiler and replacement: Oral, 1875 mg per gallon of water (0.05% solution), administered as the only source of drinking water for six days.
- Turkeys: Oral, 938 mg per gallon of water (0.025% solution), administered as the only source of drinking water for six days.
Note: Administration of sulfadimethoxine for longer than the recommended time can result in slowed growth rates and other adverse effects.

Strength(s) usually available:
- U.S.—Veterinary-labeled product(s):
  - 125 mg per mL (OTC) [Albon 12.5% Concentrated Solution; AmTech Sulfadimethoxine 12.5% Oral Solution; Di-Methox 12.5% Oral Solution; SDM Solution; Sulforal; generic].
- Canada—Veterinary-labeled product(s):
  - Not commercially available.
Withdrawal times:
- U.S.—

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>7</td>
</tr>
<tr>
<td>Chickens, turkeys</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they are not labeled for use in chickens older than 16 weeks of age, turkeys older than 24 weeks of age, preruminating calves, or lactating dairy cattle.

Package and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light.

Stability: Freezing or discoloration does not affect stability. Medication should be thawed before using.

Preparation of dosage form: Prepare fresh drinking water daily.

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.

SULFADIMETHOXINE ORAL SUSPENSION USP
Usual dose:
- Bacterial pneumonia and other respiratory infections:
- Cystitis:
- Skin and soft tissue infections—Cats and dogs: Oral, 55 mg per kg of body weight as an initial dose, followed by 27.5 mg per kg of body weight every twenty-four hours.
- Enteritis associated with coccidiosis or Salmonella—Dogs: Oral, 55 mg per kg of body weight as an initial dose, followed by 27.5 mg per kg of body weight every twenty-four hours.

Strength(s) usually available:
- U.S.—Veterinary-labeled product(s):
  - 50 mg per mL (Rx) [Albon Oral Suspension 5%].
- Canada—Veterinary-labeled product(s):
  - Not commercially available.
Withdrawal times: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Preserve in tight, light-resistant containers, and store at controlled room temperature. Label it to indicate that it is for veterinary use only. Contains the labeled amount, within ±10%. Meets the requirements for Identification and pH (5.0–7.0).

SULFADIMETHOXINE SOLUBLE POWDER USP
Usual dose:
- Bacterial pneumonia:
- Calf diphtheria:
- Necrotic pododermatitis—Calves and cattle: Oral, 55 mg per kg of body weight (2.4 to 3.3 grams per gallon) as an initial dose, followed by 27.5 mg per kg of body weight (1.2 grams per gallon) every twenty-four hours for four days.
- Coccidiosis:
- Fowl cholera—Chickens, broiler and replacement: Oral, 1892 mg per gallon of water (0.05% solution), administered as the only source of drinking water for six days.
- Turkeys: Oral, 946 mg per gallon of water (0.025% solution), administered as the only source of drinking water for six days.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

USP requirements: Preserve in tight, light-resistant containers, and store at controlled room temperature. Label it to indicate that it is for veterinary use only. Contains the labeled amount, within ±10%. Meets the requirements for Identification and pH (5.0–7.0).
Infectious coryza outbreaks—Chickens, broiler and replacement: Oral, 1892 mg per gallon of water (0.05% solution), administered as the only source of drinking water for six days.

**Strength(s) usually available**

**U.S.—**
Veterinary-labeled product(s):
28.3 grams per ounce of powder (OTC) [AmTech Sulfadimethoxine Soluble Powder; Di-Methox Soluble Powder; SDM Powder; Sulfasol; generic].

Canada—
Veterinary-labeled product(s):
Not commercially available.

**Withdrawal times**

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>7</td>
</tr>
<tr>
<td>Chickens, turkeys</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they are not labeled for use in preruminating calves, lactating dairy cattle, chickens older than 16 weeks of age, or turkeys older than 24 weeks of age.

**Packaging and storage:** Store below 40°C (104°F), preferably between 15 and 30°C (59 and 86°F), unless otherwise specified by manufacturer.

**Additional information:** Animals should maintain an adequate water intake during the treatment period.

**USP requirements:** Preserve in tight, light-resistant containers, and store at controlled room temperature. Label the Tablets to indicate that they are for veterinary use only. Contains the labeled amount, within ±10%. Meets the requirements for Identification, Disintegration (30 minutes), and Uniformity of dosage units.

**SULFADIMETHOXINE EXTENDED-RELEASE TABLETS USP**

**Usual dose:**
Bacterial pneumonia; Calf diphtheria; or Pododermatitis—Cattle: Oral, 137.5 mg per kg of body weight as a single dose.

Note: To maintain sustained release of medication, tablets should not be divided; it is recommended that animals should receive a tablet for the nearest 91 kg (200 pounds) of body weight.

**Strength(s) usually available**

**U.S.—**
Veterinary-labeled product(s):
12.5 grams (Rx) [Albon SR].
250 mg (OTC) [Albon Tablets].
5000 mg (5 grams) (OTC) [Albon Boluses].
15,000 mg (15 grams) (OTC) [Albon Boluses].

Note: The 125-mg, 250-mg, and 500-mg tablets listed above are labeled for use only in cats and dogs, while the 5-gram and 15-gram tablets are labeled for use only in cattle.

**Canada—**
Veterinary-labeled product(s):
125 mg (OTC) [S-125].
250 mg (OTC) [S-250].

**Withdrawal times**

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>21</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal time states that they are not labeled for use in lactating dairy cattle or preruminating calves.

**Additional information:** Animals should maintain an adequate water intake during the treatment period.

**Packaging and storage:** Store below 40°C (104°F), preferably between 15 and 30°C (59 and 86°F), unless otherwise specified by manufacturer.

**USP requirements:** Preserve in tight, light-resistant containers, and store at controlled room temperature. Label the Tablets to indicate that they are for veterinary use only. Contains the labeled amount, within ±10%. Meets the requirements for Identification, Disintegration (30 minutes), and Uniformity of dosage units.

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**SULFONAMIDES** Veterinary—Systemic

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Additional information:** Animals should maintain an adequate water intake during the treatment period.

**USP requirements:** Not in USP.

1Not included in Canadian product labeling or product not commercially available in Canada.

**PARENTERAL DOSAGE FORMS**

**SULFADIMETHOXINE INJECTION**

**Usual dose:**
Bacterial respiratory infections1; Cystitis1; or Skin and soft tissue infections1—Cats and dogs: Intravenous or subcutaneous, 55 mg per kg of body weight as an initial dose, followed by 27.5 mg per kg of body weight every twenty-four hours.2

Calf diphtheria1;
Pneumonia, bacterial1; or Necrotic pododermatitis1—Cattle: Intravenous, 55 mg per kg of body weight as an initial dose, followed by 27.5 mg per kg of body weight every twenty-four hours.2

Enteritis associated with coccidiosis or Salmonella1—Dogs: Intravenous or subcutaneous, 55 mg per kg of body weight as an initial dose, followed by 27.5 mg per kg of body weight every twenty-four hours.2

Note: Intramuscular injection can cause local pain and inflammation and result in lower serum concentrations of sulfadimethoxine.3

**Strength(s) usually available**

1Not included in Canadian product labeling or product not commercially available in Canada.

125 mg per mL (Rx) [Albon Injection 40%; AmTech Sulfadimethoxine Injection-40%; Di-Methox Injection-40%; SDM Injection; generic].

**Withdrawal times:**

**U.S.**—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Withdrawal time</td>
</tr>
<tr>
<td></td>
<td>Meat (days)</td>
</tr>
<tr>
<td>Cattle</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that withdrawal times have not been established for use in preruminating calves.

**Additional information:** Animals should maintain an adequate water intake during the treatment period.

**Stability:** Crystallization does not change the potency of sulfadimethoxine injection.3

**SULFAMETHAZINE**

**SUMMARY OF DIFFERENCES**

Pharmacology/pharmacokinetics: Intermediate duration of action.3

**ORAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**SULFAMETHAZINE ORAL SOLUTION**

**Usual dose:**

Calf diphtheria; or

Necrotic pododermatitis—Calves and cattle: Oral, 247.5 mg per kg of body weight as an initial dose, followed by 123.8 mg per kg of body weight every twenty-four hours for three days, administered in the only source of drinking water.4

Coccidiosis—

Chickens: Oral, 134 to 196 mg per kg of body weight a day for two days, followed by 67 to 98 mg per kg of body weight for four days, administered in the only source of drinking water.4

Turkeys: Oral, 117 to 286 mg per kg of body weight a day for two days, followed by 58.5 to 143 mg per kg of body weight for four days, administered in the only source of drinking water.4

Enteritis, bacterial—

Calves, cattle, and pigs: Oral, 247.5 mg per kg of body weight as an initial dose, followed by 123.8 mg per kg of body weight every twenty-four hours for three days, administered in the only source of drinking water.4

Fowl cholera, acute; or

Pulmonary disease—Chickens: Oral, 134 to 196 mg per kg of body weight a day for six days, administered in the only source of drinking water.4

Infectious coryza—Chickens: Oral, 134 to 196 mg per kg of body weight a day for two days, administered in the only source of drinking water.4

Pneumonia, bacterial—Calves, cattle, and pigs: Oral, 247.5 mg per kg of body weight as an initial dose, followed by 123.8 mg per kg of body weight every twenty-four hours for three days, administered in the only source of drinking water.4

Respiratory infections, bacterial—[Sheep]: Oral, 225 mg per kg of body weight the first day, followed by 112.5 mg per kg of body weight for three days, administered in the only source of drinking water.4

**Strength(s) usually available**

**U.S.**—

Veterinary-labeled product(s):

125 mg per mL (OTC) [Sulmet Drinking Water Solution 12.5%].

1Not included in Canadian product labeling or product not commercially available in Canada.
Canada—
Veterinary-labeled product(s):
125 mg per mL (OTC) \[\text{generic}\].
250 mg per mL (OTC) \[\text{Sulfa “25”; Sulfa 25%; generic}\].

Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle, chickens, turkeys</td>
<td>10</td>
</tr>
<tr>
<td>Pigs</td>
<td>15</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply when administered for a maximum of five days in cattle or pigs. Products are not labeled for use in chickens and turkeys producing eggs for human consumption, calves less than 1 month of age or fed an all-milk diet, or dairy cows 20 months of age or older.

Canada—
Veterinary-labeled product(s):
Not commercially available.

Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>10 or 12, depending on product</td>
<td>96</td>
</tr>
<tr>
<td>Calves, pigs, sheep</td>
<td>10 or 12, depending on product</td>
<td></td>
</tr>
<tr>
<td>Chickens, turkeys</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they are not labeled for use in laying birds or for use in swine feeds.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.

**SULFAMETHAZINE POWDER FOR ORAL SOLUTION**

Usual dose:
Calf diphtheria\(^1\); or
Necrotic pododermatitis\(^1\)—*Cattle*: Oral, 237.6 mg per kg of body weight as an initial dose, followed by 118.8 mg per kg of body weight every twenty-four hours for three days, administered as an individual animal drench or in the only source of drinking water\(^{[R-9]}\).
Coccidiosis\(^1\)—
*Chickens*: Oral, 128 to 187 mg per kg of body weight a day for two days, followed by 64 to 93.5 mg per kg of body weight for four days, administered in the only source of drinking water\(^{[R-9]}\).

*Turkeys*: Oral, 110 to 273 mg per kg of body weight a day for two days, followed by 55 to 136.5 mg per kg of body weight for four days, administered in the only source of drinking water\(^{[R-9]}\).

Enteritis, bacterial\(^1\); or
Pneumonia, bacterial\(^1\)—*Cattle and pigs*: Oral, 237.6 mg per kg of body weight as an initial dose, followed by 118.8 mg per kg of body weight every twenty-four hours for three days, administered as an individual animal drench or in the only source of drinking water\(^{[R-9]}\).

Fowl cholera, acute\(^1\); or
Pullorum disease\(^1\)—*Chickens*: Oral, 128 to 187 mg per kg of body weight a day for six days, administered in the only source of drinking water\(^{[R-9]}\).
Infectious coryza\(^1\)—*Chickens*: Oral, 128 to 187 mg per kg of body weight a day for two days, administered in the only source of drinking water\(^{[R-9]}\).

Strength(s) usually available\(^{[R-92]}\):

<table>
<thead>
<tr>
<th>U.S.</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterinary-labeled product(s):</td>
<td>453.5 grams of sulfamethazine powder per packet (OTC) [Salmet Soluble Powder].</td>
</tr>
</tbody>
</table>

Canada—
Veterinary-labeled product(s):
Not commercially available.

Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, cattle, chickens, turkeys</td>
<td>10</td>
</tr>
<tr>
<td>Pigs</td>
<td>15</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply when administered for a maximum of five days in cattle or pigs. Products are not labeled for use in chickens and turkeys producing eggs for human consumption, calves less than 1 month of age or fed all-milk diets, or dairy cows 20 months of age or older.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.

**SULFAMETHAZINE TABLETS**

Usual dose:
Calf diphtheria—*Calves*: Oral, 220 mg per kg of body weight as an initial dose, followed by 110 mg per kg of body weight every twenty-four hours\(^{[R-13]}\).

Enteritis associated with *Escherichia coli*—*Calves and foals*: Oral, 220 mg per kg of body weight as an initial dose, followed by 110 mg per kg of body weight every twenty-four hours\(^{[R-13]}\).

Pneumonia, bacterial—*Calves and foals*: Oral, 220 mg per kg of body weight as an initial dose, followed by 110 mg per kg of body weight every twenty-four hours\(^{[R-13]}\).
Strength(s) usually available\textsuperscript{R-92}:

U.S.—
Veterinary-labeled product(s):
  - 2.5 grams (OTC) [Sulmet Oblets].
  - 5 grams (OTC) [Sulmet Oblets].

Canada—
Veterinary-labeled product(s):
  - 15 grams (OTC) [generic].
  - 15.6 grams (OTC) [generic].

Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, cattle</td>
<td>10</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that it applies to a maximum of five days treatment. Products are not labeled for use in calves less than 1 month of age or those fed an all-milk diet, female dairy cattle 20 months of age or older, or horses intended for food.

Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, cattle\textsuperscript{R-8}</td>
<td>10 (Meat) 96 (Milk)</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply to animals given a maximum of two doses. Products are not labeled for use in calves less than 1 month of age, calves fed an all-milk diet, or dairy cattle 20 months of age or older.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.

SULFAMETHAZINE EXTENDED-RELEASE TABLETS

Usual dose:

- Calf diphtheria;
- Coccidiosis;
- Enteritis, bacterial; or
- Pneumonia, bacterial—

 Calves, 1 month of age or older: Oral, 350 to 400 mg per kg of body weight, administered as a single dose\textsuperscript{R-7; 10; 11}. The dose may be repeated in three days, if necessary\textsuperscript{R-7; 11}.

 Cattle: Oral, 330 to 350 mg per kg of body weight as a single dose\textsuperscript{R-10}. The dose may be repeated in three days, if necessary\textsuperscript{R-11}.

 Necrotic pododermatitis—Cattle: Oral, 330 to 350 mg per kg of body weight as a single dose\textsuperscript{R-10}. The dose may be repeated in three days, if necessary\textsuperscript{R-11}.

 Note: Tablets can be broken at the score line, but should not be crushed.

Strength(s) usually available\textsuperscript{R-92}:

U.S.\textsuperscript{R-7; 10; 11}—
Veterinary-labeled product(s):
  - 8 grams (OTC) [Sulfa-Max III Calf Bolus; Sustain III Calf Bolus].
  - 8.25 grams (OTC) [Sulfasure SR Calf Bolus; Suprasulf III Calf Bolus].
  - 30 grams (OTC) [Sulfasure SR Cattle Bolus; Suprasulf III Cattle Bolus].
  - 32.1 grams (OTC) [Sulfa-Max III Cattle Bolus; Sustain III Cattle Bolus].

Canada—
Veterinary-labeled product(s):
  - 8 grams (OTC) [Calfspan].
  - 8.25 grams (OTC) [Sulfasure SR Calf Tablets].
  - 32.1 grams (OTC [Sustain III].

Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, ruminating and cattle</td>
<td>8 or 12, depending on product</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply to animals given a maximum of two doses. Products are not labeled for use in calves less than 1 month of age, calves fed an all-milk diet, or dairy cattle 20 months of age or older.

Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>8, 12, or 28, depending on product</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they are not labeled for use in lactating dairy cattle.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.
Necrotic pododermatitis—Cattle: Oral, 48.8 mg sulfamethazine, 73 mg sulfanilamide, and 73 mg sulfathiazole per kg of body weight as an initial dose, followed by 24.4 mg sulfamethazine, 36.5 mg sulfanilamide, and 36.5 mg sulfathiazole per kg of body weight, administered twelve hours later.

Strength(s) usually available:

U.S.—Veterinary-labeled product(s):
Not commercially available.

Canada—Veterinary-labeled product(s):
3.9 grams sulfamethazine, 5.85 grams sulfanilamide, and 5.85 grams sulfathiazole (OTC) [Triple Sulf Bolus].

Withdrawal times:

Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>Pigs</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Note: Some products are not labeled for use in lactating dairy cattle.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from moisture.

Additional information: Animals should maintain an adequate water intake during the treatment period.

USP requirements: Not in USP.

SULFAMETHAZINE AND SULFATHIAZOLE

ORAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that are not included in U.S. product labeling or are for products not commercially available in the U.S.

SULFAQUINOXALINE

SUMMARY OF DIFFERENCES
Pharmacology/pharmacokinetics: Sulfaquinoxaline is minimally absorbed systemically and is referred to as an enteric sulfonamide.

Side/adverse effects: Clotting disorders similar to those resulting from coumarin anticoagulants have been reported in chickens and dogs.

ORAL DOSAGE FORMS

SULFAQUINOXALINE ORAL SOLUTION USP

Usual dose:

Acute fowl cholera; or
Acute fowl typhoid—Chickens and turkeys: Oral, a 0.04% solution, administered in the only source of drinking water for two to three days.

Coccidiosis—
Calves1 and cattle1: Oral, 13.2 mg per kg of body weight a day, administered in the only source of drinking water as a 0.015% solution for three to five days.

Chickens: Oral, a 0.04% solution, administered in the only source of drinking water for two to three days. Treatment should be stopped for three days, then the medication readministered as a.

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0.025% solution for two to four more days. The schedule may be repeated, if necessary.[R-14]

Turkeys: Oral, a 0.025% solution of sulfaquinoxaline, administered as the only source of drinking water for two days. Treatment should be stopped for three days, then the medication readministered as a 0.025% solution for two days; treatment is then stopped for three days, then medication is readministered as the 0.025% solution for two final days. The complete schedule may be repeated, if necessary.[R-14]

Note: For treatment of coccidiosis in chickens and turkeys, it is recommended that litter not be changed until absolutely necessary.

Strength(s) usually available[R-92]:
U.S.—
Veterinary-labeled product(s):

200 mg per mL (OTC) [Sulfa-Q 20% GENERIC].
319.2 mg per mL (OTC) [Optimed; 31.92% Sul-Q-Nox].

Canada—
Veterinary-labeled product(s):

192 mg per mL (OTC) [GENERIC].

Withdrawal times:
U.S.—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, cattle, chickens, turkeys</td>
<td>10</td>
</tr>
</tbody>
</table>

Note: Products are not labeled for use in chickens and turkeys laying eggs for human consumption, prerruminant calves, or lactating dairy cattle.

Canada—

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens, turkeys</td>
<td>12</td>
</tr>
</tbody>
</table>

Note: Products are not labeled for use in chickens and turkeys laying eggs for human consumption.

Preparation of dosage form: Fresh solutions should be prepared daily. To help avoid toxic reactions, the medication should be evenly mixed in drinking water.

Caution: People who handle this medication should avoid contact with eyes, skin, or clothing to prevent eye and skin burns. In case of contact, the areas affected should be flushed for at least fifteen minutes; medical attention should be sought for eye exposure.[R-14] Keep out of the reach of children.[R-14]

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from moisture.[R-14]

Additional information: Animals should maintain an adequate water intake during the treatment period.

Chickens: Prolonged administration of sulfaquinoxaline may result in deposition of crystals in the kidney or interference with normal blood clotting.[R-14; 95] Sulfaquinoxaline levels of greater than 0.012% in drinking water for more than twenty-four to thirty-six hours may result in reduced growth rate from decreased feed or water consumption.[R-14; 95]

USP requirements: Preserve in tight, light-resistant containers. Label it to indicate that it is for veterinary use only. Contains the equivalent of the labeled concentration of sulfaquinoxaline, within ±10%. Meets the requirements for Identification, Deliverable volume and pH (not less than 12).[R-56].
29. Sanson J, Barnett KC, Long RD. Keratonoconjunctivitis sicca in the dog associated with the administration of salicylanaussulfapyridine (salphasisul-

30. Morgan RV, Bachrach A. Keratonoconjunctivitis sicca associated with sulfon-

34. Nielsen P, Rasmussen F. Half-life, apparent volume of distribution, and protein-

43. Abdel Hamid Youssef S, El-Genify AI, El-Sayed MG, et al. Some pharma-

50. Khan FH, Nawaz M, Anwar-Ul-Hassan S. Pharmacokinetics of sulfameth-

52. Wilson RC, Hammond LS, Clark CH, et al. Bioavailability and pharmacoki-

57. Wilson RC, Hammond LS, Clark CH, et al. Bioavailability and pharmacoki-

85. Panel comment, Rec 6/20/96.
89. Sulfachlorpyridazine package label (Vetisulid powder, Solvay—US), Rec 11/3/95.
91. Sulfadimethoxine package insert (S-125, Sanofi—Canada), Rec 10/27/95.
95. Sulfathiourea package label (34% Sul-Q-Nox, Russell—US), Rec 10/23/95.
96. Sulfathiazole and sulfathiazole combination product information (Powder 21, PVL—Canada), Rec 9/94, Rec 12/1/95.
97. Sulfamethazine, sulfanilamide, and sulfathiazole product information (Triple sulfa bolus, PVL—Canada), Rec 8/92, Rec 12/1/95.
104. Extra-label use of drugs in food-producing animals (Compliance Policy Guide 7125.06). Rev 7/20/92. Food and Drug Administration Center for Veterinary Medicine.
106. Panel comment, 5/21/96.
108. Panel comment, 5/21/96.
TETRACYCLINES Veterinary—Systemic

This monograph includes information on the following: Chlortetracycline; Doxycycline; Oxytetracycline; Tetracycline.

Some commonly used brand names are:

For veterinary-labeled products—

- Agrimycin 100 [Oxytetracycline]
- Agrimycin 200 [Oxytetracycline]
- Agrimycin-343 [Oxytetracycline]
- Amomycin LA [Oxytetracycline]
- AmTech Chlortetracycline HCL soluble powder [Chlortetracycline]
- AmTech Maxim-100 [Oxytetracycline]
- AmTech Maxim-200 [Oxytetracycline]
- AmTech Oxytetracycline HCL soluble powder [Oxytetracycline]
- AmTech Tetracycline Hydrochloride soluble powder-324 [Tetracycline]
- Aureomycin 220G [Chlortetracycline]
- Aureomycin 50 Granular [Oxytetracycline]
- Aureomycin 90 Granular [Chlortetracycline]
- Aureomycin 100 Granular [Chlortetracycline]
- Aureomycin soluble powder [Chlortetracycline]
- Aureomycin soluble powder concentrate [Chlortetracycline]
- Aureomycin uterine tablets [Chlortetracycline]
- Biomycin 200 [Oxytetracycline]
- Calf scour bolus antibiotic [Tetracycline]
- Chlor 50 [Chlortetracycline]
- Chlor 100 [Chlortetracycline]
- ChlorMax 50 [Chlortetracycline]
- Chlorosal 50 [Chlortetracycline]
- CLTC 100 MR [Chlortetracycline]
- CTC 50 [Chlortetracycline]
- CTC soluble powder concentrate [Chlortetracycline]
- Duramycin 10 [Tetracycline]
- Duramycin 72-200 [Oxytetracycline]
- Duramycin 100 [Oxytetracycline]
- Duramycin-124 [Tetracycline]
- Foul brood mix [Oxytetracycline]
- Geomycin 200 [Oxytetracycline]
- Kromycin [Oxytetracycline]
- Liqumycin LA-200 [Oxytetracycline]
- Maxim-200 [Oxytetracycline]
- Ongin 62.5 [Tetracycline]
- Ongin 250 [Tetracycline]
- Ongin 1000 [Tetracycline]
- OT 200 [Oxytetracycline]
- OTC 50 [Oxytetracycline]
- OXTC 50 [Oxytetracycline]
- OXTC 100 [Oxytetracycline]
- OXTC 200 [Oxytetracycline]

For human-labeled products—

- Achromycin V [Tetracycline]
- Alsi-Doxycycline [Doxycycline]
- Apo-Doxycycline [Doxycycline]
- Apo-Doxycycline Tabs [Doxycycline]
- Apo-Tetra [Tetracycline]
- Dorge [Doxycycline]
- Doxycycline [Doxycycline]
- Doxycycline [Doxycycline]

Note: For a listing of dosage forms and brand names by country availability, see the Dosage Forms section(s).

CATEGORY:

- Antibacterial (systemic); antiprotozoal; antirickettsial.

INDICATIONS

Note: Bracketed information in the Indications section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

GENERAL CONSIDERATIONS

The tetracyclines are broad-spectrum antibiotics with activity against gram-positive and gram-negative bacteria, including some anaerobes. They are also active against chlamydia, mycoplasmas, some protozoa,[R-28; 1131] and several rickettsiae, including Anaplasma, Ehrlichia, and Haemobartonella. The activity range of the tetracyclines also includes Escherichia coli, Klebsiella species, Pasteurella species, Salmonella species, Staphylococcus species, and Streptococcus species[R-4]. Susceptibility testing has demonstrated that some coliforms, mycoplasma, streptococci, and staphylococci have developed resistance to tetracyclines.[R-21; 150] However, the breakpoints used to classify these organisms as susceptible or resistant are not validated for animal indications. Susceptibility testing should not be the sole basis for selecting tetracyclines for therapy.[R-61]

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ACCEPTED

Abortion, vibronic (prophylaxis) - Sheep: Chlortetracycline for medicated feed is indicated to aid in reduction of the incidence of vibronic abortion caused by susceptible Campylobacter fetus.

Abscesses, cervical (prophylaxis) - Pigs: Chlortetracycline for medicated feed is indicated for reduction of the incidence of abscesses caused by susceptible organisms.

Abscesses, hepatic (prophylaxis) - Cattle: Chlortetracycline for medicated feed is indicated as an aid in the prevention of hepatic abscesses in cattle.

Actinobacillosis (treatment) - Cattle: Oxytetracycline injection is indicated in the treatment of actinobacillosis (wooden tongue) caused by susceptible Actinobacillus lignieresii.

Anaplasmosis (treatment) - Cattle: Chlortetracycline for medicated feed is indicated in the control of active infection caused by susceptible Anaplasma marginale.

Diphtheria (treatment) - Cattle: Oxytetracycline injection is indicated in the treatment of diphtheria (necrotic laryngitis, necrotic necrophorus stomatitis) caused by susceptible Fusobacterium necrophorum.

Enteritis, bacterial (treatment) - The treatment of enteritis should be dependent on a specific diagnosis and knowledge of pathogen susceptibility to tetracyclines. Some pathogens associated with enteritis, such as Escherichia coli, are found to be resistant to the tetracyclines.

Calves: Chlortetracycline soluble powder, oxytetracycline tablets and tetracycline boluses and soluble powder are indicated in the control of bacterial enteritis (scours) caused by susceptible E. coli. Chlortetracycline for medicated feed and soluble powder; oxytetracycline for medicated feed injection, soluble powder, and tablets are indicated in the treatment of bacterial enteritis caused by susceptible E. coli and Salmonella species.

Cattle: Chlortetracycline for medicated feed and oxytetracycline for medicated feed injection are indicated in the control of bacterial enteritis caused by susceptible E. coli. Oxytetracycline for medicated feed and soluble powder are indicated in the treatment of bacterial enteritis caused by susceptible E. coli and Salmonella.

Pigs: Chlortetracycline soluble powder and oxytetracycline soluble powder are indicated in the control and treatment of bacterial enteritis caused by susceptible E. coli. Chlortetracycline for medicated feed and oxytetracycline injection are indicated in the treatment of bacterial enteritis (scours) caused by susceptible E. coli and Salmonella.

Sheep: Oxytetracycline for medicated feed and [tetracycline soluble powder] are indicated in the control of enteritis caused by susceptible organisms.

Turkeys, growing: Chlortetracycline soluble powder and oxytetracycline soluble powder are indicated in the control of susceptible organisms involved in the development of enteritis (bluecomb).

Turkeys: Chlortetracycline for medicated feed and [powder for oral solution] and tetracycline soluble powder are indicated in the control and treatment of enteritis caused by susceptible organisms. Oxytetracycline for medicated feed is indicated in the treatment of susceptible E. coli involved in the development of enteritis (bluecomb).

[Chickens]: Oxytetracycline soluble powder and chlortetracycline for medicated feed are indicated in the treatment of susceptible E. coli involved in the development of enteritis.

[Lambs]: Oxytetracycline for medicated feed is indicated in the reduction of bacterial enteritis in creep-fed suckling lambs.

Escherichia coli infections (treatment) - Chickens: Chlortetracycline for medicated feed is indicated as an aid in reducing mortality due to E. coli infections.

Weight gain, increased rate - Calves, cattle, chickens, pigs, sheep, and turkeys: Chlortetracycline for medicated feed and oxytetracycline for medicated feed are indicated for growth promotion and feed efficiency.

Foul brood (treatment) - Bees: Oxytetracycline for medicated feed and soluble powder are indicated in the treatment of American and European foul brood caused by susceptible organisms.

Fowl cholera (prophylaxis) - Chickens: Oxytetracycline for medicated feed and soluble powder are indicated in the prevention of fowl cholera caused by susceptible organisms.

Fowl cholera (treatment) - Chickens: Chlortetracycline soluble powder and oxytetracycline for medicated feed are indicated in the control of mortality from fowl cholera caused by susceptible Pasteurella multocida.

Furunculosis (treatment) - Salmonids (salmon and trout): Oxytetracycline for medicated feed is indicated in the control of furunculosis caused by susceptible Aeromonas salmonicida.

Gallkemia (treatment) - Lobsters: Oxytetracycline for medicated feed is indicated in the treatment of gallkemia caused by susceptible Aerococcus viridans.

Gastroenteritis (treatment) - Cats and dogs: Tetracycline oral suspension is indicated in the treatment of bacterial gastroenteritis, but use should be reserved for treatment of organisms known to be susceptible.

Hemorrhagic septicemia, bacterial (treatment) - Catfish and salmonids: Oxytetracycline for medicated feed is indicated in the control of hemorrhagic septicemia caused by susceptible Aeromonas hydrophila, A. sobria, and Pseudomonas species.

Hexamitiasis (treatment) - Turkeys: Chlortetracycline for medicated feed and oxytetracycline for medicated feed are indicated in the control of hexamitiasis, and oxytetracycline soluble powder and [tetracycline soluble powder] are indicated in the treatment of hexamitiasis caused by susceptible Hexamita meleagris.

Keratoconjunctivitis, infectious (treatment) - Cattle: Long-acting oxytetracycline injection is indicated in the treatment of keratoconjunctivitis caused by susceptible Moraxella bovis.

Leptospirosis (treatment) - Pigs: Chlortetracycline for medicated feed and oxytetracycline for medicated feed are indicated to aid in reducing the shedding of leptospirosis and the incidence of abortion. Oxytetracycline for medicated feed is indicated as an aid in the reduction of abortion and urinary shedding of leptospirosis, production of
healthier newborn pigs, and maintenance of weight gains in the presence of leptospirosis\textsuperscript{[R-122]}. Oxytetracycline injection\textsuperscript{[R-24; 45]} and soluble powder\textsuperscript{[R-11]} are indicated in the treatment of leptospirosis caused by susceptible \textit{Leptospira pomona}. Oxytetracycline can reduce the incidence of abortions and shedding of leptospirosis\textsuperscript{[R-11]} however, it can be ineffective in eliminating the organism\textsuperscript{[R-113]}.

\textbf{Cattle:} Oxytetracycline injection\textsuperscript{[R-24; 45]} is indicated in the treatment of leptospirosis caused by susceptible \textit{Leptospira pomona}.

Paratyphoid (treatment)\textsuperscript{1}—Turkeys, less than 4 weeks of age: Chlortetracycline for medicated feed\textsuperscript{[R-16; 152]} is indicated as an aid in reducing mortality from paratyphoid infection caused by susceptible \textit{Salmonella typhimurium}.

Pneumonia, bacterial (prophylaxis)—\textit{Cattle:} Oxytetracycline for medicated feed\textsuperscript{[R-117; 122]} is indicated in the prevention of pneumonia and as an aid in the reduction of losses due to bovine respiratory disease complex.

\textbf{Cattle:} Chlortetracycline soluble powder\textsuperscript{1}, oxytetracycline tablets\textsuperscript{[R-60]}, and tetracycline boluses\textsuperscript{[R-1]} are indicated in the control of pneumonia and bovine respiratory disease complex caused by susceptible organisms, including \textit{Pasteurella} species. Chlortetracycline soluble powder; oxytetracycline injection, soluble powder, and tablets\textsuperscript{[R-60; 61]}, and tetracycline boluses and soluble powder\textsuperscript{[R-1; 18]} are indicated in the treatment of pneumonia caused by susceptible organisms, including \textit{Pasteurella} species. However, due to resistance\textsuperscript{[R-51; 171; 180]} by pathogens, the tetracyclines may no longer be effective in the treatment of some types of bacterial pneumonia.

\textbf{Cattle:} Chlortetracycline for medicated feed\textsuperscript{[R-152]} is indicated in the control\textsuperscript{1} and treatment of pneumonia caused by susceptible organisms. Oxytetracycline\textsuperscript{[R-24; 45; 61]} is indicated in the treatment of pneumonia and shipping fever complex caused by susceptible \textit{Pasteurella} and \textit{Haemophilus} species. Increasing resistance to tetracyclines by strains of organisms involved in bovine pneumonia is reported\textsuperscript{[R-51; 171; 180]}.

\textbf{Pigs:} Chlortetracycline soluble powder\textsuperscript{[R-17]} is indicated in the control of pneumonia caused by susceptible \textit{Actinobacillus pleuropneumoniae} (\textit{Haemophilus} species), \textit{Pasteurella} species, and \textit{Klebsiella} species. Chlortetracycline for medicated feed\textsuperscript{[R-152]} and oxytetracycline soluble powder are indicated in the treatment of pneumonia caused by susceptible \textit{Pasteurella multocida}. Chlortetracycline soluble powder\textsuperscript{[R-17]}, oxytetracycline injection\textsuperscript{[R-24; 45]}, and tetracycline soluble powder\textsuperscript{[R-1; 18]} are indicated in the treatment of pneumonia caused by susceptible \textit{Actinobacillus pleuropneumoniae} (\textit{Haemophilus} species), \textit{Klebsiella}, and \textit{Pasteurella} species. Increasing resistance to tetracyclines by strains of organisms involved in porcine pneumonia is reported\textsuperscript{[R-50]}.

\textbf{Sheep:} Oxytetracycline for medicated feed\textsuperscript{[R-117; [injection]]; [R-24; 121]}, and soluble powder\textsuperscript{[R-6; 13]}, and [tetracycline soluble powder]\textsuperscript{[R-18]} are indicated in the treatment of pneumonia caused by susceptible organisms.

Pododermatitis (treatment)—\textbf{Cattle:} Long-acting oxytetracycline injection\textsuperscript{[R-24; 45]} is indicated in the treatment of pododermatitis (‘foot rot’) caused by susceptible \textit{Fusobacterium necrophorum}. Signs may not be completely resolved by oxytetracycline alone and other treatment or surgery may be required.

Pseudomonas disease (treatment)\textsuperscript{1}—\textit{Catfish and salmonids:} Oxytetracycline for medicated feed\textsuperscript{[R-62]} is indicated in the control of pseudomonas disease caused by susceptible organisms.

Psittacosis (treatment)\textsuperscript{1}—\textit{Cockatoos, macaws, and parrots:} Chlortetracycline for medicated feed\textsuperscript{[R-152]} is indicated in the treatment of psittacosis caused by susceptible \textit{Chlamydia psittaci}.

Respiratory disease, bacterial, chronic (prophylaxis)—\textit{Chickens:} Oxytetracycline for medicated feed\textsuperscript{[R-122]} is indicated in the prevention of chronic respiratory disease caused by susceptible organisms.

Respiratory disease, bacterial, chronic (treatment)—\textit{Chickens:} Chlortetracycline for medicated feed and soluble powder\textsuperscript{[R-16; 17; 152]}, oxytetracycline for medicated feed\textsuperscript{1} and soluble powder\textsuperscript{[R-11; 22]}, and tetracycline soluble powder\textsuperscript{[R-18; 127]} are indicated in the control of respiratory disease, including air sac disease, caused by susceptible \textit{Mycoplasma gallisepticum} and \textit{E. coli}. Chlortetracycline for medicated feed\textsuperscript{[R-16; 115]} and powder for oral solution\textsuperscript{[R-17]} are indicated in the treatment of chronic respiratory disease caused by susceptible organisms.

Skeletal tissue marking\textsuperscript{1}—\textit{Salmon, Pacific:} Oxytetracycline for medicated feed\textsuperscript{[R-117]} is indicated to mark skeletal tissue in Pacific salmon.

Skin and soft tissue infections (treatment)\textsuperscript{1}—\textbf{Cattle:} Oxytetracycline injection is indicated in the treatment of wounds infected by susceptible \textit{Staphylococcus} species or \textit{Streptococcus} species.

Synovitis, infectious (treatment)—\textit{Chickens and turkeys:} Chlortetracycline for medicated feed\textsuperscript{[R-16; 152]} and soluble powder\textsuperscript{[R-17]}, oxytetracycline for medicated feed\textsuperscript{[R-117]} and soluble powder\textsuperscript{[R-11]}, and tetracycline soluble powder\textsuperscript{[R-3]} are indicated in the control of infectious synovitis caused by susceptible \textit{Mycoplasma synoviae}. Chlortetracycline powder for oral solution\textsuperscript{[R-17]} is indicated in the treatment of infectious synovitis caused by susceptible \textit{M. synoviae}.

Ulcerc disease (treatment)—\textit{Salmonids (salmon, trout):} Oxytetracycline for medicated feed\textsuperscript{[R-62; 124]} is indicated in the control of ulcer disease caused by susceptible \textit{Haemophilus piscium}.

Urinary tract infections (treatment)\textsuperscript{1}—\textit{Cats and dogs:} Tetracycline oral suspension\textsuperscript{[R-4]} is indicated in the treatment of urinary tract infections caused by susceptible \textit{Staphylococcus} species and \textit{E. coli}. Also, concentrations of tetracycline in urine are high enough to be effective against \textit{Pseudomonas} species\textsuperscript{[R-150]}.

Uterine infections, acute (treatment)—\textbf{Cattle:} Oxytetracycline injection\textsuperscript{[R-24; 45]} is indicated in the treatment of acute metritis caused by susceptible strains of \textit{Staphylococcus} and \textit{Streptococcus} species.

\textbf{[Pigs]:} Oxytetracycline injection\textsuperscript{[R-24]} is indicated in the treatment of acute metritis caused by susceptible organisms.

\textbf{[Sheep]:} Oxytetracycline injection\textsuperscript{[R-24; 121]} is indicated in the treatment of uterine infections.

\textbf{[Arthritis, bacterial (treatment)]—Cattle and sheep:} Oxytetracycline injection\textsuperscript{[R-24; 25]} is indicated in the treatment of septic arthritis (joint ill) caused by susceptible organisms.

\textbf{[Atrophic rhinitis (treatment)]—Pigs:} Oxytetracycline for medicated feed\textsuperscript{[R-122]} is indicated for use as an aid in maintaining weight gain in pigs infected with atrophic rhinitis.

\textbf{[Blackleg (treatment)] or [Malignant edema (treatment)]—Cattle:} Oxytetracycline injection\textsuperscript{[R-24; 25; 121]} is indicated in the treatment of infections caused by susceptible \textit{Clostridia} species.
[Bloat]—Cattle: Oxytetracycline for medicated feed is indicated as an aid in reducing the incidence of bloat in young cattle on pasture and in feedlots.

[Cold water disease (treatment)]—Salmonids: Oxytetracycline for medicated feed is indicated in the treatment of cold water disease caused by susceptible *Cytophaga psychrophila*.

[Columbaris disease (treatment)]—Salmonids: Oxytetracycline for medicated feed is indicated in the treatment of columbaris disease caused by susceptible *Chondrococcus (Flexibacter) columbaris*.

[Enteric redmouth disease (treatment)]—Lamb: Chlortetracycline for medicated feed and oxytetracycline for medicated feed are indicated in the reduction of losses due to enterotoxemia in feedlot lambs.

[Erysipelas (prophylaxis)]—Pigs: Oxytetracycline injection is indicated in the treatment of erysipelas caused by susceptible organisms.

[Erysipelatococci (treatment)]—Cattle, pigs, and sheep: Oxytetracycline injection is indicated in the treatment of mastitis caused by susceptible organisms. Oxytetracycline, administered at the dosage recommended in product labeling, does not appear to be effective for the cure of *Staphylococcus aureus* infections in the dry cow.

[Enterotoxemia (treatment)]—Lamb: Chlortetracycline for medicated feed and oxytetracycline for medicated feed are indicated in the treatment of enteric redmouth disease caused by susceptible *Yersinia ruckeri*.

[Enterotoxemia (treatment)]—Lambs: Chlortetracycline for medicated feed and oxytetracycline for medicated feed are indicated in the reduction of losses due to enterotoxemia in feedlot lambs.

[Erysipelatococci (treatment)]—Pigs: Oxytetracycline injection is indicated in the treatment of erysipelatococci caused by susceptible organisms.

[Peritonitis (treatment)]—Cattle: Oxytetracycline injection is indicated in the treatment of peritonitis caused by susceptible organisms.

[Pododermatitis (prophylaxis)]—Cattle: Chlortetracycline for medicated feed is indicated as an aid in the prevention of pododermatitis.

[Potomac horse fever (treatment)1]—Horses: Oxytetracycline is used in the treatment of Potomac horse fever (equine ehrlichial colitis) caused by susceptible *Ehrlichia risticii*. Treatment of exposed animals to prevent development of disease is not recommended; the incubation period will be increased but the disease is not prevented.

[Rocky Mountain spotted fever (treatment)1]—Horses: Oxytetracycline is used in the treatment of Rocky Mountain spotted fever caused by susceptible *Rickettsia rickettsii*. Controlled clinical efficacy trials have not been conducted for any medication; however, a tetracycline is usually administered when a cat is diagnosed and doxycycline is considered the tetracycline of choice because of an expectation of fewer side effects. Cats with serious underlying viral infections, such as feline leukemia virus, are not expected to respond well to therapy.

[Leptospirosis (treatment)]—Cats: Although doxycycline is proposed in some veterinary references for use in the clearance of the lepto- spirose carrier state in dogs, there are insufficient data showing clearance or prevention of a potential carrier state to support this use as an established indication.

[Lyme disease (treatment)1]—Cats: There are insufficient data to establish the efficacy of tetracyclines in the treatment of Lyme borreliosis. Doxycycline has been effective in the resolution of early *Borrelia burgdorferi* infection in people; therefore, doxycycline and tetracycline are used to treat the infection in dogs. In dogs, however, it is uncertain whether this is the best medication to produce long-term resolution of the infection.

[Rhabdomyolysis (treatment)]—Cats: There are insufficient data to establish the efficacy of oxytetracycline in the treatment of rhabdomyolysis.

[Thromboembolic meningocerebralitis (treatment)]—Cattle: There are insufficient data to establish the efficacy of oxytetracycline in the treatment of thromboembolic meningocerebralitis; however, if cattle are diagnosed in the early stages of the disease, before recumbency,
treatment can be effective against susceptible *Haemophilus somni-*
us*. [R-161: 166]

[uterine infections, bacterial (treatment)]—*Cattle, horses, pigs, and sheep:*
Although Canadian product labeling includes the use of intraterine
chlorotetracycline, oxytetracycline, and tetracycline in the treatment of
uterine infections, there are insufficient available data concerning the
efficacy and safety of this use. Intraterine tetracycline treatment can reduce
the incidence of purerfection of retained fetal membranes and
fever associated with infection in cattle, but because it is believed to
penetrate only into the endometrium from infusion into the
uterus, [R-104: 130], parenteral antibiotics are recommended for those
animals that have evidence of infection or develop signs of septice-
emia. [R-144]. The intraterine administration of tetracyclines for
the treatment of uterine infections such as endometritis or treatment of
infection associated with retained placentas in cattle is not effective in
shortening the interval from parturition to conception, increasing
pregnancy rates, or reducing culling rates. [R-144–146]. Considering
costs, risks of residues [R-129], and a lack of significant change in long-
term fertility in cattle, there is no evidence to support the routine use of
intraterine tetracyclines in cattle, horses, pigs, and sheep.

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**REGULATORY CONSIDERATIONS**

### U.S.—
Withdrawal times have been established for chlortetracycline for
medicated feed and soluble powder; oxytetracycline soluble powder,
for medicated feed, tablets, and injection; and tetracycline soluble
powder and boluses. See the *Dosage Forms* section.

Canada—
Withdrawal times have been established for chlortetracycline for
medicated feed, and uterine tablets; oxytetracycline soluble powder,
for medicated feed, uterine infusion, and injection; and tetracycline
soluble powder, boluses, and uterine tablets. See the *Dosage Forms*
section.

### CHEMISTRY

**Source:**
Chlortetracycline—Isolated from the fungus *Streptomyces aureofaci-
ens* [R-22].

Doxycycline—Produced semisynthetically. [R-22]

Oxytetracycline—Isolated from the fungus *Streptomyces rimosus* [R-22].

Tetracycline—Produced by some streptomycins; however, it is
produced by some *Streptomyces* strains; however, it is
chemically the same. [R-113].

**Chemical name:**
Chlortetracycline hydrochloride—2-Naphthacenecarboxamide, 7-chloro-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-
pentahydroxy-6-methyl-1,11-dioxo-, monohydrochloride [4S-(4 alpha,
4a alpha, 5a alpha, 6 alpha, 12a alpha)]. [R-114].

Doxycycline—2-Naphthacenecarboxamide, 4-(dimethylamino) - 1,4,4a,
5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-
1,11-dioxo-, [4S-(4 alpha,4a alpha, 5 a alpha, 5a alpha, 6 alpha, 12a alpha)]-
hydrate. [R-114].

Doxycycline hydrochlorate—2-Naphthacenecarboxamide, 4-(dimeth-
ylamino)-1,4,4a,5,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-
methyl-1,11-dioxo-, [4S-(4 alpha,4a alpha, 5a alpha, 5a alpha, 6 beta,12a
alpha)]. [R-114].

Chlortetracycline—Produced by some streptomycins; however, it is
chemically the same. [R-113].

**Molecular formula:**
Chlortetracycline hydrochloride—C22H23ClN2O83.

Doxycycline—C22H24N2O8.

Oxytetracycline hydrochloride—C22H24N2O9.

Tetracycline hydrochloride—C22H24N2O8.

**Molecular weight:**
Chlortetracycline hydrochloride—515.34.

Doxycycline—462.45.

Oxytetracycline hydrochloride—496.89.

Tetracycline hydrochloride—480.90.

**Description:**
Chlortetracycline Hydrochloride USP—Yellow, crystalline powder. Is
odorless. Is stable in air, but exposure to strong sunlight causes it to
darken. It loses potency in solutions of pH below 2, and is rapidly destroyed by
alkali hydroxide solutions [R-128].

Oxytetracycline Hydrochloride USP—Yellow, odorless, crystalline pow-
der. Is hygroscopic. Decomposes at a temperature exceeding 180 °C,
and exposure to strong sunlight or to temperatures exceeding 90 °C in
moist air causes it to darken. Its potency is diminished in solutions
having a pH below 2, and is rapidly destroyed by alkali hydroxide
solutions [R-128].

Tetracycline USP—Yellow, odorless, crystalline powder. Is stable in air,
but exposure to strong sunlight causes it to darken. It loses potency in solutions of
pH below 2, and is rapidly destroyed by alkali hydroxide solutions [R-128].
Oxytetracycline USP—Very slightly soluble in water; freely soluble in 3 M hydrochloric acid and in alkaline solutions; sparingly soluble in alcohol.[R-128]

Tetracycline USP—Very slightly soluble in water; freely soluble in dilute acid and in alkaline hydroxide solutions; sparingly soluble in alcohol; practically insoluble in chloroform and in ether.[R-128]

Doxycycline USP—Very slightly soluble in water; freely soluble in dilute acid and in alkaline hydroxide solutions; sparingly soluble in alcohol; practically insoluble in chloroform and in ether.[R-128]

Chlortetracycline Hydrochloride USP—Sparingly soluble in water; soluble in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol; practically insoluble in chloroform and in ether.[R-128]

Bioavailability:

Oral—Oxytetracycline:

- Chickens—1% (25 mg per kg body weight [mg/kg] dose).[R-78; 79]
- Pigs—Fed: 18 to 19%.[R-77]
- Turkeys—6% (15 mg/kg dose).[R-78; 80]

Doxycycline:

- Chickens—41.3% (20 mg/kg dose).[R-64]
- Human value—90 to 95%.[R-169]

Oxytetracycline:

- Pigs—4.8% (50 mg/kg dose).[R-109]
- Piglets, weaned, 10 weeks of age—
  - By drench: 9% (20 mg/kg dose).[R-82]
  - In medicated feed for 3 days: 3.7% (400 parts per million [ppm] of feed).[R-82]
- Trout, rainbow (Oncorhynchus mykiss)—5.6% (75 mg/kg dose).[R-89]
- Turkeys—
  - Fasted: 47.6% (10 mg/kg dose).[R-85]
  - Fed: 9.4% (10 mg/kg dose).[R-85]
- Tetracycline: Pigs, fasted—23% (22 mg/kg dose).[R-74]

Intramuscular—

Oxytetracycline, conventional formulation:

- Buffalo—63.2% (22 mg/kg dose).[R-87]
- Calves, 17 days of age—61% (20 mg/kg dose).[R-99]
- Calves, 3 months of age—76 hours postinjection of 18 mg/kg dose: Buttock administration—81.1%.[R-94]
- Neck administration—93.3%.[R-94]
- Shoulder administration—99.4%.[R-94]
- Catfish, African, and trout, rainbow—85% (60 mg/kg dose).[R-90]
- Cows—80.8% (8 mg/kg dose).[R-95]; 95% (20 mg/kg dose).[R-174]
- Goats—65.5% (20 mg/kg dose).[R-81]

Oxytetracycline, long-acting formulation:

- Camels—93.7% (10 mg/kg dose).[R-88]
- Cattle—51%; 78.5%; 95% (20 mg/kg dose).[R-98; 99; 174]
- Goats—79.4% (20 mg/kg dose).[R-81]

Distribution: Tetracyclines are lipid soluble and are well distributed to most tissues. Doxycycline is the most lipid soluble and shows the greatest degree of tissue penetration.[R-28; 71]

Volume of distribution—

Doxycycline:

- Calves, ruminating—Area volume of distribution: 1.93 ± 0.15 liters per kg (L/kg).[R-76]
Pigs—Steady state volume of distribution:
Fasted—0.97 ± 0.21 L/kg.\(^{[R-77]}\)
Fed—1.39 ± 0.31 L/kg.\(^{[R-77]}\)
Turkeys—Area: 0.23 ± 0.05 L/kg.\(^{[R-78]}\)

Doxycycline:
Calves—Steady state:
Preruminating—1.81 ± 0.24 L/kg.\(^{[R-68]}\)
Ruminating—1.31 ± 0.11 L/kg.\(^{[R-68]}\)
Cats—Steady state: 0.34 ± 0.03 L/kg.\(^{[R-70]}\)
Dogs—Steady state: 0.93 ± 0.14 L/kg.\(^{[R-70]}\)
Pigs—Steady state: 0.53 ± 0.04 L/kg.\(^{[R-69]}\)

Oxytetracycline:
Buffalo—Area: 0.28 to 0.45 L/kg.\(^{[R-87]}\)
Calves, newborn to 8 months—Area: 1.67 L/kg.\(^{[R-93; 100]}\)
Camels—Steady state: 0.71 L/kg.\(^{[R-88]}\)
Cows—Area: 0.80 ± 0.03 L/kg.\(^{[R-95]}\)
Dogs—Area: 2.10 ± 0.42 L/kg.\(^{[R-84]}\)
Donkeys—
Area: 0.78 L/kg\(^{[R-92]}\).
Steady state: 0.65 L/kg\(^{[R-92]}\).
Foals—
Area: 2.19 L/kg.\(^{[R-154]}\)
Steady state: 2.17 L/kg.\(^{[R-154]}\)
Goats—Area: 1.44 L/kg.\(^{[R-81]}\)
Horses—
Apparent: 1.35 L/kg.\(^{[R-96]}\)
Area: 0.67 L/kg.\(^{[R-92]}\)
Steady state: 0.34 L/kg.\(^{[R-92]}\)
Pigs—Area:
Adult—1.8 L/kg.\(^{[R-83]}\)
Adult with pneumonia—1.53 L/kg.\(^{[R-83]}\)
Ponies—
Area: 1.05 L/kg.\(^{[R-92]}\)
Steady state: 0.47 L/kg.\(^{[R-92]}\)
Rabbits—0.86 L/kg.\(^{[R-86]}\)
Rats—Area: 0.79 L/kg.\(^{[R-91]}\)
Tetracycline:
Chickens—Steady state: 0.17 L/kg.\(^{[R-73]}\)
Pigs—Area: 4.5 ± 1.14 L/kg.\(^{[R-74]}\)
Rabbits—Area: 1.05 ± .88 L/kg.\(^{[R-72]}\)

Protein binding:
Chlortetracycline—
Cows: Moderate (47 to 51%).\(^{[R-67]}\)
Sheep: Moderate (46 to 50%).\(^{[R-67]}\)

Doxycycline—
Calves: Very high (92%).\(^{[R-68]}\)
Cats: Very high (98%).\(^{[R-70]}\)
Dogs: Very high (91%).\(^{[R-70]}\)
Pigs: Very high (93%).\(^{[R-69]}\)
Sheep: High (84 to 90%).\(^{[R-67]}\)

Oxytetracycline—
Buffalo: Moderate (42%).\(^{[R-87]}\)
Cows: Low (18 to 22%).\(^{[R-67]}\)
Horses and cows: Combined results—Moderate (50%).\(^{[R-96]}\)
Pigs, weaned, 10 weeks of age: High (75.5%).\(^{[R-82]}\)
Sheep: Low (21 to 25%).\(^{[R-67]}\)
Trot, rainbow: Moderate (55%).\(^{[R-89]}\)

Tetracycline—
Cows: Low to moderate (31 to 41%).\(^{[R-67]}\)
Sheep: Low (28 to 32%).\(^{[R-67]}\)

Bio transformation: All species—The tetracyclines are not known to be biotransformed to any significant extent before elimination.\(^{[R-28; 68–70]}\)

Half-life: Elimination—
Chlorotetracycline:
Calves, ruminant—8.3 hours.\(^{[R-76]}\)
Turkeys—0.88 hour.\(^{[R-78]}\)

Doxycycline:
Calves—
Preruminant: 9.8 hours.\(^{[R-68]}\)
Ruminant: 14.2 hours.\(^{[R-68]}\)
Cats—4.6 hours.\(^{[R-70]}\)
Chickens—4.8 hours.\(^{[R-64]}\)
Dogs—7 to 10.4 hours.\(^{[R-61; 70]}\)
Horses—Oral administration (apparent half-life): 8.7 ± 1.6 hours.\(^{[R-111]}\)
Pigs—3.9 hours.\(^{[R-69]}\)

Oxytetracycline:
Buffalo—2.8 to 3.6 hours.\(^{[R-87]}\)
Calves—
Newborn: 11.2 hours.\(^{[R-93]}\)
6 weeks of age: 3.5 to 7.2 hours.\(^{[R-93; 100; 106]}\)
6 weeks of age with induced Mannheimia Pasteurella haemolytica pneumonia: 2.5 hours.\(^{[R-106]}\)
8 months of age: 6.3 hours.\(^{[R-93]}\)
Cows—10 hours.\(^{[R-93]}\)
Dogs—6 hours.\(^{[R-84]}\)
Donkeys—6.5 hours.\(^{[R-92]}\)
Foals—6.7 to 7.3 hours.\(^{[R-154]}\)
Goats—6.5 hours.\(^{[R-81]}\)
Horses—13 hours.\(^{[R-92]}\); 15.7 hours.\(^{[R-175]}\)
Pigs—
10 weeks of age, weaned: 11.6 to 17.2 hours.\(^{[R-82]}\)
Adult: 3.8 to 6.7 hours.\(^{[R-77; 83]}\)
Adult, with pneumonia: 5.1 to 5.2 hours.\(^{[R-83]}\)
Ponies—15 hours.\(^{[R-92]}\)
Rabbits—1.3 hours.\(^{[R-86]}\)
Trout, rainbow—
Oncorhynchus mykiss: 60.3 hours.\(^{[R-89]}\)
Salmo gairdneri: 89.5 hours.\(^{[R-90]}\)
Turkeys—0.73 hour.\(^{[R-85]}\)

Tetracycline:
Cats—2.5 hours.\(^{[R-75]}\)
Chickens—2.8 hours.\(^{[R-73]}\)
Dogs—1.6 to 2 hours.\(^{[R-75]}\)
Pigs—16 hours.\(^{[R-74]}\)
Rabbits—2 hours.\(^{[R-72]}\)

Time to peak concentration/Peak serum concentration:
Chlortetracycline—Oral:
Calves (22 mg/kg dose)—
Oxytetracycline—

Doxycycline—Oral:

Horses—

Pigs,

Oral:

Multiple dosing: Horses—2 hours postadministration to a serum concentration of 0.42 mcg/mL at 2 hours after the fifth dose (five intragastric doses of 10 mg/kg administered at twelve hour intervals).

Note: The MIC90 of doxycycline has been reported as 0.5 mcg/mL for Staphylococcus aureus in horses.

Oxytetracycline—

Intramuscular:

Conventional formulation—

Calves, 14 weeks of age: 6 hours to a peak serum concentration of 5.5 ± 1.25 mcg/mL (dose of 18 mg/kg in the neck).

Catfish, African: 7 hours to a peak serum concentration of 43.4 mcg/mL (60 mg/kg dose).

Cows: 6.7 hours to a peak serum concentration of 5.7 ± 2.39 mcg/mL (dose of 8 mg/kg in the neck).

Pigs: 1.5 hours to a peak serum concentration of 6.7 ± 3.4 (dose of 20 mg/kg in the hindquarter).

Trout, rainbow: 4 hours to a peak serum concentration of 56.9 mcg/mL (60 mg/kg dose).

Long-acting formulation—

Calves, nonruminating, 5 weeks of age: 1 to 1.5 hours to a peak serum concentration of 4 mcg/mL (dose of 20 mg/kg in the gluteal muscles).

Calves, nonruminating, 6 weeks of age: 4.01 ± 2.84 hours to a peak serum concentration of 3.01 ± 0.72 mcg/mL (dose of 10 mg/kg in the hindquarter).

Calves, ruminating: 7.6 ± 4 hours to a peak serum concentration of 9.6 ± 2.6 mcg/mL (dose of 40 mg/kg in the hindquarter).

Camels: 7.3 ± 3.5 hours to a peak serum concentration of 3.49 ± 0.44 mcg/mL (10 mg/kg dose).

Cows: 5 to 10 hours to a peak serum concentration of 4.5 to 6.8 mcg/mL (dose of 10 mg/kg in the neck).

Pigs: 0.5 hour to a peak serum concentration of 6 ± 2.2 mcg/mL (dose of 20 mg/kg in the hindquarters).

Steers: 8 hours to a peak serum concentration of 3.13 mcg/mL (dose of 20 mg/kg in the hindquarters).

Tetracyclines Veterinary—Systemic

Duration of action:

Note: Duration of action may be estimated by the time target serum concentrations are maintained. Target concentrations are generally based on minimum inhibitory concentrations (MIC) for each organism. While 0.5 mcg/mL has been considered the MIC of oxytetracycline for many pathogens in the past and research studies were based on that target, there are now many pathogens with MICs of 4 to 16 mcg/mL. Duration of action may be minimal or nonexistent for these isolates.

Chlortetracycline—

Pigs: When administered 110 mg chlortetracycline per kg of feed, fed as the only ration, therapeutic plasma or tissue concentrations were not produced.

Turkeys: A single oral dose of 15 mg/kg produces serum concentrations above 0.4 mcg/mL for 8 to 10 hours.

Doxycycline—Dogs: An intravenous dose of 5 mg/kg produces serum concentrations above 2 mcg/mL for 8 hours.

Oxytetracycline—

Oxalic acid or sodium bicarbonate, or other local anesthetics may be required to treat burning.

Intramuscular:

Conventional formulation—

Calves, 14 weeks of age: 6 hours to a peak serum concentration of 5.5 ± 1.25 mcg/mL (dose of 18 mg/kg in the neck).

Catfish, African: 7 hours to a peak serum concentration of 43.4 mcg/mL (60 mg/kg dose).

Cows: 6.7 hours to a peak serum concentration of 5.7 ± 2.39 mcg/mL (dose of 8 mg/kg in the neck).

Pigs: 1.5 hours to a peak serum concentration of 6.7 ± 3.4 (dose of 20 mg/kg in the hindquarter).

Trout, rainbow: 4 hours to a peak serum concentration of 56.9 mcg/mL (60 mg/kg dose).

Long-acting formulation—

Calves, nonruminating, 5 weeks of age: 1 to 1.5 hours to a peak serum concentration of 4 mcg/mL (dose of 20 mg/kg in the gluteal muscles).

Calves, nonruminating, 6 weeks of age: 4.01 ± 2.84 hours to a peak serum concentration of 3.01 ± 0.72 mcg/mL (dose of 10 mg/kg in the hindquarter).

Calves, ruminating: 7.6 ± 4 hours to a peak serum concentration of 9.6 ± 2.6 mcg/mL (dose of 40 mg/kg in the hindquarter).

Camels: 7.3 ± 3.5 hours to a peak serum concentration of 3.49 ± 0.44 mcg/mL (10 mg/kg dose).

Cows: 5 to 10 hours to a peak serum concentration of 4.5 to 6.8 mcg/mL (dose of 10 mg/kg in the neck).

Pigs: 0.5 hour to a peak serum concentration of 6 ± 2.2 mcg/mL (dose of 20 mg/kg in the hindquarters).

Steers: 8 hours to a peak serum concentration of 3.13 mcg/mL (dose of 20 mg/kg in the hindquarters).

Tetracycline—Oral: Pigs—72 hours to a peak serum concentration of 0.6 mcg/mL (dose of 0.55 gram per kg of feed).

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Pigs: A single dose of 20 mg/kg produces serum concentrations > 0.5 mcg/mL for 35 to 48 hours[107-174]; however, the use of the long-acting formulation does not produce significantly different plasma oxytetracycline concentrations from those produced by the conventional formulation[107].

Tetracycline—Pigs: A ration containing 0.55 gram of tetracycline hydrochloride per kg of feed, fed as the only ration, produces 0.3 to 0.4 mcg/mL serum concentrations for the 96 hours that it is fed.[74] Note: These results may vary by size of pig and amount of feed intake.

Elimination:
Chlortetracycline—Total clearance:
- Calves, ruminating—2.70 ± 0.17 mL per minute per kg (mL/min/ kg).[68]
- Ruminant—1.07 mL/min/kg.[68]
- Cats—1.09 ± 0.21 mL/min/kg.[70]
- Dogs—1.7 mL/min/kg.[63-70].
- Pigs—1.67 ± 0.18 mL/min/kg.[69]

Oxytetracycline—Calves, cows, dogs, pigs, and turkeys: The conventional formulation of oxytetracycline is eliminated primarily by glomerular filtration; only a small amount (1 to 2% in pigs and turkeys) is eliminated in the bile.[61: 82; 85; 93-97]

Total clearance:
- Oxytetracycline—
  - Buffalo: 1.02 to 1.45 mL/min/kg.[87]
  - Calves, 6 to 8 weeks of age: 1.66 to 1.88[93], 2.67 to 4.67 mL/min/kg.[100]
  - Camels: 1.26 mL/min/kg.[88]
  - Dogs: 4.23 ± 1.29 mL/min/kg.[84]
  - Donkeys: 1.52 mL/min/kg.[92]
  - Foals, 4 to 5 days of age: 3.17 mL/min/kg.[154].
  - Goats: 2.67 mL/min/kg.[81].
  - Horses: 0.66 mL/min/kg.[92]
  - Pigs, 10 weeks of age: 4.17 mL/min/kg.[82]
  - Pigs, adult: 3.5 mL/min/kg.[83].
  - Ponies: 1.01 mL/min/kg.[92]
  - Rabbits: 7.23 mL/min/kg.[86].
  - Rats: 2.79 mL/min/kg.[91].

Tetracycline—Total clearance:
- Chickens—1.63 ± 0.18 mL/min/kg.[71]
- Pigs—3.08 ± 0.4 mL/min/kg.[74].
- Rabbits—6.1 ± 0.6 mL/min/kg.[72].

**PRECAUTIONS TO CONSIDER**

**SPECIES SENSITIVITY**

*All species:* Rapid intravenous administration of tetracyclines can result in cardiovascular dysfunction and collapse in any species.[13-15; 169].

**PREGNANCY/REPRODUCTION**

Tetracyclines have been shown to cross the placenta[22] and may affect fetal bone formation.[135]

**LACTATION**

Tetracyclines are distributed into milk.

**PEDIATRICS**

Use of tetracyclines during tooth development (the last 2 to 3 weeks of pregnancy to 1 month of age)[22] may cause discoloration of the bones and teeth.[4] In neonates that have not yet developed full renal function, excretion of chlortetracycline, oxytetracycline, and tetracycline may occur more slowly than in a mature animal. One exception is that 4-day-old foals have a faster elimination half-life and more rapid clearance of oxytetracycline compared to adults.[154].

**DRUG INTERACTIONS AND/OR RELATED PROBLEMS**

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (= major clinical significance):

Note: Although methoxyflurane has been suspected of increasing the potential for tetracycline-induced nephrotoxicity in people, this has not been shown to be true in dogs.[117]

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

- Antacids or
- Calcium supplements, such as calcium carbonate, or
- Iron supplements or
- Magnesium-containing laxatives or
- Sodium bicarbonate

(concurrent use with tetracyclines may result in formation of nonabsorbable complexes; also, concurrent use within 1 to 3 hours of antacid or sodium bicarbonate administration may result in decreased absorption of oral tetracyclines because of increased intragastric pH)

Phenobarbital or

Microsomal enzyme inducers, other
(concurrent use with doxycycline may result in decreased doxycycline serum concentrations due to induction of microsomal enzyme activity; adjustment of doxycycline dosage or substitution of another tetracycline may be necessary)

Tereftalic acid
(blood concentrations of chlortetracycline are increased when it is administered concurrently with tereftalic acid{R-156})

**HUMAN DRUG INTERACTIONS AND/OR RELATED PROBLEMS**{R-132}
In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monograph Tetraecylines (Systemic) in USP DI Volume I; these drug interactions are intended for informational purposes only and may or may not be applicable to the use of tetracyclines in the treatment of animals:

Cholestyramine
(concurrent use with cholestyramine may result in binding of oral tetracyclines, thus impairing their absorption; an interval of several hours between administration of cholestyramine and oral tetracyclines is recommended)

Vitamin A
(concurrent use with tetracycline has been reported to cause benign intracranial hypertension)

**LABORATORY VALUE ALTERATIONS**
The following have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive (« = major clinical significance):

With physiology/laboratory test values

Urinalysis
(transient hemoglobinuria has been reported in cattle given parenteral oxytetracycline{R-18, 45; 56})

**HUMAN LABORATORY VALUE ALTERATIONS**{R-132}
The following laboratory value alterations have been reported in humans, and are included in the human monograph Tetraecylines (Systemic) in USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of tetracyclines in the treatment of animals:

With diagnostic test results

Catecholamine determinations, urine
(may produce false elevations of urinary catecholamines because of interfering fluoroescence)

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) and Alkaline phosphatase and Amylase and Aspartate aminotransferase (AST [SGOT]) and Bilirubin
(serum concentrations may be increased)

Blood urea nitrogen (BUN)
(antianabolic effect of tetracyclines [except doxycycline] may increase BUN concentrations; in patients with significantly impaired renal function, increased serum concentrations of tetracyclines may lead to azotemia, hyperphosphatemia, and acidosis)

**MEDICAL CONSIDERATIONS/CONTRAINDICATIONS**
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (« = major clinical significance).

**Risk-benefit should be considered when the following medical problem exists:**
Renal function impairment, severe
(chlortetracycline, oxytetracycline, and tetracycline are eliminated primarily by the kidney and can accumulate in animals with severe renal dysfunction; doxycycline is only partially eliminated renally and is much less likely to accumulate{R-71})

**PATIENT MONITORING**
The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition: » = major clinical significance):

*Culture and susceptibility, in vitro, and Minimum inhibitory concentration (MIC)*
(in vitro cultures and MIC test should be done on samples collected prior to administration of tetracyclines to determine pathogen susceptibility)

**SIDE/ADVERSE EFFECTS**
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

**THOSE INDICATING NEED FOR MEDICAL ATTENTION**
Incidence rare

*All species*

**Hypersensitivity reactions, specifically anaphylaxis**{R-32; 45}
(defecation; eruption of skin plaques; frothing from the mouth; glassy-eyed appearance; labored breathing; muscle trembling; pilo-erection; prostration; restlessness; swelling of eyelids, ears, muzzle, anus, vulva or scrotum and sheath{R-45}; photosensitization{R-19})

*Cattle, dogs, and horses*

**Nephrotoxicosis**{R-29; 31: 112; 168}—with high doses, concurrent debilitating conditions, or use of outdated tetracyclines
Incidence unknown

*All species*

**Overgrowth of nonsusceptible organisms**

*Cats, cattle, dogs, horses, monkeys, rabbits, rats, and sheep*{R-33–35}

**Cardiovascular dysfunction, including atrioventricular block, atrial tachycardia, ventricular bradycardia, hypotension**
(in order of appearance—agitation or nervousness, dyspnea, muscle fasciculations, urination, defecation, collapse, death)—a dose-dependent effect{R-144} with rapid intravenous administration; **cardiovascular dysfunction, including hypertension, arterial**{R-15}—in horses given doxycycline

Note: Although the propylene glycol vehicle of some oxytetracycline preparations has been shown to have some cardiovascular effects when administered intravenously{R-133}, the calcium-binding nature of the tetracyclines has been implicated in cardiovascular dysfunction and sudden collapse in cattle and sheep after intravenous administration of tetracyclines{R-34; 35}. Although pretreatment with calcium borogluconate has been considered before intravenous
administration specific postreaction therapy for possible hypocalcemia has not been recommended.

In horses, doses of doxycycline as low as 0.2 to 0.4 mg per kg of body weight administered intravenously have caused cardiovascular dysfunction, collapse, and death. Instead of hypotension, hypertension is reported in horses given intravenous doxycycline and is associated with the other signs of cardiovascular dysfunction seen with rapid intravenous tetracycline administration in other species.

Cats

Fever (anorexia, sometimes diarrhea)—usually resolves within 48 hours of discontinuing oxytetracycline or tetracycline.

Cattle

Hemoglobinuria, transients (brownish-red urine)—with parenteral administration of oxytetracycline; hepatitis with fatty degeneration and/or bile stasis—likely seen after prolonged chloramphenicol administration.

Horses

Colitis; diarrhea, severe

Psittacine birds (cockatoos, macaws, and parrots)

Aspergillosis, increased risk of—may occur with prolonged chlorotetracycline treatment.

Rabbits

Anorexia; diarrhea—with doses administered that are two times the recommended dose.

THOSE INDICATING NEED FOR MEDICAL ATTENTION ONLY IF THEY CONTINUE OR ARE BOTHERSOME

Incidence more frequent

All species

Discoloration of teeth in young animals (yellow, brown, or grey discoloration)—when administered during late pregnancy or during period of tooth development; local tissue irritation at site of injection—may occur with intramuscular administration.

Cats and dogs

Nausea or vomiting—with oral administration, in particular, with doxycycline on an empty stomach.

HUMAN SIDE/ADVERSE EFFECTS

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Tetracyclines (Systemic) in USP DI Volume I: these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of tetracyclines in the treatment of animals:

Incidence more frequent

Central nervous system toxicity; staining of infants' or children's teeth; gastrointestinal disturbances; photosensitivity

Incidence less frequent

Fungal overgrowth; hypertrophy of the papillae; nephrogenic diabetes insipidus; pigmentation of skin and mucous membranes

Incidence rare

Benign intracranial hypertension; hepatotoxicity; pancreatitis

Note: Tetracycline-induced hepatotoxicity is usually seen as a fatty degeneration of the liver. It is more likely to occur in pregnant women, in patients receiving high-dose intravenous therapy, and in patients with renal function impairment. However, hepatotoxicity has also occurred in patients without these predisposing conditions. Tetracycline-induced pancreatitis has also been described in association with hepatotoxicity, and without associated liver disease.

OVERDOSE

For more information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

Overdose of tetracyclines in animals is unusual because very high doses are often tolerated; however, effects that have been associated with overdose in animals include nephrotoxicosis and possible hepatotoxicity.

Acute toxicity of intravenously-administered tetracyclines in many species is most often seen with rapid administration; however, intravenous doxycycline administration in horses has caused collapse even when administered over a 3- to 7-minute period. This reaction to intravenous tetracyclines is dose-dependent, but is not only associated with high doses. Administration of repeated high doses of intravenous or intramuscular oxytetracycline to calves or cattle can result in renal cortical tubular necrosis. While a single intramuscular dose of 40 mg of an oxytetracycline per kg (in a 2-pyridylidene formulation) administered to healthy calves produced no significant toxicity studies have shown that 33 to 44 mg of oxytetracycline per kg of body weight a day administered intravenously or intramuscularly for 2 or more days can produce renal protein casts, tubular necrosis, and death in calves with respiratory disease.

A similar dose of 33 mg oxytetracycline per kg of body weight administered intravenously for 3 days produces a rise in blood urea nitrogen and the appearance of renal casts in the urine of normal heifers. The vehicles used in formulations, such as propylene glycol, have been linked to reduced renal blood flow and have been suspected of exacerbating adverse effects. Tetacycline and its degradation products have been reported to also cause nephrotoxicity in cattle and foals. Serious toxicity can be expected to be more likely in animals that are already compromised by disease or dehydration.

Hepatotoxicity has been reported as a human side effect of tetracyclines and may be more common in pregnant women. Hepatic fatty degeneration has been observed in people and has been induced in mice and rats given extremely high doses (100 to 300 mg of tetracycline per kg of body weight); however, fatty infiltration of the liver was also observed in calves that had respiratory disease and that developed renal tubular necrosis after administration of two doses of 33 mg of oxytetracycline per kg of body weight 24 hours apart.

VETERINARY DOSING INFORMATION

FOR ORAL DOSAGE FORMS ONLY

For some tetracyclines, serum concentrations from animal to animal vary more widely when administered in drinking water than when administered in feed.

Unlike other tetracyclines, doxycycline can be used without dosage adjustment in animals with renal function impairment.
FOR PARENTERAL DOSAGE FORMS ONLY

Care should be taken to administer intravenous tetracyclines slowly and/or dilute them in fluids to avoid cardiovascular side effects. Intramuscular injection of oxytetracycline will affect the quality of meat for a prolonged period. Whenever possible, subcutaneous administration should be chosen.\[R-33–35\]

DIET/NUTRITION

Oral tetracyclines are absorbed more efficiently when administered without food, particularly without foods containing divalent or trivalent metals, such as milk or milk replacer. Doxycycline absorption appears to be less affected than other tetracyclines.

FOR TREATMENT OF ADVERSE EFFECTS

Recommended treatment consists of the following:

- **For anaphylaxis**
  - Parenteral epinephrine.
  - Oxygen administration and respiratory support.

FOR TREATMENT OF ACUTE REACTIONS TO INTRAVENOUS ADMINISTRATION

Recommended treatment consists of the following:

- Intravenous fluids.
- Oxygen administration and respiratory support.

Note: Because the specific causes of acute reactions may be difficult to immediately determine, an electrocardiogram should be monitored when possible to identify cardiac arrhythmias and direct the course of therapy.

CHLORTETRACYCLINE

ADDITIONAL DOSING INFORMATION

When possible, oral chlortetracycline should be administered 1 hour before or 2 hours after milk replacer.\[R-1\]

MUCOSAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

CHLORTETRACYCLINE UTERINE TABLETS

Usual dose:

Note: (Cattle)—Although the efficacy and safety are not currently established, an intrauterine dose of 500 to 1000 mg administered as a single dose after parturition is included in Canadian product labeling. \[R-118\]  

- Bacterial enteritis; or  
- Bacterial pneumonia: Oral, 22 mg per kg of body weight a day, administered in the only source of drinking water. \[R-17\]  
- Fowl cholera: Oral, 1000 mg (1 gram) per gallon of water, administered in the only source of drinking water.  
- Synovitis: Oral, 200 to 400 mg per gallon of water (approximately 11 to 29.5 mg per kg of body weight a day), administered in the only source of drinking water. \[R-143\]  
- Infectious synovitis: Oral, 400 mg per gallon of water (approximately 7 to 37 mg per kg of body weight a day), administered in the only source of drinking water. \[R-143\]  

Note: Environmental and health conditions may affect the intake of water and the amount of medication consumed. \[R-143\]  

Administration of medication in food or water to animals with pneumonia or other infections can be affected by reduced feed and water intake. \[R-109\]  

Strength(s) usually available: \[R-58\]

U.S.—\[R-17\]  
- Veterinary-labeled products:  
  - 25 grams per pound of powder (OTC) [Aureomycin Soluble Powder].  
  - 64 grams per pound of powder (OTC) [AmTech Chlortetracycline HCL Soluble Powder; Aureomycin Soluble Powder Concentrate; CTC Soluble Powder Concentrate; Pennchlor 64 Soluble Powder].
CHLORTETRACYCLINE FOR MEDICATED FEED

Usual dose:

Calves—
Improved feed efficiency and increased weight gain for calves weighing up to 250 pounds: Oral, 0.22 mg per kg of body weight a day administered in the feed, fed as the only ration.[R-16; 152]
Improved feed efficiency and increased weight gain for calves weighing 250 to 400 pounds: Oral, 25 to 70 mg per animal a day administered in the feed, fed as the only ration.[R-16; 152]

Pigs—
Enteritis: Oral, 22 mg per kg of body weight a day, administered in the feed and fed as the only ration.[R-152]

Cattle—
Anaplasmosis (treatment): Cattle weighing < 700 pounds—Oral, 350 mg per animal a day, administered in the feed and fed as the only ration.[R-16; 152]
Cattle weighing ≥ 700 pounds—Oral 1.1 mg per kg of body weight a day, administered in the feed and fed as the only ration.[R-152]

Bacterial enteritis: Oral, 22 mg per kg of body weight a day, administered in the feed and fed as the only ration.[R-152]

Bacterial pneumonia (control): Oral, 350 mg per animal a day administered in the feed, fed as the only ration.[R-16; 152]

Improved feed efficiency and increased rate of weight gain: Oral, 22 mg per kg of body weight a day, administered in the feed and fed as the only ration.[R-152]

Pododermatitis (prophylaxis): Oral, 0.22 mg per kg of body weight a day or 70 mg per animal a day, administered in the feed and fed as the only ration.[R-116]

Note: Canadian product labeling lists a dose in the treatment of vibriolic abortion: Oral, 400 grams per ton of feed, fed as the only ration.[R-152]

Ducks: Fowl cholera: Oral, 200 to 400 grams per ton of feed (approximately 17.6 to 61.6 mg per kg of body weight a day) administered in the feed, fed as the only ration.[R-16; 152]

Pigs—
Cervical abscesses (prophylaxis): Oral, 50 to 100 grams per ton of feed, fed as the only ration.[R-115]

Bacterial enteritis or bacterial pneumonia: Oral, 22 mg per kg of body weight a day, administered in the only ration.[R-152]

Improved feed efficiency and increased rate of weight gain: Oral, 10 to 50 grams per ton of feed, fed as the only ration.[R-152]

For reducing the shedding of leptospirosis and the incidence of associated abortion: Oral, 400 grams per ton of feed, fed as the only ration for fourteen days.[R-152]

Note: Canadian product labeling lists a dose in the treatment of enteritis and for increasing feed efficiency and improving weight gain of 50 to 100 grams per ton of feed (55 to 110 grams per metric ton [1000 kg] of feed), fed as the only ration.[R-116]

Sheep—

Vibrionic abortion (prophylaxis): Oral, 80 mg per animal a day administered in the feed, fed as the only ration continuously during pregnancy.[R-16; 152]

Sheep, growing: Improved feed efficiency and increased rate of weight gain: Oral, 20 to 50 grams per ton of feed, fed as the only ration.[R-16]

Note: Product labeling with the above withdrawal times states that they apply when cattle and pigs are treated for a maximum of five days and chickens and turkeys are treated for a maximum of fourteen days. Not labeled for use in laying hens, preruminating calves, or lactating dairy cattle.

Note: USP requirements: Preserve in tight containers, protected from light. Label it to indicate that it is intended for oral veterinary use only. Contains the labeled amount, within –10% to +25%. Meets the requirement for Loss on drying (not more than 2.0%).[R-128]

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from light.

Preparation of dosage form: Fresh solutions should be prepared every 24 hours. When administered in a galvanized waterer, fresh solutions should be prepared every 12 hours.

Incompatibilities: Administration 1 hour before or 2 hours after giving milk or milk replacers is recommended. Chlortetracycline hydrochloride soluble powder should not be mixed with milk replacers.

USP requirements: Preserve in tight containers, protected from light. Label it to indicate that it is intended for oral veterinary use only. Contains the labeled amount, within –10% to +25%. Meets the requirement for Loss on drying (not more than 2.0%).[R-128]

Note: Product labeling with the above withdrawal times states that they apply when cattle and pigs are treated for a maximum of five days and chickens and turkeys are treated for a maximum of fourteen days. Not labeled for use in laying hens, preruminating calves, or lactating dairy cattle.

Note: USP requirements: Preserve in tight containers, protected from light. Label it to indicate that it is intended for oral veterinary use only. Contains the labeled amount, within –10% to +25%. Meets the requirement for Loss on drying (not more than 2.0%).[R-128]

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from light.

Preparation of dosage form: Fresh solutions should be prepared every 24 hours. When administered in a galvanized waterer, fresh solutions should be prepared every 12 hours.

Incompatibilities: Administration 1 hour before or 2 hours after giving milk or milk replacers is recommended. Chlortetracycline hydrochloride soluble powder should not be mixed with milk replacers.

USP requirements: Preserve in tight containers, protected from light. Label it to indicate that it is intended for oral veterinary use only. Contains the labeled amount, within –10% to +25%. Meets the requirement for Loss on drying (not more than 2.0%).[R-128]

Note: Product labeling with the above withdrawal times states that they apply when cattle and pigs are treated for a maximum of five days and chickens and turkeys are treated for a maximum of fourteen days. Not labeled for use in laying hens, preruminating calves, or lactating dairy cattle.

Note: USP requirements: Preserve in tight containers, protected from light. Label it to indicate that it is intended for oral veterinary use only. Contains the labeled amount, within –10% to +25%. Meets the requirement for Loss on drying (not more than 2.0%).[R-128]
Turkeys—

Bacterial enteritis: Oral, 55 mg per kg of body weight a day, administered in the only ration \(^{[R-16; 152]}\).

Note: Canadian product labeling lists a dose in the treatment of enteritis of 100 to 200 grams per ton of feed (110 to 220 grams per metric ton [1000 kg] of feed), fed as the only ration \(^{[R-116]}\).

Hexamitiasis \(^3\): Oral, 400 grams per ton of feed, fed as the only ration \(^{[R-16; 152]}\).

Synovitis \(^1\): Oral, 200 grams per ton of feed, fed as the only ration \(^{[R-16; 152]}\).

[Increased egg production; or sinusitis (prophylaxis): Oral, 100 to 200 grams per ton of feed (110 to 220 grams per metric ton [1000 kg] of feed), fed as the only ration.]

Turkeys, growing, less than 4 weeks of age—Paratyphoid \(^1\): Oral, 400 grams per ton of feed, fed as the only ration \(^{[R-115]}\).

Turkeys, growing—Improved efficiency or; increased rate of weight gain: Oral 10 to 50 grams per ton of feed, fed as the only ration \(^{[R-16; 152]}\).

[Lambs]:—Enterotoxemia: Oral, 20 grams per ton of feed (22 grams per metric ton [1000 kg] of feed), fed as the only ration.

Note: Environmental and health conditions may affect the intake of water and the amount of medication consumed. \(^{[R-17]}\)

Administration of medication in food or water to animals with pneumonia or other infections can be affected by reduced feed and water intake \(^{[R-109]}\).

Strength(s) usually available \(^{[R-58]}\):

U.S.—

Veterinary-labeled products:

110 grams per kg of premix (OTC) [Aureomycin 50 Granular; ChlorMax 50; CTC 50; Pennchlor 50G; Pennchlor 50 Meal].

154 grams per kg of premix (OTC) [Pennchlor 70 Meal].

198 grams per kg of premix (OTC) [Aureomycin 90 Granular; Pennchlor 90G].

220 grams per kg of premix (OTC) [Aureomycin 100 Granular; CLTC 100 MR; Pennchlor 100 Hi-Flot Meal; Pennchlor 100MR].

Canada—

Veterinary-labeled products:

110 grams per kg of premix (OTC) [Aureomycin 110G; Chlor 50; Chlorsol-50].

220 grams per kg of premix (OTC) [Aureomycin 220G; Chlor 100].

Withdrawal times \(^{[R-58]}\):

Note: With chlortetracycline oral premix, withdrawal times vary greatly from product to product and may differ from those listed below.

See also individual manufacturer’s labeling.

U.S.—\(^{[R-123]}\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, cattle</td>
<td>0, 1, or 2, depending on product and dose</td>
<td>Chickens</td>
<td>0 or 1, depending on product and dose</td>
</tr>
<tr>
<td>Pigs, sheep, turkeys</td>
<td>0</td>
<td></td>
<td>0 for some products</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply when the product is fed to calves at a dose of up to 70 mg per animal per day, and to cattle at a dose of 350 mg per animal per day or 1.1 mg per kg of body weight a day in feed, to chickens at 500 grams or more per ton of feed for a maximum of five days, to pigs at 400 grams or less per ton of feed or 22 mg per kg of body weight a day for up to fourteen days, and to sheep when fed 80 mg per animal per day or 20 to 50 grams per ton of feed.

Note: Not labeled for use in lactating dairy cows. \(^{[R-16]}\)

Some products are not labeled for use in chickens, ducks, or turkeys producing eggs for human consumption. \(^{[R-152]}\)

When fed at 22 mg per kg of body weight a day:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves, cattle</td>
<td>0 or 10, depending on product</td>
</tr>
<tr>
<td>Chickens, pigs, turkeys</td>
<td>7</td>
</tr>
<tr>
<td>Lambs</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply when the product is fed to chickens and turkeys at 55 to 220 mg per kg of feed, to pigs at 55 to 110 mg per kg of feed, to calves at 55 mg per kg of feed, to lambs at 22 mg per kg of feed, and to cattle at 0.22 mg per kg of body weight or 70 mg per animal.

Note: Not labeled for use in lactating dairy cows. \(^{[R-16]}\)

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

USP requirements: Not in USP.

\(^{1}\)Not included in Canadian product labeling or product not commercially available in Canada.

**DOXYCYCLINE**

**SUMMARY OF DIFFERENCES**

Pharmacology/pharmacokinetics: More completely absorbed from the gastrointestinal tract than the tetracyclines developed earlier and absorption is less likely to be affected by food or calcium or other divalent or trivalent metals. Doxycycline is also more lipid-soluble than other tetracyclines. In dogs, doxycycline is eliminated primarily through intestinal excretion. \(^{[R-6; 34]}\)

Precautions: Medical considerations—Doxycycline is only partially eliminated renally and is less likely to accumulate in animals with renal function impairment; it can be used without dosage adjustment.

Side/adverse effects: Horses—Intravenous administration can lead to cardiovascular dysfunction and death. \(^{[R-34]}\)
ORAL DOSAGE FORMS
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

Stability: After reconstitution, suspensions retain their potency for 14 days at room temperature.

DOXYCYCLINE FOR ORAL SUSPENSION USP

Usual dose: [Rocky Mountain spotted fever][1—Dogs: Oral, 5 mg per kg of body weight every twelve hours for fourteen days. Note: [Cats][2—Although the efficacy has not been established, an oral dose of 5 mg per kg of body weight every twelve hours for twenty-one days has been used in the treatment of feline infectious anemia[R-147; 151]. For chlamydial infections or respiratory infections in cats, a dose of 5 mg per kg of body weight every twelve hours or 10 mg per kg of body weight every twenty-four hours has been used[R-151].

[Dogs][3—Although the efficacy has not been established, an oral dose of 10 mg per kg of body weight every twelve hours for two to three weeks has been used for the treatment of ehrlichiosis; this regimen is based on a clinical trial that found, however, that only two out of five dogs treated with the above dose and a twenty-four-hour dosing interval for one week were cleared of Ehrlichia canis, as shown by negative blood and tissue cultures[R-40]. A dose of 5 mg per kg of body weight every twelve hours for six to eight weeks has been used in the treatment of ehrlichiosis to decrease the risk of side effects[R-176], however, the efficacy of this regimen has not been confirmed. Retesting serum immunofluorescent antibody for E. canis two months posttreatment is recommended, and retreatment should be started if values have not dropped significantly.[R-40]

Strength(s) usually available:

U.S.—

Veterinary-labeled products:
Not commercially available.

Human-labeled products:
5 mg (base) per mL when reconstituted according to manufacturer’s instructions (Rx) [Vibramycin].

Canada—

Veterinary-labeled products:
Not commercially available.

Human-labeled products:
Not commercially available.

Packaging and storage: Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

Stability: After reconstitution, suspensions retain their potency for 14 days at room temperature.

Auxiliary labeling:
• Shake well.

USP requirements: Preserve in tight, light-resistant containers. Contains one or more suitable buffers, colors, diluents, flavors, and preservatives. Contains the labeled amount, within –10% to +25% when constituted as directed. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume, pH (5.0–6.5, in the suspension constituted as directed in the labeling), and Water (not more than 3.0%).[R-128]

DOXYCYCLINE CALCIUM ORAL SUSPENSION USP

Usual dose: See Doxycycline for Oral Suspension USP.

Strength(s) usually available:

U.S.—

Veterinary-labeled products:
Not commercially available.

Human-labeled products:
10 mg (base) per mL (Rx) [Vibramycin].

Canada—

Veterinary-labeled products:
Not commercially available.

Human-labeled products:
Not commercially available.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container. Protect from freezing.

Auxiliary labeling:
• Shake well.

USP requirements: Preserve in tight, light-resistant containers. Prepared from Doxycycline Hyclate, and contains one or more suitable buffers, colors, diluents, flavors, and preservatives. Contains an amount of doxycycline calcium equivalent to the labeled amount of doxycycline, within –10% to +25%. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume, and pH (6.5–8.0).[R-128]

DOXYCYCLINE HYCLATE CAPSULES USP

Usual dose: See Doxycycline for Oral Suspension USP.

Strength(s) usually available:

U.S.—[R-115]

Veterinary-labeled products:
Not commercially available.

Human-labeled products:
50 mg (base) (Rx) [Vibramycin; generic],
100 mg (base) (Rx) [Vibramycin; generic].

Canada—

Veterinary-labeled products:
Not commercially available.

Human-labeled products:
100 mg (base) (Rx) [Alti-Doxycycline; Apo-Doxy; Doxycin; Doxytec (lactose); Novo-Doxycycline; Nu-Doxycycline; Vibramycin].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

USP requirements: Preserve in tight, light-resistant containers. Contains one or more suitable buffers, colors, diluents, flavors, and preservatives. Contains the labeled amount, within –10% to +20%. Meets the requirements for Identification, Dissolution (80% in 30 minutes in water in
Apparatus 2 at 75 rpm), Uniformity of dosage units, and Water (not more than 8.5%).

**DOXYCYCLINE HYCLATE DELAYED-RELEASE CAPSULES USP**

Note: Delayed-release capsules must be swallowed whole and, in general, absorption of delayed-release dosage forms is unpredictable in animals. Doxycycline Hyclate Delayed-release Capsules USP are not recommended for use in animals.

**Strength(s) usually available:**

U.S.—

Veterinary-labeled products:

Not commercially available.

Human-labeled products:

100 mg (base) (Rx) [Doryx (lactose)].

Canada—

Veterinary-labeled products:

Not commercially available.

Human-labeled products:

Not commercially available.

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

**USP requirements:** Preserve in tight, light-resistant containers. The label indicates that the contents of the Capsules are enteric-coated. Contain an amount of doxycycline hyclate equivalent to the labeled amount of doxycycline, within –10% to +20%. Meet the requirements for Identification, Dissolution (85% in 90 minutes in water in Apparatus 2 at 75 rpm), Uniformity of dosage units, and Water (not more than 5.0%).

Not included in Canadian product labeling or product not commercially available in Canada.

**PARENTERAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S. The dosing and strengths of the dosage forms available are expressed in terms of doxycycline base (not the hyclate salt).

**DOXYCYCLINE FOR INJECTION USP**

**Usual dose:**

Note: [Docts]—Although the efficacy has not been established, an intravenous dose of 3 to 5 mg (base) per kg of body weight every twelve hours has been used in the treatment of susceptible bacterial infections.

This dose is based on pharmacokinetic studies.

**Size(s) usually available:**

U.S.—

Veterinary-labeled products:

Not commercially available.

Human-labeled products:

100 mg (base) (Rx) [Vibramycin].

200 mg (base) (Rx) [Vibramycin].

Canada—

Veterinary-labeled products:

Not commercially available.

Human-labeled products:

Not commercially available.

**Packaging and storage:** Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light.

**Preparation of dosage form:** To prepare initial dilution for intravenous use, 10 mL of sterile water for injection or other suitable diluent (see manufacturer’s package insert) should be added to each 100-mg vial or 20 mL of diluent should be added to each 200-mg vial. The resulting solution containing the equivalent of 100 to 200 mg of doxycycline may be further diluted in 100 to 1000 mL or in 200 to 2000 mL of suitable diluent, respectively.

**Stability:**

After reconstitution, intravenous infusions of doxycycline hyclate retain their potency for twelve hours at room temperature or for seventy-two hours if refrigerated at concentrations of 100 mcg (0.1 mg) to 1 mg per mL in suitable fluids (see manufacturer’s package insert). Intravenous infusions of doxycycline hyclate retain their potency for six
hours at room temperature at concentrations of 100 mcg (0.1 mg) to 1 mg per mL in lactated Ringer’s injection or 5% dextrose and lactated Ringer’s injection. Infusions must be protected from direct sunlight during administration.

If frozen immediately after reconstitution with sterile water for injection, solutions at concentrations of 10 mg per mL retain their potency for up to eight weeks at –20 °C (–4 °F). Once thawed, solutions should not be refrozen.

**Additional information:**
Concentrations of less than 100 mcg (0.1 mg) per mL or greater than 1 mg per mL are not recommended.

Infusions may be administered over a one- to four-hour period. Rapid administration should be avoided.

**USP requirements:**
Preserve in Containers for Sterile Solids, protected from light. Contains an amount of doxycycline hyclate equivalent to the labeled amount of doxycycline, within –10% to +20%. Meets the requirements for Constituted solution, Identification, Bacterial endotoxins, Sterility, pH (1.8–3.3, in the solution constituted as directed in the labeling), Loss on drying (not more than 4.0%), and Particulate matter.[R-128]

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**OXYTETRACYCLINE**

**ADDITIONAL DOSING INFORMATION**
When possible, oral oxytetracycline should be administered 1 hour before or 2 hours after milk replacer.[R-1]

**MUCOSAL DOSAGE FORMS**
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**OXYTETRACYCLINE HYDROCHLORIDE UTERINE SUSPENSION**

**Usual dose:**
Note: [Cows]—Although the efficacy and safety are not currently established, an intrauterine dose of 3.9 to 4.4 mg per kg of body weight, administered as a single dose[R-12], is included in Canadian product labeling for the treatment of uterine infections.

**Strength(s) usually available[R-58],[R-59]:**
U.S.—
Veterinary-labeled products:
Not commercially available.
Canada—[R-12]
Veterinary-labeled products:
50 mg per mL (Rx) [Kelamycin].

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### Withdrawal times:

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows</td>
<td>18</td>
<td>24</td>
</tr>
</tbody>
</table>

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

**Preparation of dosage form:** Warm to body temperature to ease administration.[R-12]

**Stability:** Preparation may darken on standing, but the potency remains unaffected.[R-12]

**USP requirements:** Not in USP.

**ORAL DOSAGE FORMS**
Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**OXYTETRACYCLINE HYDROCHLORIDE SOLUBLE POWDER USP**

**Usual dose:**

**Bees**—American and European foul brood: Oral, 200 mg per colony once every four to five days for three treatments in the spring and/or fall. Powder is dusted on the outer parts of the frames or mixed as a syrup and fed in feeder pails or in the combs.[R-6; 61; 134]

Note: Honey from infected colonies should not be used for the preparation of medicated syrup.

**Calves and cattle**—
Bacterial enteritis: Oral, 22 mg per kg of body weight every twenty-four hours, administered in the only source of drinking water or as a drench.[R-61]

Bacterial pneumonia¹: Oral, 22 mg per kg of body weight every twenty-four hours, administered in the only source of drinking water or as a drench.[R-61]

**Chickens**—
Chronic respiratory disease; or fowl cholera: Oral, 400 to 800 mg per gallon of water (approximately 22 to 59 mg per kg of body weight a day), administered as the only source of drinking water.[R-11]

Synovitis¹: Oral, 200 to 400 mg per gallon of water, administered as the only source of drinking water.[R-11; 13; 61]

[Bacterial enteritis]: Oral, 200 to 400 mg per gallon of water, administered as the only source of drinking water.[R-6; 13]

**Pigs**—
Bacterial enteritis: Oral, 22 mg per kg of body weight, administered in the only source of drinking water.[R-11; 13; 61]

Bacterial pneumonia: Oral, 22 mg per kg of body weight, administered in the only source of drinking water.[R-6; 13]

¹Not included in Canadian product labeling or product not commercially available in Canada.
Leptospirosis: Oral, 22 mg per kg of body weight, administered in the only source of drinking water.

Sheep—
Bacterial enteritis: Oral, 22 mg per kg of body weight every twenty-four hours, administered in the only source of drinking water.

Bacterial pneumonia: Oral, 22 mg per kg of body weight every twenty-four hours, administered in the only source of drinking water.

Turkeys, growing—Bacterial enteritis: Oral, 55 mg per kg of body weight a day for seven to fourteen days.

Notes:
- The withdrawal times for oxytetracycline soluble powder vary greatly from product to product and may differ from those listed below.
- See also individual manufacturer labeling.
- Bees: To avoid contamination of honey, oxytetracycline hydrochloride soluble powder should be fed early in the spring or fall before the main honey flow begins. Honey stored during treatment should be removed following last medication and cannot be used for human food.

Strength(s) usually available:

U.S.—
Veterinary-labeled products:
- 25 grams per pound of powder (OTC) [AmTech Oxytetracycline HCL Soluble Powder; Terramycin Soluble Powder; Terra-Vet Soluble Powder].
- 166 grams per pound of powder (OTC) [Oxytetr Soluble; Tetravet-CA; Tetryx HCA Soluble Powder].
- 343 grams per pound of powder (OTC) [Agrimycyn-343; AmTech Oxytetracycline HCL Soluble Powder-343; Oxytet-343 Water Soluble Powder; Pennox 343 Soluble Powder; Terramycin-343 Soluble Powder; Terra-Vet Soluble Powder 343; GENERIC].

Canada—
Veterinary-labeled products:
- 11 mg per gram of powder (OTC) [Foul Brood Mix].
- 55 mg per gram of powder (OTC) [Oxytetr-A; Oxytetr-25-S].
- 62.5 mg per gram of powder (OTC) [Oxysol-62.5; Oxytet-SP].
- 220 mg per gram of powder (OTC) [Oxy Tetra Forte].
- 250 mg per gram of powder (OTC) [Oxy 250; Oxysol-250; Oxytet-250 Concentrate].
- 1 gram per gram of powder (OTC) [Oxy 1000; Oxysol-1000].

Note:
The above withdrawal times states that treatment of calves, cattle, pigs, and sheep should be for a maximum of five days and chickens and turkeys for a maximum of fourteen days. Not labeled for use in lactating dairy cattle, preruminating calves, or birds producing eggs for human consumption.

Note:
The above withdrawal times states that they apply to doses of 5 to 10 mg per kg of body weight every twelve hours for three to five days for calves, 10 mg per kg of body weight every twelve hours for three or four days for pigs, 50 mg per L of drinking water for three or four days for chickens and turkeys, and 5 mg per kg of body weight every twelve hours for three or four days for sheep. These products are not labeled for use in lactating dairy cattle or birds producing eggs for human consumption.

**Preparation of dosage form:**
Oxytetracycline soluble powder can be mixed with water and administered as a drench. Fresh drinking water and drench solutions should be prepared daily as recommended by the manufacturer.

**Stability:** Stable for twenty-four hours.

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Note: Environmental and health conditions may affect the intake of water and the amount of medication consumed. Administration of medication by food or water to animals with pneumonia or other infections can be affected by reduced feed and water intake.

**Withdrawal times:**

Note: With oxytetracycline soluble powder, withdrawal times vary greatly from product to product and may differ from those listed below. See also individual manufacturer labeling.

Bees: To avoid contamination of honey, oxytetracycline hydrochloride soluble powder should be fed early in the spring or fall before the main honey flow begins. Honey stored during treatment should be removed following last medication and cannot be used for human food.

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.
**Incompatibilities:** Milk replacer—Oxytetracycline is bound to milk replacer at a rate of 63%; this is a binding that is not readily reversible. Administration of oral oxytetracycline in milk replacer will result in lower bioavailability.

**USP requirements:** Preserve in well-closed containers. A mixture of Oxytetracycline Hydrochloride and one or more suitable excipients. Label it to indicate that it is for oral veterinary use only. Contains the labeled amount, within ±10%. Meets the requirements for Identification, pH (1.5–3.0, in the solution obtained as directed in the labeling). Loss on drying (not more than 3.0%, and Minimum fill [R-128].

**OXYTETRACYCLINE FOR MEDICATED FEED**

**Usual dose:**

**Bees,** honey—Foul brood: Oral, 200 mg per colony of bees every four to five days in the spring and/or fall [R-117]. Powder is dusted on the outer parts of the frames or mixed as a syrup and fed in feeder pails or in the combs [R-117].

Note: Honey from infected colonies should not be used for the preparation of medicated syrup [R-117].

**Calves**—

Bacterial enteritis: Oral, 22 mg per kg of body weight a day [R-117].

Note: Canadian labeling lists a dose of 50 grams per ton (55 grams per metric ton [1000 kg]) in the treatment of bacterial enteritis [R-26].

Improved feed efficiency 1; or increased weight gain 1 in calves weighing less than 113.6 kg (250 to 400 pounds): Oral 0.11 to 0.22 mg per kg of body weight a day, administered in the feed and fed as the only ration [R-117].

Improved feed efficiency 1; or increased weight gain 1 in calves weighing 113 to 181 kg (250 to 400 pounds): Oral, 25 mg per animal a day, administered in the feed and fed as the only ration [R-117].

Note: According to product labeling, when administered in milk replacer, the 22 mg per kg of body weight dose is indicated in the treatment of bacterial enteritis only [R-117].

**Catfish** 1—Hemorrhagic septicaemia; or pseudomonas disease: Oral 55 to 82.5 mg per kg of body weight a day for a maximum of ten days, administered in the feed and fed as the only ration [R-27].

**Cattle**—

Bacterial enteritis 1: Oral, 22 mg per kg of body weight a day [R-117].

Bacterial pneumonia, acute (prophylaxis and treatment) 1: Oral, 500 to 2000 mg (2 grams) per animal a day, administered in the feed and fed as the only ration for three to five days prior to shipping and three to five days after shipping [R-122; 117].

Bacterial pneumonia (treatment) 1: Oral, 22 mg per kg of body weight a day, administered in feed and fed as the only ration for seven to fourteen days [R-117].

Improved feed efficiency 1; or increased weight gain 1, in growing cattle weighing over 400 pounds: Oral, 75 mg per animal a day, administered in the feed and fed as the only ration [R-117].

[Bloat]—Oral, 75 mg per animal a day, administered in the feed and fed as the only ration [R-26].

**Chickens**—

Chronic respiratory disease, specifically air sacculitis, reduction in associated mortality 1: Oral, 500 grams per ton of feed, fed as the only ration [R-117].

Chronic respiratory disease (control): Oral, 400 grams per ton of feed, fed as the only ration [R-117].

Note: Canadian labeling lists a dose of 100 grams per ton (110 grams per metric ton [1000 kg]) in the treatment of chronic respiratory disease [R-26].

Fowl cholera 1; or synovitis: Oral, 100 to 200 grams per ton of feed, fed as the only ration [R-117].

Improved feed efficiency 1 and increased weight gain 1: Oral, 10 to 50 grams per ton of feed, fed as the only ration [R-117].

**Lobsters**—Gaffkemia: Oral, 2.2 grams per kg of feed, fed as the only ration [R-27; 124].

**Pigs**—

Bacterial enteritis: Oral, 22 mg per kg of body weight a day, administered in the feed and fed as the only ration [R-117].

Note: Canadian labeling lists a dose of 100 grams per ton (110 grams per metric ton [1000 kg]) in the treatment of bacterial enteritis [R-26].

Improved feed efficiency 1 and increased weight gain 1: Oral, 10 to 50 grams per ton of feed, fed as the only ration [R-117].

For reducing the shedding of leptospirosis and reducing the incidence of associated abortions: Oral, 22 mg per kg of body weight per animal a day, administered in the feed and fed as the only ration [R-117].

Note: Canadian labeling lists a dose of 500 grams per ton (550 grams per metric ton [1000 kg]) in the treatment of leptospirosis [R-26].

Improved feed efficiency and increased weight gain 1: Oral, 10 to 50 grams per ton of feed, fed as the only ration [R-117].

[Atrophic rhinitis]: Oral, 50 grams per ton (55 grams per metric ton [1000 kg]) of feed, fed as the only ration [R-26].

Note: Different feeding regimens will result in differences in actual mg of oxytetracycline per kg of body weight consumed by individual pigs [R-117].

Therapeutic serum concentrations of > 0.5 mcg/mL were not produced when 550 mg of oxytetracycline per kg of feed was administered to 30-kg pigs in one study [R-107].

An oral dose of 54 to 108 mg per kg of body weight a day (concentrations of 1600 and 2400 mg of oxytetracycline per kg of feed) was reported to be required to produce 1 mcg per mL serum concentrations in pigs [R-110].

Salmon, Pacific 1—Marking of skeletal tissue: Oral, 250 mg per kg of body weight a day [R-27].

**Salmonids**—[Cold water disease]; [columnaris disease]; [enteric red- mouth disease]; furunculosis; hemorrhagic septicaemia 1; pseudomonas disease 1; or ulcer disease: Oral, 55 to 82.5 mg per kg of body weight a day, administered in the feed and fed as the only ration [R-27; 124].

**Sheep** 1—

Bacterial enteritis; or bacterial pneumonia: Oral 22 mg per kg of body weight per animal a day, administered in the feed and fed as the only ration [R-117].

**Turkeys**—

Bacterial enteritis (bluecomb): Oral, 55 mg per kg of body weight a day, administered in the feed and fed as the only ration [R-117].

Note: Canadian labeling lists a dose of 100 grams per ton (110 grams per metric ton [1000 kg]) of feed, fed as the only ration [R-26].

Hexamitiasis 1: Oral, 100 grams per ton of feed, fed as the only ration [R-117].
Improved feed efficiency\(^1\) and increased weight gain\(^1\): Oral, 10 to 50 grams per ton of feed, fed as the only ration\[^R-117\].

Synovitis: Oral, 200 grams per ton of feed, fed as the only ration\[^R-26\].

[Sinusitis]: Oral, 100 grams per ton (110 grams per metric ton \([1000\ kg]\)) of feed, fed as the only ration\[^R-26\].

[Lambs—]

Bacterial enteritis: Oral, 100 grams per ton (110 grams per metric ton \([1000\ kg]\)) of feed, fed as the only ration\[^R-26\].

Enterotoxemia: Oral, 20 grams per ton (22 grams per metric ton \([1000\ kg]\)) of feed, fed as the only ration\[^R-26\].

Note: Environmental and health conditions may affect the intake of water and the amount of medication consumed\[^R-17\]. Administration of medication by food or water to animals with pneumonia or other infections can be affected by reduced feed and water intake\[^R-109\].

Strength(s) usually available\[^R-58\]:

U.S.—\[^R-62;\ 122\]

Veterinary-labeled products:

110 grams per kg of premix (OTC) \([OTC\ 50;\ OXTC\ 50;\ Pennox\ 50\ Meal;\ Terramycin\ 50]\).

220 grams per kg of premix (OTC) \([OTC\ 100;\ Pennox\ 100\ Hi-Flo\ Meal;\ Pennox\ 100-MR;\ Terramycin\ 100;\ Terramycin\ 100\ For\ Fish]\).

440 grams per kg of premix (OTC) \([OTC\ 200;\ Pennox\ 200\ Hi-Flo\ Meal;\ Terramycin\ 200]\).

Canada—\[^R-26;\ 55\]

Veterinary-labeled products:

110 grams per kg of premix (OTC) \([Oxy-110;\ Oxysol-110;\ Oxytetracycline\ 50;\ Terramycin-50]\).

220 grams per kg of premix (OTC) \([Oxy-220;\ Oxysol-220;\ Oxytetracycline\ 100;\ Terramycin-100]\).

440 grams per kg of premix (OTC) \([Oxy-440;\ Oxysol-440;\ Oxytetracycline\ 200;\ Terramycin-200;\ Terramycin-Aqua]\).

Withdrawal times\[^R-58\]:

Note: Bees—To avoid contamination of honey, oxytetracycline hydrochloride soluble powder should be fed early in the spring or fall before the main honey flow begins. Honey stored during therapy should be removed following the last medication and should not be used for human food\[^R-117\].

U.S.—\[^R-27;\ 186\]

When fed 500 grams per ton of feed:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If fed low-calcium feed</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Note: Not labeled for chickens producing eggs for human consumption\[^R-117\].

When fed up to 400 grams per ton of feed:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If fed low-calcium feed</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Note: Not labeled for chickens producing eggs for human consumption\[^R-117\].

When fed up to 200 grams per ton of feed:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkeys</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Not labeled for turkeys producing eggs for human consumption\[^R-117\].

When fed to turkeys at 200 grams or more per ton of feed, and to cattle, pigs, and sheep at 22 mg/kg:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bees</td>
<td>42 (honey)</td>
<td></td>
</tr>
<tr>
<td>Catfish</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Calves (same products), cattle, sheep, turkeys</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lobsters</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Pacific salmon</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Pigs</td>
<td>0 or 5, depending on product</td>
<td></td>
</tr>
<tr>
<td>Salmonids</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Note: Not labeled for poultry producing eggs for human consumption\[^R-117\]. A withdrawal time has not been established for preruminating calves for some products\[^R-117\].

Canada\[^R-26;\ 55\]

When fed to turkeys at 200 grams or more per ton of feed, and to cattle, pigs, and sheep at 22 mg/kg:

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
<th>Meat (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bees</td>
<td>28 (honey)</td>
<td></td>
</tr>
<tr>
<td>Calves</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Chickens, pigs, turkeys</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Lambs</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lobsters</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Salmonids, 10 °C or warmer</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Salmonids, below 10 °C</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

Note: Not labeled for poultry producing eggs for human consumption\[^R-117\]. Withdrawal time has not been established for preruminating calves\[^R-117\].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form: For use in dry feeds only, as indicated on manufacturer’s labeling. Should not be used without diluting\[^R-122\].

Incompatibilities: Salmonid and lobster feeds having a high ash content (calcium, copper, iron, or zinc) may bind oxytetracycline and prevent absorption. Oxytetracycline also should not be administered with feeds containing bentonite\[^R-124\].

Additional information: U.S.—For fish, this medication should not be used when water temperature is below 16.7 °C (62 °F) for catfish or below 9 °C (48.2 °F) for salmonids\[^R-62\].

USP requirements: Not in USP.
OXYTETRACYCLINE TABLETS USP

Usual dose:
Bacterial enteritis\(^1\); or
Bacterial pneumonia\(^1\)—Calves:
Control—Oral, 5.5 mg per kg of body weight every twelve hours.\(^{[R-2; 60]}\)
Treatment—Oral, 11 mg per kg of body weight every twelve hours for up to four days.\(^{[R-2; 60]}\)

Strength(s) usually available\(^{[R-58]}\):
U.S.—\(^{[R-2; 60]}\)
Veterinary-labeled products:
250 mg (OTC) [Terramycin Sours Tablets].
500 mg (OTC) [Oxy 500 Calf Bolus].
1000 mg (OTC) [Oxy 1000 Calf Bolus].

Canada—
Veterinary-labeled products:
Not commercially available.

Withdrawal times:
U.S.—\(^{[R-60]}\)

| Species | Withdrawal time |
|---------|----------------|----------------|
| Calves  | 0 or 7, depending on product |

Note: Product labeling with the above withdrawal time states that it applies when calves are treated for up to four days.
Products are not labeled for use in preruminating calves\(^{[R-58]}\).

USP requirements: Preserve in tight, light-resistant containers. Contain the labeled amount, within ±10% to ±20%. Meet the requirements for Identification, Dissolution (75% in 45 minutes in 0.1 N hydrochloric acid in Apparatus 1 at 100 rpm), Uniformity of dosage units, and Water (not more than 7.5%).\(^{[R-128]}\)

\(^1\)Not included in Canadian product labeling or product not commercially available in Canada.

PARENTERAL DOSAGE FORMS

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

OXYTETRACYCLINE INJECTION USP

Usual dose:
Cattle—Actinobacillosis\(^1\); [bacterial arthritis]; bacterial enteritis; [blackleg/malignant edema]; diphtheria\(^1\); [leptospirosis]; [mastitis]; [omphalophlebitis]; [peritonitis]; pneumonia and bovine respiratory disease complex; pododermatitis; skin and soft tissue infections\(^2\); or uterine infections: Intramuscular or intravenous, 6.6 to 11 mg per kg of body weight every twenty-four hours.\(^{[R-24; 121]}\)

Note: For uterine infections in cattle, an [intravenous dose of 11 mg per kg of body weight every twelve hours]\(^1\) has been recommended, based on distribution studies\(^{[R-104]}\). The shortened dosing interval will require an extended withdrawal time\(^{[R-14]}\).

For pneumonia caused by Pasteurella, an [intravenous dose of 11 mg per kg of body weight every twelve hours]\(^1\) has been recommended, based on pharmacokinetic changes in calves with induced pneumonia\(^{[R-106]}\); however, this regimen is usually reserved for serious cases. The shortened dosing interval will require an extended withdrawal time\(^{[R-14]}\).

For [thromboembolic meningoencephalitis]\(^1\), a dose of 11 mg per kg of body weight every twenty-four hours has been recommended; however, there are no specific research data to support the efficacy of this use\(^{[R-178; 179]}\).

[Pigs]—Bacterial enteritis; bacterial pneumonia; erysipelas; leptospirosis; mastitis; or uterine infections: Intramuscular or intravenous, 6.6 to 11 mg per kg of body weight every twenty-four hours.\(^{[R-10]}\)

Note: No more than 10 mL should be injected per site in adult cattle and no more than 5 mL per site in pigs. Less mature animals should have decreasing volumes injected per site (but not total mg per kg of body weight) so that small animals receive 0.5 to 2 mL per injection site. Intramuscularly administered oxytetracycline should be injected slowly.\(^{[R-21]}\) Intramuscularly administered oxytetracycline causes a notable tissue reaction (see note on slaughtertrim below under Withdrawal times).

[Horses]—Ehrlichiosis (Ehrlichiosis equi); or Potomac horse fever (Ehrlichiosis risticii): Intravenous, 10 mg per kg of body weight every twenty-four hours.\(^{[R-46; 48; 92; 138]}\)

Note: Gastrointestinal side effects are possible following oxytetracycline administration to horses.

The above dose is based on clinical trials and retrospective dose-response studies.

[Foals]—Although the efficacy and safety have not been established, a single intravenous dose of 44 mg of oxytetracycline per kg of body weight has been used in the treatment of flexural limb deformities in newborn foals, based on controlled studies in healthy foals\(^{[R-157; 158]}\). The dose is most often administered as a single intravenous dose of 2 to 3 grams per foal\(^{[R-158]}\) or as an intravenous dose of 1.5 grams per foal, repeated in twenty-four hours. In some cases, clinicians have repeated an initial 2- to 3-gram dose twenty-four hours following the initial dose.\(^{[R-20; 157]}\)

Studies have demonstrated the safety, including lack of renal toxicity, of doses of up to 54.5 to 75 mg per kg of body weight, administered two times, twenty-four hours apart, to twenty newborn foals\(^{[R-20; 158]}\); however, because high doses of oxytetracyclines have been associated with renal toxicity in many species\(^{[R-15]}\), some clinicians prefer to test renal function before treatment. It is recommended that this high dose of oxytetracycline not be administered to foals with any systemic illness or disorder predisposing to renal compromise, including dehydration or endotoxemia.

[Sheep]—Bacterial arthritis; bacterial pneumonia; mastitis; or uterine infections: Intramuscular or intravenous, 6.6 mg per kg of body weight every twenty-four hours\(^{[R-24; 121]}\).

Strength(s) usually available\(^{[R-58]}\):
U.S.—
Veterinary-labeled products:
100 mg per mL (OTC) [Agrimycin 100; AnTech Maxim-100; Duramycin 100; Oxybiotic-100; Oxytetracycline 100; Oxy-Mycin 100; Pramycin 100; Terra-Vet 100; Tetroxy-100].

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Stability:
Diluted medication should be used or discarded immediately.

Withdrawal times:

```markdown
<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>18, 19, 20, or 22, depending on product</td>
</tr>
<tr>
<td>Pigs, sheep</td>
<td>18</td>
</tr>
</tbody>
</table>
```

Note: Product labeling listing the above withdrawal times states that they apply to a dose of 6.6 to 11 mg per kg of body weight a day in cattle for a maximum of four days. Not labeled for use in lactating cattle or preruminating calves. Cattle slaughtered within 20 days of intramuscular administration of oxytetracycline may require trimming of the injection sites and surrounding tissues during dressing procedure.

Packaging and storage:
Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

Preparation of dosage form:
For intravenous administration, dilution in water for injection or physiological saline is recommended. Doses of up to 2500 mg (50 mL) can be diluted in 250 mL of diluent, and larger doses in 500 mL of diluent.

Stability:
Diluted medication should be used or discarded immediately after mixing. Solution may darken on standing but this color change does not affect the potency of the medication.

USP requirements:
Preserve in single-dose or in multiple-dose containers, protected from light. A sterile solution of Oxytetracycline with or without one or more suitable anesthetics, antioxidants, buffers, complexing agents, preservatives, and solvents. Contains the labeled amount, within −10% to +20%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, and pH (8.0–9.0).

OXYTETRACYCLINE INJECTION USP (LONG-ACTING)

Note: The formulations listed below have a viscosity excipient intended to prolong therapeutic serum antibiotic concentrations. These products are believed to differ from other oxytetracycline injection products only in the rate of absorption from intramuscular injection; moreover, some studies using oxytetracycline products with 2-pyrrolidone viscosity excipient have failed to show that the duration of action is significantly prolonged over that of the conventional formulation after intramuscular injection, when they are administered at the same dose. As such, use of the long-acting formulations at standard doses of 6 to 11 mg per kg of body weight may not result in a prolonged duration of action. Also, there is no difference in duration of action between conventional and long-acting formulations when they are administered intravenously.

Usual dose:
**Cattle**—Actinobacillosis; bacterial enteritis; bacterial pneumonia and bovine respiratory disease complex; diphtheria; keratoconjunctivitis; leptospirosis; metritis, acute; pododermatitis; or skin and soft tissue infections. Intramuscular, intravenous, or, when labeled, subcutaneous. 6.6 to 11 mg per kg of body weight every twenty-four hours for four days.

Note: When it is impractical to give cattle more than a single dose for the treatment of keratoconjunctivitis or pneumonia, an intramuscular or, when labeled, subcutaneous dose of 20 mg per kg of body weight administered as a single dose is recommended. In calves, [40 mg per kg of body weight as a single dose] has been used in the treatment of *bacterial pneumonia* that is unresponsive to 20 mg per kg of body weight, based on pharmacokinetic and toxicity data; however, the clinical efficacy was not established in this study. This higher dose should not be repeated because of the risk of adverse effects.

For [thromboembolic meningoencephalitis] in cattle, a dose of 11 mg per kg of body weight every twenty-four hours has been recommended; however, there are no specific research data to support the efficacy of this use.

**Pigs**—Bacterial enteritis; bacterial pneumonia; or leptospirosis. Intramuscular. 6.6 to 11 mg per kg of body weight every twenty-four hours for four days.

Note: When it is impractical to give pigs more than a single dose for the treatment of pneumonia, an intramuscular dose of 20 mg per kg of body weight administered as a single dose is recommended. In sows—Bacterial enteritis in suckling pigs: Intramuscular, 6.6 mg per kg of body weight, administered once eight hours before farrowing or immediately after farrowing.

Note: No more than 10 mL should be administered intramuscularly at any one site in adult cattle. No more than 5 mL should be injected intramuscularly at any one site in adult pigs. Injections should be administered deep into the fleshy part of the muscle. Less mature animals should have size-dependent decreasing volumes injected per site so that small calves receive only 1 to 2 mL per injection site.

Strength(s) usually available:

Vaccines:

- **Nature** (USP) [Agrimycin 200; AniTech Maxim-200; Biomycin 200; Duramycin 72-200; Geomyxin 200; Liqamycin LA-200; Maxim-200; OT 200; OxyBiotic-200; Oxyfur 200; Oxy-Mycin 200; Oxyshot LA; Pennox 200 Injectable].

Note: The above products contain the following viscosity excipients: Biomycin 200 contains polyethylene glycol; Duramycin 72-200, Liqamycin LA-200, Maxim-200; and Pennox 200 contain 2-pyrrolidone; and Oxyshot LA contains N-methylpyrrolidone.

Veterinary-labeled products:

- **OxyLA** [Alamycin LA; Biomycin 200; Liqamycin LA-200; Oxy LA; Oxygeneine LA; Oxyvet 200 LA; Tetraject LA].

300 mg per mL (OTC) [Tetradure LA 300].
Withdrawal times\(^{R-58}\):

**U.S.—\(^{R-3; 5; 45; 153}\)**

Note: If oxytetracycline injection is administered to calves as a single intramuscular dose of 40 mg per kg of body weight, there is some evidence to suggest that a withdrawal time of 49 days would be sufficient to avoid residues, based on tissue depletion studies of the parent drug.\(^{R-101}\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Pigs</td>
<td>28 or 42, depending on product</td>
<td></td>
</tr>
</tbody>
</table>

Note: Some products are not labeled for use in lactating dairy cattle and list the above withdrawal times. Product labeling listing the above withdrawal times states that they apply to a dose of 6.6 to 11 mg per kg of body weight a day for a maximum of four days or 20 mg per kg of body weight administered as a single dose.

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>28</td>
<td>96</td>
</tr>
<tr>
<td>Pigs</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply to a dose of 6.6 to 11 mg per kg of body weight a day for a maximum of four days or 20 mg per kg of body weight administered as a single dose.

**Canada—\(^{R-25; 120}\)**

<table>
<thead>
<tr>
<th>Species</th>
<th>Meat (days)</th>
<th>Milk (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle and pigs</td>
<td>21 or 28, depending on product</td>
<td></td>
</tr>
</tbody>
</table>

Note: Product labeling listing the above withdrawal times states that they apply to a dose of 20 mg per kg of body weight administered once. Not labeled for use in lactating dairy cattle. One product recommends a 42-day withdrawal to avoid excess trim at the injection site.\(^{R-58}\)

**Packaging and storage:** Store between 15 and 30 °C (59 and 86 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer.

**Auxiliary labeling:** Protect from excessive moisture.\(^{R-9}\)

**USP requirements:** Not in USP.

**TETRACYCLINES Veterinary—Systemic**

**ADDITIONAL DOSING INFORMATION**

When possible, oral tetracycline should be administered 1 hour before or 2 hours after milk replacer.\(^{R-1}\)

**MUCOSAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**TETRACYCLINE UTERINE TABLETS**

**Usual dose:**

Note: [Cows] and [mares]—Although the efficacy and safety are not currently established, the use of a 4-gram bolus administered as a single intrauterine dose is included in Canadian product labeling\(^{R-9}\) for the treatment of uterine infections. The dose may be repeated in two days if necessary.\(^{R-9}\)

**Strength(s) usually available:**

**U.S.—**

Veterinary-labeled products:

- Not commercially available.

**Canada—**\(^{R-9}\)

Veterinary-labeled products:

- 4 grams (OTC) [Tetra 4000; Tetrabol].

**Withdrawal times:**

**Canada—**\(^{R-9}\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows</td>
<td>18</td>
</tr>
<tr>
<td>Pigs</td>
<td>72</td>
</tr>
</tbody>
</table>

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer.

**Auxiliary labeling:** Protect from excessive moisture.\(^{R-9}\)

**USP requirements:** Not in USP.

**ORAL DOSAGE FORMS**

Note: Bracketed information in the Dosage Forms section refers to uses that either are not included in U.S. product labeling or are for products not commercially available in the U.S.

**TETRACYCLINE BOLUSES USP**

**Usual dose:** Bacterial enteritis; or bacterial pneumonia—Calves: Oral, 11 mg per kg of body weight every twelve hours for five days.\(^{R-1}\)

**Strength(s) usually available**\(^{R-58}\):

**U.S.—**\(^{R-1}\)

Veterinary-labeled products:

- 500 mg (OTC) [Calf Scour Bolus Antibiotic; 5-Way Calf Scour Bolus].

**Canada—**\(^{R-9}\)

Veterinary-labeled products:

- 4 grams (OTC) [Tetra 4000; Tetrabol].

\(^{1}\)Not included in Canadian product labeling or product not commercially available in Canada.
Withdrawal times\[R-58;\]

U.S.—\(R-1\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves</td>
<td>12, 14 or 24, depending on product</td>
</tr>
</tbody>
</table>

Canada—\(R-9\)

<table>
<thead>
<tr>
<th>Species</th>
<th>Withdrawal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves</td>
<td>5</td>
</tr>
<tr>
<td>Cattle</td>
<td>18</td>
</tr>
</tbody>
</table>

Note: Product labeling with the above withdrawal times state that they apply to a dose of 20 mg per kg of body weight a day for three to five days.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:
- Protect from excessive moisture.\(R-9\)

USP requirements: Preserve in tight containers. Label Boluses to indicate that they are intended for veterinary use only. Contain the equivalent of the labeled amount of tetracycline hydrochloride, within −10% to +20%. Meet the requirements for Identification. Uniformity of dosage units, and Loss on drying (not more than 3.0%; or for Boluses −10% to +20%. Meet the requirements for Identification, Dissolution (80% in 60 minutes, 90 minutes for 500-mg capsules, in water in Apparatus 2 at 75 rpm). Uniformity of dosage units, Loss on drying (not more than 4.0%), and Limit of 4-epianhydrotetracycline (not more than 3.0%).\(R-128\)

TETRACYCLINE HYDROCHLORIDE CAPSULES USP

Usual dose: Calves and pigs—Bacterial enteritis; or bacterial pneumonia: Oral, 11 mg per kg of body weight every twelve hours, administered in the only source of drinking water for three to five days.\(R-19\)

Chicken—Chronic respiratory disease; or infectious synovitis: Oral, 27.5 mg per kg of body weight every twelve hours, administered in the only source of drinking water for seven to fourteen days.\(R-19\)

Turkeys—Infectious synovitis; or bacterial enteritis: Oral, 27.5 mg per kg of body weight every twelve hours, administered in the only source of drinking water for seven to fourteen days.\(R-19\)

Sheep—Bacterial enteritis; or respiratory tract diseases: Oral, 40 mg per kg of body weight every twelve hours for four to five days.\(R-18\)

Note: Environmental and health conditions may affect the intake of water and the amount of medication consumed.\(R-17\) Administration of medication by food or water to animals with pneumonia or other infections can be affected by reduced feed and water intake.\(R-109\)

Strength(s) usually available\(R-58;\)

U.S.—\(R-8; 19\)

Veterinary-labeled products:
- 250 mg (Rx) [Achromycin V; GENERIC].
- 500 mg (Rx) [Achromycin V; GENERIC].

Canada—
Veterinary-labeled products:
- Not commercially available.

Human-labeled products:
- 250 mg (Rx) [Apo-Tetra; Novo-Tetra; Nu-Tetra].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

USP requirements: Preserve in tight, light-resistant containers. Contain the labeled amount, within −10% to +25%. Meet the requirements for Identification, Dissolution (80% in 60 minutes, 90 minutes for 500-mg capsules, in water in Apparatus 2 at 75 rpm). Uniformity of dosage units, Loss on drying (not more than 4.0%), and Limit of 4-epianhydrotetracycline (not more than 3.0%).\(R-128\)

TETRACYCLINE HYDROCHLORIDE SOLUBLE POWDER USP

Usual dose:

- Calves and pigs—Bacterial enteritis; or bacterial pneumonia: Oral, 11 mg per kg of body weight every twelve hours, administered in the only source of drinking water for three to five days.\(R-19\)
- Chicken—Chronic respiratory disease; or infectious synovitis: Oral, 27.5 mg per kg of body weight every twelve hours, administered in the only source of drinking water for seven to fourteen days.\(R-19\)
- Turkeys—Infectious synovitis; or bacterial enteritis: Oral, 27.5 mg per kg of body weight every twelve hours, administered in the only source of drinking water for seven to fourteen days.\(R-19\)
- Sheep—Bacterial enteritis; or respiratory tract diseases: Oral, 40 mg per kg of body weight every twelve hours for four to five days.\(R-18\)

Note: Environmental and health conditions may affect the intake of water and the amount of medication consumed.\(R-17\) Administration of medication by food or water to animals with pneumonia or other infections can be affected by reduced feed and water intake.\(R-109\)

Strength(s) usually available\(R-58;\)

U.S.—\(R-8; 19\)

Veterinary-labeled products:
- 25 grams per pound of powder (OTC) [Duramycin 10; PolyOtic Soluble Powder; Solu-Tet; Tet-Sol 10].
- 324 grams per pound of powder (OTC) [AmTech Tetracycline Hydrochloride Soluble Powder-324; Duramycin-324; Solu-Tet 324; Tet-324; Tetra Bac 324; Tetrosol Soluble Powder; Tet-Sol 324; GENERIC].

Canada—\(R-18\)

Veterinary-labeled products:
- 55 mg per gram of powder (OTC) [Tetra 55; GENERIC].
- 62.5 mg per gram of powder (OTC) [Onycin 62.5; Tetracycline 62.5 Soluble Powder].
- 250 mg per gram of powder (OTC) [Onycin 250; Tetra 250; Tetracycline 250; Tetracycline 250 Concentrate Soluble Powder; Tetramed 250].
- 1000 mg per gram of powder (OTC) [Onycin 1000; Tetra 1000; Tetracycline 1000; Tetramed 1000].
**Withdrawal times:**

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<th>Withdrawal time</th>
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</thead>
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<tr>
<td>Calves</td>
<td>4 or 5, depending on product</td>
</tr>
<tr>
<td>Chickens, pigs, turkeys</td>
<td>4 or 7, depending on product</td>
</tr>
</tbody>
</table>

**Packaging and storage:** Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer.

**Preparation of dosage form:** Fresh solutions should be prepared every 24 hours when administered in plastic or stainless steel waterers and every 12 hours when administered in galvanized waterers.

**Stability:** Solutions are stable for 24 hours.

**USP requirements:** Preserve in tight containers. Label it to indicate that it is intended for veterinary use only. Contains the labeled amount of tetracycline hydrochloride, within –10% to +25%. Meets the requirements for Identification, Uniformity of dosage units (single-unit containers), Deliverable volume, pH (3.5–6.0), and Limit of 4-epianhydrotetracycline (not more than 5.0%).

**TETRACYCLINE ORAL SUSPENSION USP**

**Usual dose:** Bacterial gastroenteritis\(^1\) or urinary tract infections\(^1\)—Cats and dogs: Oral, 14 to 22 mg per kg of body weight every six to eight hours. See also Tetracycline Hydrochloride Capsules USP.

**Strength(s) usually available:**

<table>
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<th>Species</th>
<th>Strength(s)</th>
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<tbody>
<tr>
<td>U.S.</td>
<td>100 mg per mL (Rx) [Panmycin Aquadrops].</td>
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<tr>
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<td>Not commercially available.</td>
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</table>

**Packaging and storage:** Store between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from light.

**REFERENCES**

8. Tetracycline package label (Solu-Tet 324, Alpharma—US).
12. Oxytetracycline package label (Kalmecyn, PVL—Canada).
18. Tetracycline package insert (Oxyacin 250, Vetquinol—Canada).
24. Oxytetracycline package insert (Oxyvet 100 LP, Vetquinol—Canada).
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56. Oxytetracycline package insert (Oxy-Tet 100, Vedco—US), discontinued product.


150. Panel comment, Rec 3/1/96.


171. Panel comment, Rec 3/14/96.

172. Panel comment, Rec 3/14/96.


177. Panel consensus, 5/16/96.


179. Manufacturer comment, Rec 5/10/96.

**Indications Index**

Note: Both labeled and extra-labeled indications are included in this index without differentiation. Please consult the individual monograph Indications section for US and Canadian product labeling status for each species and for more information on when use is appropriate. This reference does not include every antimicrobial product available; therefore, it should not be assumed that all medications appropriate for a given indication are listed or that those not listed are inappropriate. Because clinical variables play an important role in choice of antimicrobial treatment, it cannot be assumed that the agents listed for any indication are interchangeable in a particular situation. Indications may be found under more than one Indications subheading (Accepted, Acceptance not established, Unaccepted) when recommended for more than one species or medication within a monograph. Indications below can be found under the Accepted subheading of the listed monograph's Indications section for at least one species unless “Not estab” is stated. “Not estab” signifies a drug monograph in which the indication is listed under the Acceptance not established subheading. Unaccepted uses have not been indexed. Listing as Accepted, Acceptance not established, or Unaccepted in a monograph is not meant to signify label versus extra-label status.

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## Dosing Index

Note: Both labeled and extra-labeled dosage recommendations are included in this index without differentiation. Please consult the individual monograph for US and Canadian product labeling status for each species and for more information on when use is appropriate.

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