MACROLIDES (Veterinary—Systemic)

This monograph includes information on the following:
Azithromycin; Clarithromycin; Erythromycin; Tilmicosin; Tulathromycin; Tylosin.

Some commonly used *brand names* are: For veterinary-labeled products—

Draxxin [Tulathromycin]
Erythro-200 [Erythromycin Base]
Erythro-Med [Erythromycin Phosphate]
Gallimycin [Erythromycin Phosphate]
Gallimycin-50 [Erythromycin Thiocyanate]
Gallimycin-100 [Erythromycin Base]
Gallimycin-100P [Erythromycin Thiocyanate]
Gallimycin-200 [Erythromycin Base]
Gallimycin PFC [Erythromycin Phosphate]
Micotil [Tilmicosin Phosphate]
Pulmotil 90 [Tilmicosin Phosphate]
Pulmotil Premix [Tilmicosin Phosphate]
Tylan 10 [Tylosin Phosphate]
Tylan 40 [Tylosin Phosphate]
Tylan 50 [Tylosin Base]
Tylan 100 [Tylosin Phosphate]
Tylan 200 [Tylosin Base]
Tylan Soluble [Tylosin Tartrate]
Tylosin 10 Premix [Tylosin Phosphate]
Tylosin 40 Premix [Tylosin Phosphate]
Tyloved [Tylosin Base]

For human-labeled products—

Apo-Erythro [Erythromycin Base]
Apo-Erythro E-C [Erythromycin Base]
Apo-Erythro-S [Erythromycin Stearate]
Biaxin [Clarithromycin]
Biaxin XL [Clarithromycin]
E-Base [Erythromycin Base]
E-Mycin [Erythromycin Base]
Erybid [Erythromycin Base]
ERYC [Erythromycin Base]
Ery-Tab [Erythromycin Base]
Erythro-500 [Erythromycin Stearate]
Erythrocin [Erythromycin Lactobionate; Erythromycin Stearate]
Erythromid [Erythromycin Base]
Erythromycine [Erythromycin Stearate]
Novo-rythro [Erythromycin Estolate]
Nu-Erythromycin-S [Erythromycin Stearate]
PCE [Erythromycin Base]
Zithromax [Azithromycin]

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

Category: Antibacterial (systemic).

Indications

Note: The text between [EL-US] and [EL] describes uses that are not included in U.S. product labeling. Text between [EL-CAN] and [EL] describes uses that are not included in Canadian product labeling.

The [EL-US] or [EL-CAN] designation can signify a lack of product availability in the country indicated. See the *Dosage Forms* section of this monograph to confirm availability.

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 *Actinomyces* 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-53} such as *Histophilus somni* (*Haemophilus somnus*),{R-89} *Mannheimia (Pasteurella) haemolytica,* and *Pasteurella multocida*.{R-53} 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 *Actinomyces* also are extremely resistant to tilmicosin.{R-99}

Tulathromycin has been demonstrated to be active against respiratory pathogens of cattle and pigs, including *Actinobacillus pleuropneumonia, Bordetella bronchiseptica, Haemophilus parasuis, Histophilus somni, Mannheimia haemolytica, Mycoplasma bovis, Mycoplasma hyopneumoniae,* and *Pasteurella multocida*.{R-130}

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

Evidence Quality

A Good evidence to support a recommendation for use
B Moderate evidence to support a recommendation for use
C Insufficient evidence to support a recommendation for use
D Moderate evidence to support a recommendation against use
E Good evidence to support a recommendation against use

Evidence Type

1 Species-specific evidence from at least one large randomized and controlled trial (RCT) or multiple small RCTs
2 Species-specific evidence from a small RCT, disease models, large case studies, pharmacokinetic studies using surrogate endpoints, or evidence from well-designed trials in a different species that is considered appropriate for comparison
3 Dramatic results from either well-designed, species-specific trials without controls or small case studies
4 Pharmacokinetic studies without surrogate endpoints
5 *In vitro* studies
6 Opinions of respected authorities on the basis of clinical experience or reports of expert committees

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, another macrolide 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. An *in vitro* study and a retrospective clinical study have shown clarithromycin to be at least as effective as erythromycin in the treatment of *Rhodococcus equi* infection in foals.{R-137; 138} In dogs, clarithromycin has been shown to have a shorter half-life than azithromycin,{R-119; 124} but information for its clinical use in animals is otherwise limited.

Accepted

Abscesses, hepatic (prophylaxis)—*Cattle,* beef: Tylosin granulated is indicated for reduction in incidence of hepatic abscesses caused by susceptible *Fusobacterium necrophorum* and *Actinomyces pyogenes.*{R-48; 49}

EL,CAN Atrophic rhinitis (treatment)EL—*Pigs:* Tylosin granulated is indicated for maintaining weight gain and feed efficiency in the presence of atrophic rhinitis infections.{R-49}

EL,CAN Arthritis, infectious (treatment)EL—*Pigs:* Tylosin injection is indicated in the treatment of swine arthritis caused by susceptible *Mycoplasma hyosynoviae.*{R-51; 52}

EL,CAN Coryza, infectious (prophylaxis)—*Chickens:* Erythromycin thiocyanate for medicated feed is indicated as an aid in the prevention of infectious coryza caused by susceptible organisms.EL{R-9; 54}

Coryza, infectious (treatment)—*Chickens:* Erythromycin phosphate powder for oral solution is indicated as an aid in the control and treatment of infectious coryza caused by susceptible organisms, including *Haemophilus gallinarum.*{R-3; 9}

EL,CAN Diphtheria (treatment)EL—*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)—*Pigs:* Tylosin granulated is indicated in the prevention of swine dysentery.{R-48; 49}

Dysentery, swine (treatment)—*Pigs:* Tylosin granulated is indicated in the control of swine dysentery caused by susceptible organisms.{R-48; 49} 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)—

Piglets, 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}

EL,US Enteritis, necrotic (treatment)EL—*Chickens,* broiler: Tylosin tartrate powder for oral solution is indicated as an aid in the treatment of necrotic enteritis caused by susceptible *Clostridium perfringens.*{R-126}

Enterotoxemia (prophylaxis)—*Lambs,* newborn: Erythromycin injection is indicated in the prevention of dysentery in lambs.{R-7; 111}

Erysipelas (treatment)—*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; or

Weight gain, increased rate—

EL,CAN *Chickens,* including laying chickensEL: Tylosin granulated is indicated for increased rate of weight gain and improving feed efficiency.{R-49}

Pigs: Tylosin granulated is indicated for improving feed efficiency and growth promotion.{R-48; 49}

EL,CAN Foulbrood, American (treatment)EL—*Bees,* honey: Tylosin tartrate powder for oral solution is indicated in the treatment of American foulbrood (*Paenibacillus larvae*).{R-127}

Leptospirosis—*Sows,* farrowing: Erythromycin injection is indicated in the management of leptospirosis in sows at farrowing time.{R-7; 111}

Metritis (treatment)—

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)—

Cattle: Erythromycin injection is indicated in the treatment of pneumonia and bovine respiratory disease caused by susceptible bacteria, including *Pasteurella multocida*.{R-7; 111} 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-53} Tilmicosin injection is indicated in Canadian product labeling for the treatment of bovine respiratory disease associated with susceptible *M. haemolytica* or *P. multocida* during the first 30 days calves are in the feedlot.{R-65; 112} EL,CAN Tulathromycin 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 associated with susceptible bacteria, including *Histophilus somni, Mannheimia haemolytica,* and *Pasteurella multocida.*{R-129} It is also indicated in the treatment of bovine respiratory disease associated with susceptible *Mycoplasma bovis.*EL 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}

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}

EL,CAN Tulathromycin injection is indicated in the treatment of swine respiratory disease associated with susceptible bacteria, including *Actinobacillus pleuropneumoniae, Bordetella bronchiseptica, Haemophilus parasuis,* and *Pasteurella multocida.*EL{R-129} Tylosin injection is indicated in the treatment of pneumonia caused by susceptible bacteria, including *P. multocida*.{R-51; 52}

Sheep: Tilmicosin injection is indicated in the treatment of ovine respiratory disease associated with *Mannheimia (Pasteurella) haemolytica*.{R-6; 65; 112}

EL,US,CAN *Foals*EL: Azithromycin, clarithromycin, or erythromycin, administered in combination with rifampin, has been used in the treatment of *Rhodococcus equi* pneumonia (Evidence rating: A-3).{R-4; 13; 14; 83; 121; 122; 137-139} In one retrospective study, clarithromycin, combined with rifampin, appeared to be the most effective of the three macrolides.{R-137} Efficacy studies of these macrolides to compare their administration with and without rifampin have not been performed.

Pododermatitis (treatment)—*Cattle,* beef and nonlactating dairy: Erythromycin injection and EL,CAN tylosin injectionEL are indicated in the treatment of pododermatitis caused by susceptible organisms.{R-7; 51; 52; 111}

Proliferative enteropathy, porcine (prophylaxis and treatment)—*Pigs:* Tylosin granulated and [EL,US]tylosin tartrate powder for oral solution[EL] are indicated in the prevention and control of porcine proliferative enteropathy (ileitis) associated with susceptible *Lawsonia intracellularis.*{R-49; 126}

Respiratory disease, chronic (treatment)—

Chickens, broiler and replacement: Erythromycin phosphate powder for oral solution and erythromycin thiocyanate for medicated feed 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{R-50; 66} is indicated in the control of and as an aid in the treatment of chronic respiratory disease, and [EL,CAN]tylosin granulated[EL] is indicated as an aid in the control of chronic respiratory disease caused by susceptible *M. gallisepticum.*{R-49}

[EL,CAN]*Turkeys*[EL]: Erythromycin thiocyanate for medicated feed is indicated for reduction of lesions and to decrease the severity of chronic respiratory disease.{R-9; 54; 64}

Respiratory tract infections, bacterial (treatment)—

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:* [EL,US]Erythromycin phosphate powder for oral solution[EL] and tylosin tartrate powder for oral solution are indicated to maintain weight gain and feed efficiency in the presence of infectious sinusitis caused by susceptible *M. gallisepticum.*{R-50}

[EL,US]Synovitis, infectious (prophylaxis)[EL]—*Chickens* and *turkeys:* Erythromycin phosphate powder for oral solution is indicated in the management of infectious synovitis.{R-9}

[EL,US,CAN]Enteritis, *Campylobacter* (treatment)[EL]—*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} The zoonotic potential of this organism should be considered.{R-146} See also *Enteritis, Campylobacter* under *Potentially effective* below.

[EL,US,CAN]Pyoderma (treatment)[EL]—*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}

Potentially effective

[EL,US,CAN]Chlamydial infections (treatment)[EL]—*Cats: In vitro* studies and clinical trials of azithromycin in the treatment of respiratory tract and urinary chlamydial infections in human patients have demonstrated efficacy;{R-33-35; 113} however, a controlled study of cats suggests azithromycin is less effective than doxycycline in the treatment of chlamydophilosis and should only be considered for patients intolerant of doxycyline therapy (Evidence rating: B-2).{R-134}

[EL,US,CAN]Cryptosporidiosis (treatment)[EL]—*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.

[EL,US,CAN]Diarrhea, chronic (treatment)[EL]—*Dogs:* There are insufficient data to establish the efficacy of tylosin in the treatment of chronic diarrhea or to define the specific mechanism of action for its effect. Tylosin tartrate powder for oral solution is used, based on case studies that suggest tylosin can be effective in controlling large bowel and/or small bowel diarrhea that has not responded to other treatment and for which specific causes have been ruled out (Evidence rating: B-3).{R-84-86; 101; 102; 135; 136} Concurrent therapies that limit the length of time tylosin is administered can be important in avoiding the problems associated with long-term antibiotic treatment. In one study, change to a diet that partially controlled diarrhea, before beginning tylosin administration for ten days, was successful in controlling chronic diarrhea for at least three months in some dogs.{R-135}

[EL,US,CAN]Enteritis, *Campylobacter* (treatment)[EL]—*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} The zoonotic potential of this organism should be considered.{R-146}

[EL,US,CAN]Mastitis (treatment)[EL]—*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}

[EL,US,CAN]Respiratory tract infections (treatment)[EL], including,

[EL,US,CAN]Bronchitis (treatment)[EL]

[EL,US,CAN]Laryngitis (treatment)[EL]

[EL,US,CAN]Pneumonia (treatment)[EL]

[EL,US,CAN]Tracheobronchitis (treatment)[EL], or

[EL,US,CAN]Tracheitis (treatment)[EL]—*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}

[EL,US,CAN]Rocky Mountain spotted fever (treatment)[EL]—*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 be more effective.{R-123-125}

Regulatory Considerations

U.S.—

Withdrawal times have been established for erythromycin injection, erythromycin phosphate powder for oral solution, tilmicosin phosphate, tulathromcyin injection, tylosin injection, tylosin phosphate, and tylosin tartrate (see the

Dosage Forms section).

Azithromycin and clarithromycin are not labeled for use in animals.

Canada—

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 *Saccharopolyspora erythraeus*.{R-7}

Tilmicosin—Produced semisynthetically{R-53} by chemical modifications of desmycosin.{R-1}

Tulathromycin—Semisynthetic derivative of erythromycin.{R-130}

Tylosin—Produced by a strain of the actinomycete *Streptomyces fradiae*.{R-55}

Chemical group:

Azalide antibiotic, a subclass of macrolides—Azithromycin.{R-116}

Macrolide antibiotics (macrocyclic lactones)—Clarithromycin, erythromycin, tilmicosin, and tylosin.{R-1; 117}

Triamilide antibiotic, a subclass of macrolides—Tulathromycin.{R-129}

Chemical name:

Azithromycin—1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-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, [2*R*-(2*R**,3*S**,4*R**,5*R**,8*R**,10*R**,11*R**,12*S**,13*S**,14*R**)]-.{R-16}

Clarithromycin—Erythromycin, 6-*O*-methyl-.{R-16}

Erythromycin—Erythromycin.{R-16}

Erythromycin estolate—Erythromycin, 2′-propanoate, dodecyl sulfate (salt).{R-16}

Erythromycin ethylsuccinate—Erythromycin 2′-(ethyl butanedioate).{R-16}

Erythromycin lactobionate—Erythromycin mono(4-*O*-*beta*-D-galacto-pyranosyl-D-gluconate) (salt).{R-16}

Erythromycin stearate—Erythromycin octadecanoate (salt).{R-16}

Tilmicosin phosphate—Tylosin, 4^A-*O*-de(2,6-dideoxy-3-*C*-methyl-*alpha*-L-*ribo*-hexopyranosyl)-20-deoxo-20-(3,5-dimethyl-1-piperidinyl)-, [20(*cis*)]-, phosphate (1:1) (salt).{R-16}

Tylosin—(10*E*,12*E*)-(3*R*,4*S*,5*S*,6*R*,8*R*,14*S*,15*R*)-14-[(6-deoxy-2,3-di-*O*-methyl-*beta*-D-allopyranosyl)oxymethyl]-5-[[3,6-dideoxy-4-*O*-(2,6-dideoxy-3-C-methyl-*alpha*-L-*ribo*-hexopyranosyl)-3-dimethylamino-*beta*-D-glucopyranosyl]oxy]-6-formylmethyl-3-hydroxy-4,8,12-trimethyl-9-oxoheptadeca-10,12-dien-15-olide.{R-100}

Tulathromycin—Present in two isomeric forms in a 9:1 ratio:{R-16; 129}

Component A—(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-*alpha*-L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

Component B—(2R,3R,6R,8R,9R,10S,11S,12R)-11-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-*alpha*-L-ribo-hexopyranosyl]oxy]-2-[(1S,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one.

Molecular formula:

Azithromycin—$C_{38}H_{72}N_2O_{12}\cdot 2H_20$.{R-16}

Clarithromycin—$C_{38}H_{69}NO_{13}$.{R-16}

Erythromycin—$C_{37}H_{67}NO_{13}$.{R-16}

Erythromycin estolate—$C_{40}H_{71}NO_{14}\cdot C_{12}H_{26}O_4S$.{R-16}

Erythromycin ethylsuccinate—$C_{43}H_{75}NO_{16}$.{R-16}

Erythromycin lactobionate—$C_{37}H_{67}NO_{13}\cdot C_{12}H_{22}O_{12}$.{R-16}

Erythromycin stearate—$C_{37}H_{67}NO_{13}\cdot C_{18}H_{36}O_2$.{R-16}

Tilmicosin phosphate—$C_{46}H_{80}N_2O_{13}\cdot H_3O_4P$.{R-16}

Tulathromycin—$C_{41}H_{79}N_3O_{12}$ (components A & B).{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 lactobionate—1092.22.{R-16}

Erythromycin stearate—1018.40.{R-16}

Tilmicosin phosphate—967.13.{R-16}

Tulathromycin—806.08.{R-16}

Tylosin—916.10.{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 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}

Tulathromycin—White to off-white crystalline powder.{R-130}

Tylosin USP—White to buff-colored powder.{R-22}

pKa:

Erythromycin base—8.8.{R-18; 19}

Tilmicosin—7.4; 8.6.{R-94}

Tulathromycin—8.6, 9.6, 9.9 (3 basic amino groups).

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 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}

Tulathromycin—Readily soluble in water at pH 8.0 or below.{R-

{R-130} Approximately fifty times more soluble in hydrophilic than hydrophobic media.{R-129}

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.{R-1; 5; 119} A post-antibiotic effect can be produced; the duration is both drug and pathogen-dependent.{R-129} The macrolides are thought to enter the cell and reversibly bind to the 50 S ribosomal subunit, inhibiting translocation of peptides, thereby inhibiting protein synthesis.{R-5} Although macrolides bind to mitochondrial ribosomes, as does chloramphenicol, macrolides are unable to cross the mitochondrial membrane and so do not produce bone marrow suppression in mammals.{R-119}

Resistance can occur by target site modification, drug inactivation, or drug efflux.{R-133} 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.{R-1}

Absorption:

Azithromycin—Oral administration: Shown to be fairly well absorbed in cats (bioavailability of 58%), dogs (bioavailability of >90%), and foals (bioavailability of 39 to 56%).{R-120-123}

Clarithromycin—Oral administration:

Dogs—Shown to be fairly well absorbed in dogs (bioavailability of 70 to 79%).{R-124}

Foals—In one study, clarithromycin could be measured in the serum 10 to 20 minutes after intragastric administration of 10 mg/kg. Absorption half-life was 0.59 minutes.{R-139}

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.{R-1; 2} However, absorption of enteric-coated and delayed-release dosage forms can be unpredictable in animals.{R-21} 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;{R-1} 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.{R-18}

Tulathromycin—

Intramuscular administration: *Pigs*—Rapidly and well absorbed.{R-132}

Subcutaneous administration: *Calves*—Rapidly absorbed, generally within 15 minutes.{R-129}

Tylosin—Intramuscular administration: Bioavailability—*Goats:* 72.6% (15 mg per kg of body weight [mg/kg] dose).{R-72}

Distribution:

Widely distributed in the body.{R-1; 68} Ion trapping and the high lipid solubility of the macrolides generally causes tissue concentrations to be higher (often many times higher) than serum concentrations.{R-1; 70}

Azithromycin—Tissue concentrations can be as much as 100 times serum concentrations and concentrations in leukocytes can be 200 to 300 times serum concentrations.{R-115; 119}

Cats: Azithromycin appears to distribute well, although sometimes slowly, into a variety of tissues. High tissue to plasma ratios are produced. In one study, brain tissue, eye, femur, lung, and skin concentrations of azithromycin were still rising when the last sample was taken, 72 hours after the dose.{R-120}

Dogs: A single dose of azithromycin produced high tissue concentrations, often with a tissue to serum ratio of 100 to one; azithromycin concentrations in eye and brain tissue exceeded serum concentrations by 20- and 1.2-fold, respectively.{R-123}

Foals: Azithromycin peak concentration in polymorphonuclear leukocytes (PMN) was 27.3 mcg per mL (mcg/mL) while peak plasma concentration was 0.72 mcg/mL after a single 10-mg/kg oral dose. The drug persisted in PMNs for 120 hours while it was only detected in plasma for about 24 hours.{R-121}

Clarithromycin—Widely distributed into tissues and enters leukocytes and macrophages.{R-115}

Erythromycin—In the calf, lung tissue erythromycin concentrations were found to be approximately three times higher than serum concentrations from 8 to 24 hours after intramuscular administration.{R-28}

Tilmicosin and tylosin—Tylosin concentrations in lung tissue are many times higher than in serum from 2 to 36 hours after a single intramuscular administration;{R-70} tilmicosin concentrations in lung tissue are many times higher than in serum for at least 96 hours after a single subcutaneous administration.{R-104}

Tulathromycin—*Calves* and feeder *pigs:* Rapidly and extensively distributed.{R-129; 131; 132} Lung tissue concentration peaks higher than plasma concentration twenty-four hours after single intramuscular or subcutaneous administration and is maintained over time at a markedly higher concentration in lung tissue than is found in plasma.{R-129; 131; 132}

Half-life: Azithromycin in leukocytes—

Foals: 49.2 hours.{R-121}

Human data: 34 to 57 hours.{R-115}

Elimination:

Azithromycin—

Cats: More than 50% of the drug is eliminated unchanged in the bile. One major metabolite resulting from N-demethylation and two minor metabolites also appear in the bile.{R-120}

Human information: More than 50% of the drug is eliminated unchanged through biliary excretion while 4 to 14%, depending on route of administration, is eliminated unchanged in the urine.{R-115}

Clarithromycin—*Human information:* 20 to 40% is eliminated unchanged in the urine.{R-115}

Erythromycin—Primarily hepatic; metabolite and a small amount of active drug are excreted to a large degree in the bile but are also excreted in urine and milk. After oral administration, high concentrations of erythromycin may be eliminated in the feces.{R-1; 29}

Tilmicosin—*Cattle:* Of the total subcutaneous dose administered, 24% has been recovered in the urine and 68% in the feces.{R-53}

Tulathromycin—By biliary and renal excretion.{R-129} In cattle and pigs, one-half and two thirds of the dose, respectively, are eliminated in the feces.{R-131; 133} More than 90% of the dose is eliminated as unchanged drug.{R-129}

Duration of action:

Tilmicosin—*Cattle*, healthy or acutely pneumonic: 3 days, minimum (based on maintenance of >3.12 mcg/mL lung concentration [minimum inhibitory concentration 95% for *M. haemolytica*] with a subcutaneous dose of 10 mg/kg).{R-53; 103; 104}

Tylosin—*Goats:* 12 hours (based on maintenance of >1 mcg/mL serum concentration with an intramuscular dose of 15 mg/kg).{R-72}

Precautions to Consider

Species sensitivity

Erythromycin:

Cattle—Oral administration of erythromycin phosphate or erythromycin stearate has caused severe diarrhea in ruminating calves.{R-28} 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.{R-26} In adult horses, the risk of severe diarrhea makes the use of erythromycin controversial.{R-2}

Tilmicosin:

All species—To avoid cardiotoxicity, tilmicosin should not be administered intravenously.{R-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.{R-81} A physician should be consulted immediately in cases of accidental injection.{R-53}

Dogs—In laboratory dogs, tachycardia and decreased cardiac contractility have been noted in response to tilmicosin injection{R-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{R-81; 100}

Horses—Administration of tilmicosin to horses at intramuscular or subcutaneous doses >10 mg/kg is likely to lead to toxicity.{R-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.{R-53; 100}

Tylosin: *Horses*—Injection of tylosin has been fatal to horses.{R-51; 52}

Cross-sensitivity and/or related problems

Patients that are hypersensitive to one macrolide may be hypersensitive to a different macrolide.{R-116; 117}

Pregnancy/Reproduction

Azithromycin: 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.{R-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.{R-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.{R-115} 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.{R-115} FDA human pregnancy category C.{R-115}

Erythromycin: Erythromycin crosses the placenta; however, there is no evidence of teratogenicity or other effects when female rats are fed erythromycin base during pregnancy.{R-17} In people, erythromycin estolate has been associated with reversible hepatotoxicity in some women during pregnancy.

Tilmicosin, tulathromycin, and tylosin: Safety in breeding or pregnant animals has not been established.{R-53; 129}

Lactation

Clarithromycin is excreted into milk.{R-117} The distribution of azithromycin into milk has not yet been demonstrated.{R-116}

Erythromycin, tilmicosin, and tylosin concentrations in milk can be much higher than concentrations in serum.{R-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).{R-87} Tilmicosin should not be administered to lactating dairy cattle because of impractical withdrawal times.{R-74}

In mastitis-free cattle, systemic tylosin is distributed into milk at concentrations that are therapeutic for some mastitis pathogens; however, tylosin 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 tylosin, interfering with the medication's ability to reach sufficient concentrations in milk to be effective against some organisms.{R-79; 80}

Pediatrics

In animals up to 1 month of age, the hepatic clearance of macrolides may be slower than in adult animals.{R-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:

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) {R-53}

Cisapride
(medications, such as clarithromycin, erythromycin, or troleandomycin, that inhibit cytochrome P450 3A4 [CYP3A] can lead to increased serum concentrations of cisapride, for which the enzyme is the primary mode of elimination, and thereby cause sometimes fatal cardiac arrhythmias in human beings; although arrhythmias could not be induced in one study of dogs administered cisapride and erythromycin concurrently, this interaction may be an issue in animals susceptible to QT interval prolongation [See also *Human drug interactions* below])**{R-37; 147; 148}**

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)[R-1]
Epinephrine
(in pigs, the intravenous administration of epinephrine potentiates the lethality of intravenously administered tilmicosin)[R-53]
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)[R-87]

Human drug interactions[R-115]

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)
Cisapride or
Pimozide or
Terfenadine
(concurrent administration 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 these medications by clarithromycin; concurrent use is contraindicated)
Cyclosporine or
Digoxin or
Hexobarbital or
Phenytoin or
Terfenadine
(concurrent use with macrolide antibiotics has been associated with increased serum concentration of these medications)
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)[R-116]
(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 of azithromycin by approximately 24%, but has no effect on the AUC; oral azithromycin should be administered at least 1 hour before or 2 hours after aluminum- and magnesium-containing antacids)

For clarithromycin

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)
Ototoxic 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 macrolides in animals are rarely described. Human laboratory value alterations have been reported for azithromycin, clarithromycin, and erythromycin and are included in the following section.

Human laboratory value alterations[R-115]

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
Alanine aminotransferase (ALT [SGPT]) and
Aspartate aminotransferase (AST [SGOT]) and
Creatine kinase (CK) and
Gamma-glutamyltransferase (GGT) and
Lactate dehydrogenase (LDH)
(serum values may be increased)
Bilirubin, serum and
Potassium, serum
(concentrations may be increased)

For clarithromycin

With physiology/laboratory test values
Alanine aminotransferase (ALT [SGPT]) and
Alkaline phosphatase (ALP) and
Aspartate aminotransferase (AST [SGOT]) and

Bilirubin, total, and
Gamma-glutamyltransferase (GGT) and
Lactate dehydrogenase (LDH)
(serum values may be increased)
Blood urea nitrogen (BUN) and
Serum creatinine
(concentration may be elevated)
White blood cell count (WBC)
(may be decreased)

For erythromycin

With diagnostic test results
Aspartate aminotransferase (AST [SGOT])
(use of erythromycin may interfere with AST [SGOT] determinations if azonefast violet B or diphenylhydrazine colorimetric tests are used)
Catecholamines, urinary
(erythromycin may produce false elevations of urinary catecholamines because of interference with the fluorometric determination)

With physiology/laboratory test values
Alanine aminotransferase (ALT [SGPT]) and
Alkaline phosphatase (ALP) and
Aspartate aminotransferase (AST [SGOT]) and
Bilirubin, total
(serum values may be increased by all erythromycins, but more commonly by erythromycin estolate)

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
(macrolides are hepatically metabolized;[R-29] although hepatotoxicity has not been reported in animals, erythromycin estolate has, on uncommon occasions, been associated with hepatotoxicity in people; therefore, consideration of risk is recommended[R-1])

Hypersensitivity
(animals that have had a previous reaction may be much more likely to react on subsequent administration)[R-129]

Renal function impairment, severe
(clarithromycin elimination is reduced in human patients with renal function impairment, particularly those with a creatinine clearance < 30 mL per minute; it is recommended that the dose be reduced by one-half or that the dosage interval be doubled)[R-115]

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 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[R-1]

Cats and dogs

Gastrointestinal effects (anorexia, diarrhea, vomiting)—particularly with erythromycin[R-1; 96]

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.[R-59; 60] In one survey, 41% of pet owners reported that their dogs (19 of 46) vomited following administration of oral erythromycin stearate.[R-96] This increase in gastric motility has not been shown to occur in response to tylosin[R-67] and, although vomiting may occur in response to tylosin administration, it occurs infrequently.

Cattle

Diarrhea—associated with oral erythromycin dosage forms;[R-28]

Foals

Diarrhea, mild and self-limiting to severe;[R-137] ***hyperthermia***—with erythromycin;[R-140; 144] ***injection site reaction, severe***—if tilmicosin is administered subcutaneously;[R-141] ***respiratory distress***—with erythromycin[R-140]

Note: *Rapid intravenous administration* of erythromycin lactobionate to foals has been reported to quickly cause elevated heart and respiratory rate, hyperthermia, mild to severe wheals, kicking at abdomen, and colic followed by diarrhea.[R-144] Intravenous bolus administration of azithromycin has been reported to cause ataxia, trembling, weakness, and yawning in foals.[R-122]

Diarrhea has been reported in foals in association with azithromycin, clarithromycin, or erythromycin. Severe diarrhea requiring fluid replacement may be equally likely to occur with any of these three antibiotics.[R-137]

Foals reported to develop *hyperthermia* and *respiratory distress* with oral erythromycin administration were being treated for pneumonia; however, foals with pneumonia in the same retrospective study did not develop these signs when treated with other antimicrobials.[R-140]

Horses

Diarrhea, severe—with erythromycin; considered more likely in adult horses than in foals[R-2; 142]

Pigs

Diarrhea, erythema, and pruritis—with tylosin;[R-51] ***edema, rectal, and partial anal prolapse***—with erythromycin and tylosin[R-2; 51]

Those indicating need for medical attention only if they continue or are bothersome

All species

Pain and/or swelling at the site of injection, transient—with parenteral administration[R-29; 53; 129]

Note: *Injection site reactions* have been reported with azithromycin, erythromycin, tilmicosin, tulathromycin, and tylocin.[R-29; 53; 129] Discoloration and edema of subcutaneous tissue can occur; the potential for trim loss is noted in labeling of products for food-producing animals.[R-129]

Cattle and *pigs*

Hypersalivation, transient—associated with tulathromycin administration[R-129]

Human side/adverse effects[R-115]

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***

Incidence rare

Cardiac toxicity, especially QT prolongation and torsades de pointes; 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 or 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.**

Lethal dose

For azithromycin: *Mice* and *rats*—The LD_{50} for oral administration is 3000 to 4000 mg per kg of body weight (mg/kg).{R-118}

For tilmicosin: The median lethal dose of oral tilmicosin in fasted rats is 800 mg/kg and in nonfasted rats is 2250 mg/kg.{R-107} The acute median lethal dose of subcutaeously administered tilmicosin in mice is 97 mg/kg, and in rats is 185 mg/kg. {R-53}

Clinical effects of toxicity

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—

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.{R-81}

Other species

Cardiotoxicity

Note: Intravenous tilmicosin administration can be fatal and should be avoided in all species, including cattle and sheep, for which products are labeled for subcutaneous use.{R-6; 81; 129} In all species tested, the primary adverse effect is *cardiotoxicity*.{R-53; 81} Susceptibility to toxicity with intramusuclar or subcutaneous administration has been reported in goats and pigs,{R-81; 129} and may also be found in other species.

An intravenous dose of 10 mg/kg or less causes signs of toxicity and, in some cases, death in calves, cattle, goats, horses, and sheep.{R-81} In healthy cattle, subcutaneous doses of up to 30 mg/kg every 3 days for a total of three doses have been specified as the highest nontoxic dose, because the mild evidence of myocardial necrosis seen with three 50-mg/kg doses administered 72 hours apart{R-53} 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.{R-53; 100} In contrast, three of four pigs administered a 20-mg/kg intramuscular dose of tilmicosin and all 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.{R-81; 100}

Oral tilmicosin caused no ill effects in pigs when administered at a dose of 2000 parts per million (ppm) in the only ration for 42 days or 4000 ppm for 21 days.{R-107} Oral doses of 4 mg/kg a day administered to dogs for up to a year caused no observable adverse effects.{R-107}

For tulathromycin

Cattle

Cardiovascular changes

Note: The subcutaneous administration of 12.5 to 15 mg/kg (5 to 6 times the labeled dose) of tulathromycin to feeder calves caused no clinical signs of cardiovascular toxicity and no macroscopic tissue lesions. Minimal to mild myocardial degeneration was reported in one of six calves given a single dose of 12.5 mg/kg and two of six calves given 15 mg/kg.{R-129}

Treatment of tilmicosin toxicity

For tilmicosin: The treatment of tilmicosin-induced cardiotoxicosis is not yet well established. The increased heart rate and decreased contractility seen with toxicity may be due to calcium channel blockade. In dogs, intravenous calcium has offset tachycardia and negative ionotrophy, restoring arterial pulse pressure.{R-53} Dobutamine may partially remedy the negative ionotropic effects; beta-adrenergic antagonists, such as propanolol, exacerbate it in dogs.{R-6} Epinephrine potentiated the lethality of intravenously administered tilmicosin in pigs.{R-6; 53}

General Dosing Information

Macrolides are primarily bacteriostatic, with potential for a time-dependent bactericidal action, particularly with high concentrations.{R-1; 5; 119} A post-antibiotic effect can be produced; the duration is both drug and pathogen-dependent.{R-129} Activity of the macrolides is highest in tissues and in environments with elevated pH.{R-1}

Tulathromycin susceptibility testing: The *in vitro* activity of tulathromycin depends on the initial pH of the test medium.{R-133} A small shift in pH of the medium will produce a markedly different minimum inhibitory concentration (MIC) value, making standardization of test medium pH crucial for consistent results.

Breakpoints determined by the Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards) for tilmicosin in the treatment of bovine respiratory disease (*Mannheimia haemolytica;* also applicable to *Pasteurella multocida*)[{R-128}]

Zone diameter (millimeters)	MIC (mcg/mL)	Interpretation
≥ 14	≤ 8	Susceptible
11–13	16	Intermediate
≤ 10	≥ 32	Resistant

Note: The disk content is 15 mcg.[{R-128}]

Breakpoints determined by CLSI for tilmicosin in the treatment of swine respiratory disease (*Pasteurella multocida* and *Actinobacillus pleuropneumoniae*)[{R-128}]

Zone diameter (millimeters)	MIC (mcg/mL)	Interpretation
≥ 11	≤ 16	Susceptible
—	—	Intermediate
≤ 10	≥ 32	Resistant

Note: The disk content is 15 mcg.[{R-128}]

Human data:

Note: Breakpoints have not been established for animals.

Breakpoints determined by CLSI for erythromycin in the treatment of *Enterococcus* species and *Staphylococcus* species[{R-128}]

Zone diameter (millimeters)	MIC (mcg/mL)	Interpretation
≥ 23	≤ 0.5	Susceptible
14–22	1–4	Intermediate
≤ 13	≥ 8	Resistant

Note: The disk content is 15 mcg.[{R-128}]

Breakpoints determined by CLSI for erythromycin in the treatment of streptococci[{R-128}]

Zone diameter (millimeters)	MIC (mcg/mL)	Interpretation
≥ 21	≤ 0.25	Susceptible
16–20	0.5	Intermediate
≤ 15	≥ 1	Resistant

Note: The disk content is 15 mcg.[{R-128}]

Resistance to macrolides can occur by target site modification, drug inactivation, or drug efflux.[{R-133}] 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.[{R-1}]

For oral dosage forms only

Tylosin is more stable than erythromycin in acid environments and therefore can be administered orally without enteric coating.[{R-58}]

For parenteral dosage forms only

Only the lactobionate salt of erythromycin can be administered intravenously. Other parenteral erythromycin 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.[{R-28}] Even with intramuscular injection, the effect of erythromycin on edible tissues should be considered before administration.[{R-95}] High-dose intravenous administration should be avoided unless the lactobionate form is used[{R-82}] 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,[{R-53}] epinephrine is not contraindicated for anaphylaxis due to tilmicosin.[{R-100}]

AZITHROMYCIN

Summary of Differences

Pharmacology/pharmacokinetics: Distribution—Azithromycin concentrates in tissues, particularly in leukocytes, macrophages and fibroblasts and is slowly released from leukocytes.[{R-120; 121}] The intracellular reservoir of azithromycin produces effective drug concentrations in interstitial fluids even after the plasma concentrations have declined below detectable levels.[{R-121}] Azithromycin can be delivered to infected tissues and early abscesses via leukocytes.[{R-119}]

Oral Dosage Forms

Note: The text between [EL:US] and [EL] describes uses not included in U.S. product labeling. Text between [EL:CAN] and [EL] describes uses that are not included in Canadian product labeling.

The [EL:US] or [EL:CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

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:

[EL:US,CAN]*Cats*—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.[{R-120; 123; 125-7}] 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.

Specifically in the treatment of *chlamydial infections,* a dose of 10 to 15 mg per kg of body weight was administered to five cats every twenty-four hours for three days, then twice a week for twenty-two days. Two cats were administered the same dose daily for twenty-five days, with no reported adverse effects. However, only one of five cats with induced infection was cleared of *Chlamydophila felis*.[EL][{R-134}]

[EL:US,CAN]*Dogs*—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.[{R-120; 123; 125-7}] 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.[EL]

[ELUS,CAN] *Rhodococcus equi* pneumonia—*Foals:* Oral, 10 mg per kg of body weight every twenty-four hours for five days, followed by 10 mg per kg of body weight every forty-eight hours.{R-121; 122}

Note: The above dose has been administered concurrently with 5 mg rifampin per kg of body weight every twelve hours.{R-137} The doses recommended are based on a retrospective clinical study and a pharmacokinetic study of foals.[EL]

Strength(s) usually available:{R-116}

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, anticaking 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%).{R-22}

AZITHROMYCIN TABLETS

Usual dose: See *Azithromycin For Oral Suspension USP*.

Strength(s) usually available:{R-116}

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [*Zithromax* (lactose); GENERIC].

500 mg (Rx) [*Zithromax* (lactose); GENERIC].

600 mg (Rx) [*Zithromax* (lactose); GENERIC].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [*Zithromax* (lactose); GENERIC].

500 mg (Rx) [*Zithromax* (lactose); GENERIC].

600 mg (Rx) [*Zithromax* (lactose); GENERIC].

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}

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;* GENERIC].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (Rx) [*Zithromax;* GENERIC].

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}

CLARITHROMYCIN

Oral Dosage Forms

Note: The text between [ELUS] and [EL] describes uses not included in U.S. product labeling. Text between [ELCAN] and [EL] describes uses that are not included in Canadian product labeling.

The [ELUS] or [ELCAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

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 are 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 [EL]US,CAN*dogs*[EL], but did not attempt to recommend duration of therapy.{R-124} There are no reports of specific dosing regimens in common usage.

[EL]US,CAN*Rhodococcus equi* pneumonia—*Foals:* Oral, 7.5 mg per kg of body weight every twelve hours.{R-137-139}

Note: The above dose has been administered concurrently with 5 mg rifampin per kg of body weight every twelve hours.{R-137} The doses recommended are based on a retrospective clinical study and a pharmacokinetic study of foals.[EL]

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%), Uniformity of dosage units (for powder packaged in single-unit containers), and Deliverable volume (for powder packaged in multiple-unit containers).{R-22}

CLARITHROMYCIN TABLETS USP

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

Strength(s) usually available:{R-115}

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [*Biaxin;* GENERIC].

500 mg (Rx) [*Biaxin;* GENERIC].

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 USP

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-115}

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (Rx) [*Biaxin XL;* GENERIC].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (Rx) [*Biaxin XL*].

Packaging and storage: Store at 25 °C (77 °F), with brief excursions between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by the manufacturer. Protect from light.

USP requirements: Preserve in well-closed containers, protected from light. Store at 25°, excursions permitted between 15 and 30 °. When more than one Dissolution test is given, the labeling states the Dissolution Test used only if Test 1 is not used. Contain the labeled amount, within ±10%. Meet the requirements for Identification, Dissolution (for Test 1—for Label L_1: Amount dissolved [individual limits]—not more than 65% in 30 minutes, 55–85% in 45 minutes, not less than 75% in 60 minutes, and not less than 85% in 120 minutes; for Level L_2: Amount dissolved [individual limits]—not more than 75% in 30 minutes, 45–95% in 45 minutes, not less than 65% in 60 minutes and not less than 75% in 120 minutes, and Amount dissolved [average limits]—not more than 65% in 30 minutes, 55–85% in 45 minutes, not less than 75% in 60 minutes, and not less than 85% in 120 minutes; for Level L_3: Amount dissolved [individual limits]—not more than 2 Tablets release more than 75%, and no individual Tablet releases more than 85% in 30 minutes, not more than 2 Tablets are outside the range of 45 to 95%, and no individual Tablet is outside the range of 35–105% in 45 minutes, not more than 2 Tablets release less than 65% and no individual Tablet releases less than 55% in 60 minutes, and not more than 2 Tablets release less than 75%, and no individual Tablet releases less than 65% in 120 minutes, and Amount dissolved [average limits]—not more than 65% in 30 minutes, 55–85% in 45 minutes, not less than 75% in 60 minutes, and not less than 85% in 120 minutes in 0.3 M phosphate buffer [pH 6.0] in Apparatus 2 at 75 rpm; for Test 2—Not more than 20% in 2 hours, 45–70% in 12 hours, and not less than 80% in 24 hours in 0.05 M phosphate buffer [pH 6.8] containing 0.5% of sodium lauryl sulfate in Apparatus 1 at 100 rpm), Loss on drying (not more than 5.0%), Uniformity of dosage units, and Residual solvents.{R-22}

ERYTHROMYCIN BASE

Oral Dosage Forms

Note: The text between [EL]US and [EL] describes uses not included in U.S. product labeling. Text between [EL]CAN and [EL] describes uses that are not included in Canadian product labeling.

The [EL-US] or [EL-CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

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].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (Rx) [*Apo-Erythro E-C; ERYC*].

333 mg (Rx) [*Apo-Erythro E-C; ERYC*].

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, Dissolution (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: [EL-US,CAN]Pyoderma—*Dogs:* Oral, 10 to 20 mg per kg of body weight every eight to twelve hours.[EL]{R-30; 42-44; 60}

Note: The above dosage recommendation is based on current clinical practice rather than specific canine pharmacokinetic data. The absorption of enteric-coated tablets in dogs can be unpredictable.{R-21}

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}

Note: Tablets that are enteric-coated meet the requirements for Erythromycin Delayed-release Tablets.{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) [*E-Mycin; Ery-Tab;* 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):

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 the 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 Dissolution Test with which the product complies. Contain the labeled amount, within –10% to +20%. Meet the requirements for Identification, Dissolution (Method B: 75% in 60 minutes for Stage 1 and 60 minutes for Stage 2 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%).{R-22}

Parenteral Dosage Forms

Note: The text between [EL-US] and [EL] describes uses not included in U.S. product labeling. Text between [EL-CAN] and [EL] describes uses that are not included in Canadian product labeling.

The [EL-US] or [EL-CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

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}

Withdrawal times—US and Canada: Meat—7 days.{R-7; 111}

Canadian product labeling states that the recommended withdrawal time applies to a dose of 22 mg per kg of body weight every twenty-four hours; this dose should not be administered to pigs < 2.25 kg of body weight.{R-7}

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}

Withdrawal times—US and Canada: Meat—3 days.{R-7; 111}

Canadian product labeling states that the recommended withdrawal time applies to a dose of 11 mg per kg of body weight every twenty-four hours; this dose should not be administered to lambs < 4.5 kg of body weight.{R-7}

Leptospirosis; or

Metritis—*Sows,* farrowing: Intramuscular, 1.1 to 3.3 mg per kg of body weight every twenty-four hours.{R-111}

Withdrawal times—US and Canada: Meat—7 days.{R-7; 111}

Canadian product labeling states that the recommended withdrawal time applies to a dose of 2.2 to 6.6 mg per kg of

body weight a day in pigs and, to avoid excessive trim, pigs should not be slaughtered for 10 days after the last injection.{R-7}

Metritis;

Pneumonia, bacterial; or

Pododermatitis—*Cattle:* Intramuscular, 1.1 to 2.2 mg per kg of body weight every twenty-four hours.{R-111}

Withdrawal times—US and Canada: Meat—14 days, Milk—72 hours.{R-7; 111} Canadian product labeling states that the recommended withdrawal times apply to doses of 2.2 to 4.4 mg per kg of body weight a day in cattle. To avoid excessive trim, cattle should not be slaughtered for 21 days after the last injection.{R-7}

Respiratory tract infections, bacterial (treatment)—

Pigs (treatment of pneumonia and respiratory syndrome): Intramuscular, 1.1 to 3.3 mg per kg of body weight every twenty-four hours.{R-111}

Withdrawal times—US and Canada: Meat—7 days.{R-7; 111} Canadian product labeling states that the recommended withdrawal time applies to a dose of 2.2 to 6.6 mg per kg of body weight a day in pigs and, to avoid excessive trim, pigs should not be slaughtered for 10 days after the last injection.{R-7}

Sheep (treatment of upper respiratory tract infections): Intramuscular, 1.1 mg per kg of body weight every twenty-four hours.{R-111}

Withdrawal times—US and Canada: Meat—3 days.{R-7; 111} Canadian product labeling states that the recommended withdrawal time applies to a dose of 2.2 mg per kg of body weight a day in sheep and, to avoid excessive trim, sheep should not be slaughtered for 10 days after the last injection.{R-7}

Note: Injections should be made deep into the muscle. Erythromycin injection should not be administered intravenously or subcutaneously.

Strength(s) usually available:

U.S.—{R-8}

Veterinary-labeled product(s):

100 mg per mL (OTC) [*Gallimycin-100*].

Canada—{R-7; 8}

Veterinary-labeled product(s):

100 mg per mL (OTC) [*Gallimycin-100*].

200 mg per mL (OTC) [*Erythro-200; Gallimycin-200*].

Note: At time of this writing, Canadian veterinary erythromycin injection products have been unavailable for at least a year.

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.{R-22}

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: The dosing and strengths of the dosage forms available are expressed in terms of erythromycin base (not the estolate salt).

The text between EL[US] and EL describes uses not included in U.S. product labeling. Text between EL[CAN] and EL describes uses that are not included in Canadian product labeling.

The EL[US] or EL[CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

ERYTHROMYCIN ESTOLATE ORAL SUSPENSION USP

Usual dose: EL[US,CAN]*Rhodococcus equi* pneumonia—*Foals:* Oral, 25 mg (base) per kg of body weight every six hours.EL{R-13; 14; 26; 143}

Note: The above dose has also been administered concurrently with 5 mg rifampin per kg of body weight.{R-13; 14; 143}

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

25 mg (base) per mL (Rx) [GENERIC].

50 mg (base) per mL (Rx) [GENERIC].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

25 mg (base) per mL (Rx) [*Novo-rythro*].

50 mg (base) per mL (Rx) [*Novo-rythro*].

Packaging and storage: Store between 2 and 8 °C (36 and 46 °F), unless otherwise specified by the manufacturer. Store in a tight container.

Auxiliary labeling:

- Refrigerate.
- Shake well.

USP requirements: Preserve in tight containers, in a cool 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 LACTOBIONATE

Parenteral Dosage Forms

Note: The strengths of the dosage forms available are expressed in terms of erythromycin base (not the lactobionate salt).

The text between EL[US] and EL describes uses not included in U.S. product labeling. Text between EL[CAN] and EL describes uses that are not included in Canadian product labeling.

The EL[US] or EL[CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

ERYTHROMYCIN LACTOBIONATE FOR INJECTION

USP

Usual dose: [EL][US,CAN]Antibacterial—*Foals:* Intravenous, 5 mg (base) per kg of body weight, administered slowly every six hours.[EL]{R-26; 143; 144}

Note: Caution is advised when administering this medication. Rapid intravenous administration of erythromycin lactobionate to foals has been reported to quickly cause elevated heart and respiratory rates, hyperthermia, wheals, or colic, followed by diarrhea.{R-145} The risk of adverse reactions appears to be reduced by diluting the dose and administering slowly by infusion.

Size(s) usually available:

U.S.—{R-39}

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

Human-labeled product(s):
500 mg (base) (Rx) [*Erythrocin;* GENERIC].
1 gram (base) (Rx) [*Erythrocin;* GENERIC].

Canada—

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

Human-labeled product(s):
500 mg (base) (Rx) [*Erythrocin;* GENERIC].
1 gram (base) (Rx) [*Erythrocin;* 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: 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.{R-22}

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 for five days.{R-3; 9}

Coryza, infectious—*Chickens:* Oral, 500 mg per gallon of water, administered as the only source of drinking water for seven days.{R-3}

Enteritis (bluecomb)—*Turkeys:* Oral, 500 mg per gallon of water, administered as the only source of drinking water for seven days.{R-3}

[EL][US]Sinusitis, infectious[EL]—*Turkeys:* Oral, 130 mg per liter of water, administered as the only source of drinking water for five days.{R-9}

[EL][US]Synovitis, infectious[EL]—*Chickens* and *turkeys:* Oral, 130 mg per liter of water, administered as the only source of drinking water for five days.{R-9}

Withdrawal times—US and Canada: *Chickens* and *turkeys*—Meat: 1 day.{R-3; 9} 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 per liter rather than per gallon of drinking water.

Note: Dosage ranges for birds are approximate, based on variable water consumption and animal size.

[EL][US,CAN]*Rhodococcus equi* pneumonia—*Foals:* Oral, 25 mg per kg of body weight every six hours.{R-18; 143}

Note: The above dose has also been administered concurrently with 5 mg rifampin per kg of body weight every twelve hours.{R-13; 14; 143} The doses recommended are based on pharmacokinetic studies in foals.[EL]

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) [*Erythro-Med; Gallimycin*].
260 mg (231.2 mg base) per gram (OTC) [*Gallimycin PFC*].

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: The dosing and strengths of the dosage forms available are expressed in terms of erythromycin base (not the stearate salt).

The text between [EL-US] and [EL] describes uses not included in U.S. product labeling. Text between [EL-CAN] and [EL] describes uses that are not included in Canadian product labeling.

The [EL-US] or [EL-CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

ERYTHROMYCIN STEARATE ORAL SUSPENSION

Usual dose:

[EL-US,CAN]Enteritis, *Campylobacter—Dogs:* Oral, 10 mg (base) per kg of body weight every eight hours.[EL] {R-10}

[EL-US,CAN]*Rhodococcus equi* pneumonia—*Foals:* Oral, 25 mg (base) per kg of body weight every six hours. {R-18; 137; 143}

Note: The above dose has also been administered concurrently with 5 mg rifampin per kg of body weight every twelve hours.{R-13; 14; 137} The dose recommended is based on a retrospective clinical study of foals and a pharmacokinetic study of horses.[EL]

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*].

50 mg (base) per mL (Rx) [*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.

Auxiliary labeling:

- Refrigerate.
- Shake well.

USP requirements: Not in USP.{R-22}

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;* 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; Erythromycine; Nu-Erythromycin-S*].

500 mg (base) (Rx) [*Apo-Erythro-S; Erythro-500*].

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%).{R-22}

ERYTHROMYCIN THIOCYANATE

Oral Dosage Forms

Note: 1.08 grams of thiocyanate salt equal 1 gram of erythromycin base.{R-54}

The text between [EL-US] and [EL] describes uses not included in U.S. product labeling. Text between [EL-CAN] and [EL] describes uses that are not included in Canadian product labeling.

The [EL-US] or [EL-CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

ERYTHROMYCIN THIOCYANATE FOR MEDICATED FEED

Usual dose:

[EL-CAN]Coryza, infectious (prophylaxis)[EL]—*Chickens:* Oral, 100 grams (93 grams of base) per ton of feed, fed as the only ration for seven to fourteen days.{R-54}

Withdrawal times—US: Meat—1 day. Not labeled for use in birds producing eggs for human consumption.{R-54}

Respiratory disease, chronic (treatment)—*Chickens* and [EL-CAN]*turkeys*[EL]: Oral, 200 grams (185 grams of base) per ton of feed, fed as the only ration.{R-54}

Withdrawal times—US: *Chickens*—Meat: 2 days. *Turkeys*—Meat: None.{R-54} Not labeled for use in birds producing eggs for human consumption.{R-54} Canada: *Chickens*—Meat: 1 day.{R-64} Product labeling states that the withdrawal applies to a dose of 220 grams per metric ton (1000 kg) of feed for five to eight days.{R-64} Not labeled for use in birds producing eggs for human consumption.

Strength(s) usually available:

U.S.—{R-8; 54}

Veterinary-labeled product(s):

220 grams (203 grams of base) per kg of premix (OTC) [*Gallimycin-100P*].

Note: At the time of most recent update, this product was reported to be temporarily unavailable.

Canada—{R-8; 64}

Veterinary-labeled product(s):

110 grams (102 grams of base) per kg of premix (OTC) [*Gallimycin-50*].

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.{R-22}

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.{R-53}

Parenteral administration of tilmicosin to pigs by any route often is fatal.{R-53}

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}

Withdrawal times—US and Canada: Meat—7 days.{R-107; 114} Canadian product labeling lists a dose of 200 grams per metric tonne (1000 kg), fed as the only ration for twenty-one days.

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 (Veterinary Feed Directive) [*Pulmotil 90*].

Canada—

Veterinary-labeled product(s):

200 grams (base) per kg (OTC) [*Pulmotil Premix*].

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: The dosing and strengths of the dosage form available are expressed in terms of tilmicosin base (not the phosphate salt).

The text between [EL US] and [EL] describes uses not included in U.S. product labeling. Text between [EL CAN] and [EL] describes uses that are not included in Canadian product labeling.

The [EL US] or [EL CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

TILMICOSIN INJECTION USP

Usual dose: Pneumonia, bacterial—

Cattle: Subcutaneous, 10 mg (base) per kg of body weight as a single dose.{R-53}

Withdrawal times—US and Canada: Meat—28 days.{R-53; 65; 112} Not labeled for use in lactating cattle.

Note: A single subcutaneous tilmicosin dose of 10 mg per kg of body weight administered to lactating dairy cattle 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}

Sheep: Subcutaneous, 10 mg (base) per kg of body weight as a single dose.{R-6; 65; 112} Administration to lambs weighing less than 15 kg is not recommended, because safety has not been established.{R-6}

Withdrawal times—US and Canada: Meat—28 days.{R-6; 65; 112} Not labeled for use in lactating sheep, if the milk is intended for human consumption.{R-92}

Note: Intravenous tilmicosin administration is fatal and to be avoided in all species.{R-6} Other parenteral routes of administration have been fatal to pigs and nonhuman primates. Any species other than cattle and sheep may be relatively susceptible to toxicity.{R-6} See also *Caution* below.

Intramuscular administration causes a local reaction that may cause trim loss. No more than 15 mL should be administered per injection site.{R-53}

Administration of tilmicosin injection to horses is not recommended; subcutaneous administration produces a severe local reaction.{R-141}

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*].

Packaging and storage: Store at or below 30 °C (86 °F). Protect from light.{R-53}

Caution: Injection of tilmicosin in humans has been associated with fatalities.{R-6} Toxicity occurs in the cardiovascular system and may be due to calcium channel blackade. Extreme caution should be exercised to avoid self-injection. An automatically powered syringe should not be used for administration.{R-53}

In case of accidental human injection, immediate medical attention is recommended, while applying ice or cold pack to the injection site during transport.{R-6}

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 °C. 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}

TULATHROMYCIN

Summary of Differences

Pharmacology/pharmacokinetics: Rapidly and well absorbed with parenteral administration.

Parenteral Dosage Forms

Note: The text between [EL US] and [EL] describes uses not included in U.S. product labeling. Text between [EL CAN] and [EL] describes uses that are not included in Canadian product labeling.

The [EL US] or [EL CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

TULATHROMYCIN INJECTION

Usual dose: [EL CAN]Pneumonia[EL]—

Cattle: Subcutaneous, 2.5 mg per kg of body weight, as a single dose.{R-129}

Withdrawal times—US: *Cattle*—Meat: 18 days. This product is not labeled for use in female dairy cattle twenty months of age or older or for calves to be processed for veal.{R-129}

Pigs: Intramuscular, 2.5 mg per kg of body weight, as a single dose.{R-129}

Withdrawal times—US: *Pigs*—Meat: 5 days.{R-129}

Note: Administration in the neck area is recommended. In cattle, no more than 10 mL per injection site is recommended and, in pigs, no more than 2.5 mL per site.{R-129} Administration as directed may cause a transient local tissue reaction that can result in trim loss of edible tissues at slaughter.

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

100 mg per mL (Rx) [*Draxxin*].{R-129}

Canada—

Veterinary-labeled product(s):

Not commercially available.

Packaging and storage: Store at or below 25 °C (77 °F), unless otherwise specified by manufacturer.{R-129}

USP requirements: Not in USP.{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: The text between EL[US] and EL describes uses not included in U.S. product labeling. Text between EL[CAN] and EL describes uses that are not included in Canadian product labeling.

The EL[US] or EL[CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

TYLOSIN INJECTION

Usual dose:

EL[CAN]Arthritis, infectiousEL;

Erysipelas;

Pneumonia; or

Swine dysentery—*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.{R-51; 52} When used to treat swine dysentery, tylosin injection should be followed by administration of medication in feed or drinking water.{R-51}

Withdrawal times—US and Canada: Meat—14 days.{R-51; 52; 55} United States product labeling states that the withdrawal times apply to a maximum treatment period of 3 days in pigs.{R-51; 52} Canadian product labeling states that the withdrawal time applies to a dose of 2.2 to 8.8 mg per kg of body weight every 24 hours. To avoid excessive trim, swine should not be slaughtered for 21 days after treatment.{R-55}

EL[CAN]DiphtheriaEL;

Metritis;

Pneumonia; or

EL[CAN]PododermatitisEL—*Cattle,* beef and nonlactating dairy: Intramuscular, 17.6 mg per kg of body weight every twenty-four hours.{R-51; 52; 55}

Note: In cattle, no more than 10 mL per injection site is recommended.{R-51; 52}

Withdrawal times—US and Canada: Meat—21 days.{R-51; 52; 55} United States product labeling states that the withdrawal time applies to a maximum treatment period of 5 days in cattle.{R-51; 52} Not labeled for use in lactating dairy cattle.{R-51} Canadian product labeling states that to avoid excessive trim, cattle should not be slaughtered for 42 days after treatment.{R-55}

Note: EL[US,CAN]Respiratory tract infections—*Cats* and *dogs:* A dose of 6.6 to 11 mg per kg of body weight every twelve to twenty-four hours has been used.EL{R-108}

Strength(s) usually available:{R-8}

U.S.—

Veterinary-labeled product(s):

50 mg per mL (OTC) [*Tylan 50; TyloVed*].

200 mg per mL (OTC) [*Tylan 200; TyloVed;* GENERIC].

Canada—{R-55}

Veterinary-labeled product(s):

200 mg per mL (OTC) [*Tylan 200*].

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}

TYLOSIN PHOSPHATE

Oral Dosage Forms

Note: The text between EL[US] and EL describes uses not included in U.S. product labeling. Text between EL[CAN] and EL describes uses that are not included in Canadian product labeling.

The EL[US] or EL[CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

TYLOSIN GRANULATED USP

Usual dose:

Abscesses, hepatic (prophylaxis)—*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}

Withdrawal times—US and Canada—Meat: None. Canadian product labeling lists a dose of 11 grams per metric tonne (1000 kg) of feed.

EL[CAN]Atrophic rhinitisEL—*Pigs:* Oral, 100 grams per ton of feed, fed as the only ration.{R-49}

Withdrawal times—US: Meat—None.{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 granulated should follow an initial treatment with tylosin powder for oral solution in the drinking water for three to ten days.{R-49; 100}

Withdrawal times—US and Canada: Meat—None.{R-49} When tylosin granulated is administered concurrently with tylosin tartrate powder for oral solution, a withdrawal time of 2 days is necessary.{R-48; 49}

Feed efficiency, improvement of; or

Increased weight gain—

[EL CAN] *Chickens* [EL]: Oral, 4 to 50 grams per ton of feed, fed as the only ration.{R-49}

Withdrawal times—US: Meat—None.{R-49}

Pigs:

Pre-starter or starter: Oral, 20 to 100 grams per ton of feed, fed as the only ration.{R-48; 49}

Grower: Oral, 20 to 40 grams per ton of feed, fed as the only ration.{R-48; 49}

Finisher: Oral, 10 to 20 grams per ton of feed, fed as the only ration.{R-48; 49}

Withdrawal times—US and Canada: Meat—None.{R-49}

Canadian product labeling lists a dose of 11 to 44 grams per metric tonne (1000 kg) of feed.

Proliferative enteropathy, porcine (prophylaxis and treatment)—

Pigs: Oral, 100 grams per ton of feed, fed as the only ration for three weeks.{R-49}

Withdrawal times—US and Canada: Meat—None.{R-49}

[EL CAN] Respiratory disease, chronic [EL]—

Chickens, broiler: Oral, 800 to 1000 grams per ton of feed, fed as the only ration.

Chickens, replacement: Oral, 1000 grams per ton of feed, fed as the only ration.

Withdrawal times—US: Meat—5 days.{R-49}

Note: Medication should be administered in feed to chickens up to 5 days of age, then administered again for twenty-four to forty-eight hours to chickens 3 to 5 weeks of age.

Strength(s) usually available:{R-8}

U.S.—

Veterinary-labeled product(s):

22 grams per kg (10 grams per pound) of premix (OTC) [*Tylan 10*].

88 grams per kg (40 grams per pound) of premix (OTC) [*Tylan 40*].

220 grams per kg (100 grams per pound) of premix (OTC) [*Tylan 100*].

Canada—

Veterinary-labeled product(s):

22 grams per kg of premix (OTC) [*Tylan 10; Tylosin 10 Premix*].

88 grams per kg of premix (OTC) [*Tylan 40; Tylosin 40 Premix*].

220 grams per kg of premix (OTC) [*Tylan 100*].

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.{R-49}

Caution: When handling and mixing medication, protective clothing and impervious gloves should be used. Contact with human skin should be avoided.{R-49}

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 to indicate that it is for animal use only. Label it also 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.{R-22}

TYLOSIN TARTRATE

Oral Dosage Forms

Note: 1.1 grams of tylosin tartrate equals 1 gram of tylosin base.{R-90} The dosing and strengths of the dosage forms available are expressed in terms of the base.

The text between [EL US] and [EL] describes uses not included in U.S. product labeling. Text between [EL CAN] and [EL] describes uses that are not included in Canadian product labeling.

The [EL US] or [EL CAN] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

TYLOSIN TARTRATE POWDER FOR ORAL SOLUTION

Usual dose:

Dysentery, swine; or

[EL US] Proliferative enteropathy, porcine [EL]—*Pigs:* Oral, 250 mg per gallon of water, as the only source of drinking water for three to ten days.{R-50; 126}

Withdrawal times—US and Canada: Meat—2 days.{R-66}

[EL CAN] Foulbrood, American [EL]—*Bees,* honey: Oral, 200 mg per bee colony, mixed in twenty grams of powdered sugar and administered as a dust applied over the top bars of the brood chamber once a week for three doses.{R-127}

Withdrawal times—US: Treatment should be completed at least 4 weeks before the main honey flow.{R-127} To avoid contaminating production honey, treatment is typically performed in the spring and/or fall.{R-127}

[EL US] Necrotic enteritis [EL]—*Chickens:* Oral, 150 mg (base) per liter in the only source of drinking water for five days.{R-126}

Withdrawal times—Canada: Meat—1 day.{R-50; 66} Not labeled for use in birds producing eggs for human consumption.{R-50}

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.{R-50}

Withdrawal times—US and Canada: Meat—1 day.{R-50; 66} Not labeled for use in birds producing eggs for human consumption.{R-50}

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.{R-50}

Withdrawal times—US: Meat—5 days.{R-50} Canada: Meat—3 days.{R-66}

Note: [EL US,CAN] Diarrhea, chronic—*Dogs:* There are insufficient data to establish the efficacy of tylosin in the treatment of chronic diarrhea in dogs; however, an oral dose of 11 mg per kg of body weight every eight hours or 20 mg per kg of body weight every twenty-four hours has been recommended.{R-84; 135} Some dogs with diarrhea that had only a moderate response to diet were controlled for long periods when diet change was combined with a ten-day regimen of tylosin tartrate.[EL]{R-135}

Note that reformulation is necessary for administration to dogs.[EL]{R-109}

Size(s) usually available:{R-8; 50}

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) [*Tylan Soluble*].

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]

Table 1. Pharmacology/Pharmacokinetics

Drug	Protein Binding (%)	Elimination Half-life (hr)	Volume of Distribution (L/kg)	Clearance (mL/min/kg)	Route; Dose (mg/kg)	Tmax (hr)	Cmax (mcg/mL)	Bioavail-ablity (%)
Azithromycin								
Cats[R-120]		35	Vd_{ss} 23	10.7	IV; 5			
					PO; 5	0.85	0.97	58
Dogs (beagles) [R-123]	16–26*	29	Vd_{ss} 12		IV; 24			
					PO; 24	0.33	4.2	97
Foals, 8- to 14-weeks[R-121]		16	Vd_{area} 12.4	10	IV; 5			
		16.3	Vd_{ss} 11.6					
					PO; 10	1.4	0.72	39
Foals, 6- to 10-weeks[R-122]		20.3	Vd_{area} 22.3	10.4	IV; 10			
			Vd_{ss} 18.6					
					PO; 10	1.8	0.57	56
Human data[R-115]	7–50†	11 to 14	Vd_{ss} 33		PO: 500 mg total dose	2 to 3	0.4	37
Rats[R-123]	14–29*	32	Vd_{ss} 84		IV; 20			
					PO; 20	2.0	0.29	46
Clarithromycin								
Dogs (crossbred beagles)[R-124]		3.9	Vd_{ss} 1.4	4.3	IV; 10			
Fed					PO; 10	1.6	3.3	70
Fasted					PO; 10	1.7	3.5	79
Foals[R-139]					PO; 10§	1.5	0.9	
Erythromycin								
Calves[R-23]		2.2	Vd_{area} 1.5	7.8	IV; 15			
Cattle[R-21]	18				IV/IM; 20			
[R-25]		3.2	Vd_{area} 0.79	2.9	IV; 12.5			
Dogs[R-62]		1.7	Vd_{ss} 2.7	21	IV; 10			
Horses, foals[R-26]		1	Vd_{area} 2.3 to 7.2		IV; 5 to 20			
Mice[R-62]		0.7	Vd_{ss} 3.6	77	IV; 10			
Pigeons[R-27]		0.9			IV; 20			
					PO; 100			10
Rabbits[R-62]		0.7	Vd_{ss} 6.8	53	IV; 10			
Rats[R-62]		0.7	Vd_{ss} 9.3	73	IV; 25			
Sheep[R-21]	23				IV/IM; 20			
Tilmicosin								
Cattle[R-91]					SC; 10	1.8	0.13	
[R-104]					SC; 10	1	0.71	
Tulathromycin								
Calves, 181 to 246 kg[R-131; 133]	40	65‡	Vd_{area} 11.1	3.0	IV; 2.5			
					SC; 2.5	0.25	0.41	91
Pigs, 2 to 3 months of age[R-132]	40	68‡	Vd_{ss} 13.2	3.0	IV; 2.5			
					IM; 2.5	0.25	0.62	88
Tylosin								
Calves, newborn[R-73]		2.3	Vd_{area} 4.4	24.5	IV; 10			
Calves, 1 week to 9 months		1 to 1.5	Vd_{area} 3.6 to 4.4	32 to 48	IV; 10			
Calves, 7 weeks[R-69]		1.2	Vd_{area} 2.5	23.7	IV; 10			
Chickens[R-71]	30							
Cattle[R-20]	33.5				IV/IM; 20			
[R-25; 80]		1.6	Vd_{area} 1.1	7.8	IV; 12.5			
[R-79]		2.1			IV; 20			

Dogs[R-68]		0.9	Vd_{area} 1.7	22	IV; 10 IM; 10	0.5	1.5	
Goats[R-72]	38	3	Vd_{area} 1.7	6.8	IM; 15	4.2	2.4	73
Sheep[R-20]	38				IV/IM; 20			
[R-79]		2.1			IV; 20			

*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.
‡Harmonic mean
§Intragastric administration

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