Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Tulathromycin Injection 100 mg/mL in 50, 100, 250, & 500 mL vials: *Draxxin®* (Pfizer); Approved for use in cattle and swine. Cattle intended for human consumption must not be slaughtered within 18 days from the last treatment. Do not use in female dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

HUMAN-LABELED PRODUCTS: None

TYLOSIN

(*tye*-loe-sin) Tylan®

MACROLIDE ANTIBIOTIC

Prescriber Highlights

- Macrolide antibiotic related to erythromycin, used primarily in cattle & swine; sometimes used orally in cats/dogs for chronic colitis
- Contraindications: hypersensitivity to it or other macrolide antibiotics; probably contraindicated in horses
- Adverse Effects: Pain & local reactions after IM injection, GI upset (anorexia, & diarrhea). May cause severe diarrheas if administered PO to ruminants or by any route to horses. SWINE: edema of rectal mucosa & mild anal protrusion with pruritus, erythema, & diarrhea

Uses/Indications

Although the injectable form of tylosin is approved for use in dogs and cats, it is rarely used parenterally in those species. Oral tylosin is sometimes recommended for the treatment of chronic colitis in small animals (see Doses), but controlled studies documenting its efficacy have not been performed.

Tylosin is also used clinically in cattle and swine for infections caused by susceptible organisms.

Pharmacology/Actions

Tylosin is thought to have the same mechanism of action as erythromycin (binds to 50S ribosome and inhibits protein synthesis) and exhibits a similar spectrum of activity. It is a bacteriostatic antibiotic. Tylosin may also have immunomodulatory effects on cell-mediated immunity. In dogs, tylosin increases concentrations of enterococci (*Enterococcus fecalis*) in the jejunum. Enterococci are thought to have probiotic effects.

For more specific information on organisms where tylosin is usually active, refer to the erythromycin monograph; cross-resistance with erythromycin occurs.

Pharmacokinetics

Tylosin tartrate is well absorbed from the GI tract, primarily from the intestine. The phosphate salt is less well absorbed after oral administration. Tylosin base injected SC or IM is reportedly rapidly absorbed.

Like erythromycin, tylosin is well distributed in the body after systemic absorption, with the exception of penetration into the CSF. The volume of distribution of tylosin is reportedly 1.7 L/kg in small animals and 1–2.3 L/kg in cattle. In lactating dairy cattle, the milk to plasma ratio is reported to be between 1–5.4.

Tylosin is eliminated in the urine and bile apparently as unchanged drug. The elimination half-life of tylosin is reportedly 54 minutes in small animals, 139 minutes in newborn calves, and 64 minutes in calves 2 months of age or older.

Contraindications/Precautions/Warnings

Tylosin is contraindicated in patients hypersensitive to it or other macrolide antibiotics (*e.g.*, erythromycin). Most clinicians feel that tylosin is contraindicated in horses, as severe and sometimes fatal diarrheas may result from its use in that species.

Adverse Effects

Most likely adverse effects with tylosin are pain and local reactions at intramuscular injection sites, and mild GI upset (anorexia and diarrhea). Tylosin may induce severe diarrheas if administered orally to ruminants or by any route to horses. In swine, adverse effects reported include edema of rectal mucosa and mild anal protrusion with pruritus, erythema, and diarrhea.

Reproductive/Nursing Safety

In a system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***B*** (*Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term.*)

Overdosage/Acute Toxicity

Tylosin is relatively safe in most overdose situations. The LD_{50} in pigs is greater than 5 g/kg orally, and approximately 1 g/kg IM. Dogs are reported to tolerate oral doses of 800 mg/kg. Long-term (2 year) oral administration of up to 400 mg/kg produced no organ toxicity in dogs. Shock and death have been reported in baby pigs overdosed with tylosin, however.

Drug Interactions

Drug interactions with tylosin have not been well documented. It has been suggested that tylosin may increase **digoxin** blood levels with resultant toxicity. It is suggested to refer to the erythromycin monograph for more information on potential interactions.

Laboratory Considerations

- Macrolide antibiotics may cause falsely elevated values of **AST** (SGOT), and **ALT** (SGPT) when using colorimetric assays.
- Fluorometric determinations of **urinary catecholamines** can be altered by concomitant macrolide administration.

Doses

- **DOGS:**

  When using *Tylan® Soluble* (100 grams per bottle) powder: Using volumetric containers to measure powders is not necessarily accurate, but 1 level teaspoonful (5 mL) of powder contains approximately 2.5–2.7 grams of tylosin; 1/8th of a teaspoonful contains approximately 325 mg tylosin.

  a) For small intestinal bacterial overgrowth: 10–20 mg/kg PO q12h; recommended for chronic cases, may require therapy for as long as 6 weeks. (Ludlow and Davenport 2000)

  b) For adjunctive treatment of IBD: 10 mg/kg PO three times daily. Therapeutic trial for 21 days to evaluate efficacy. (Simpson 2003a)

c) For clostridial colitis: 10–40 mg/kg PO twice daily. Practically (using the wettable powder): 1/16th of teaspoon 2–3 times daily for dogs (<7kg); 1/8th of a teaspoon 2–3 times a day for medium dogs (7–15 kg); and 1/4 teaspoon 2–3 times a day for larger dogs (>15 kg). Mix with food to hide unpleasant taste or put into capsules. Animals with chronic clostridial colitis can often be controlled with one treatment every 2–3 days. (Willard 2006a)

d) For IBD and antibiotic responsive diarrhea: 20–40 mg/kg PO q12h (Marks 2007b)

■ **CATS:**

When using *Tylan® Soluble* (100 grams per bottle) powder: Using volumetric containers to measure powders is not necessarily accurate, but 1 level teaspoonful (5 mL) of powder contains approximately 2.5–2.7 grams of tylosin; 1/8th of a teaspoonful contains approximately 325 mg tylosin.

a) For adjunctive treatment of IBD: 10 mg/kg PO three times daily. Therapeutic trial for 21 days to evaluate efficacy. (Simpson 2003a)

b) For treatment of IBD or diarrheas caused by *C. perfringens*: 20–40 mg/kg PO twice daily (Marks 2002)

c) For IBD: 40 mg/kg PO q12h (Zoran 2007)

d) For clostridial colitis: 10–40 mg/kg PO twice daily. Practically (using the wettable powder): 1/16th of teaspoon 2–3 times daily. Mix with food to hide unpleasant taste or put into capsules. Animals with chronic clostridial colitis can often be controlled with one treatment every 2–3 days. (Willard 2006a)

■ **FERRETS:**

For susceptible infections:

a) 10 mg/kg PO once to twice daily (Williams 2000)

■ **RABBITS, RODENTS, SMALL MAMMALS:**

a) Rabbits: 10 mg/kg PO, SC, IM q12–24h (Ivey and Morrisey 2000)

b) Gerbils, Hamsters, Rats: 10 mg/kg SC q24h (Adamcak and Otten 2000)

■ **CATTLE:**

For susceptible infections:

a) 17.6 mg/kg IM once daily. Continue treatment for 24 hours after symptoms have stopped, not to exceed 5 days. Do not inject more than 10 mL per site. Use the 50 mg/mL formulation in calves weighing less than 200 pounds. (Package insert; *Tylosin® Injection*—TechAmerica)

b) For bronchopneumonia and fibrinous pneumonia in cattle associated with penicillin G-refractory *C. pyogenes* infections or other bacteria sensitive to tylosin and resistant to sulfas, penicillin G and tetracyclines: using Tylosin 200 mg/mL: 44 mg/kg IM q24h. Recommend a 21-day slaughter withdrawal at this dosage. (Hjerpe 1986)

c) 5–10 mg/kg IM or slow IV once daily; not to exceed 5 days (Huber 1988a)

d) Tylosin base injectable: 10 mg/kg IM initially, then 6 mg/kg IM q8h (q8–12h in calves) (Baggot 1983)

■ **SWINE:**

For susceptible infections:

a) 8.8 mg/kg IM twice daily. Continue treatment for 24 hours after symptoms have stopped, not to exceed 3 days. Do not inject more than 5 mL per site. (Package insert; *Tylosin® Injection*—TechAmerica)

b) 5–10 mg/kg until 24 hours after remission of disease signs; not to exceed 3 days therapy (Huber 1988a)

c) Tylosin base injectable: 12.5 mg/kg IM q12h (Baggot 1983)

■ **SHEEP & GOATS:**

For susceptible infections:

a) 10 mg/kg, treatment not to exceed 5 days (Huber 1988a)

■ **BIRDS:**

For susceptible infections:

a) For initial therapy in caged birds for upper respiratory infections (especially if mycoplasma suspected).

Using 200 mg/mL injectable: 40 mg/kg IM. Used in combination with aminoglycosides. (McDonald 1989)

b) For initial therapy of upper respiratory infections and air sacculitis. Using 50 mg/mL or 200 mg/mL injectable: 10–40 mg/kg IM twice daily or three times daily (Clubb 1986)

c) 30 mg/kg IM q12h (Hoeffer 1995)

■ **REPTILES:**

For susceptible infections:

a) For tortoises: 5 mg/kg IM once daily for at least 10 days. Used primarily for chronic respiratory infections or when Mycoplasma is suspected (Gauvin 1993)

b) All species: 5 mg/kg IM once daily (Jacobson 1999)

Monitoring

■ Clinical efficacy

■ Adverse effects

Chemistry/Synonyms

A macrolide antibiotic related structurally to erythromycin, tylosin is produced from *Streptomyces fradiae*. It occurs as an almost white to buff-colored powder with a pK_a of 7.1. It is slightly soluble in water and soluble in alcohol. Tylosin is considered highly lipid soluble. The tartrate salt is soluble in water. The injectable form of the drug (as the base) is in a 50% propylene glycol solution.

Tylosin may also be known as Desmycosin, tilosina, tylozin, tylosiini, tylosinum, tylozyna or *Tylan®*.

Storage/Stability/Compatibility

Unless otherwise instructed by the manufacturer, injectable tylosin should be stored in well-closed containers at room temperature. Tylosin, like erythromycin, is unstable in acidic (pH <4) media. It is not recommended to mix the parenteral injection with other drugs.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Note: The product *Tylan® Plus Vitamins* was used extensively orally in companion animals, but has been withdrawn from the market. *Tylan® Soluble* may be substituted, but is significantly more concentrated than *Tylan® Plus Vitamins* and dosage sizes (teaspoons are not equivalent) will be different.

Tylosin Injection: 50 mg/mL, 200 mg/mL; *Tylan®* (Elanco); generic; (OTC). Approved for use in nonlactating dairy cattle, beef cattle, swine, dogs, and cats. Slaughter withdrawal (at labeled doses): cattle = 21 days; swine = 14 days. **Note:** Although this author (Plumb) was unable to locate parenteral products approved for use in lactating dairy animals, one source (Huber 1988a) states that tylosin has a 72 hour milk withdrawal for dairy cattle, and 48 hour milk withdrawal in dairy goats and sheep. Contact FARAD for more information before using in lactating dairy animals.

Tylosin Tartrate Powder: (approximately 2.5–2.7 grams/level teaspoonsful) in 100 g bottles; *Tylan® Soluble* (Elanco); (OTC). Approved for use in turkeys (not layers), chickens (not layers) and swine. Slaughter withdrawal swine = 2 days; chickens = 1 day; turkeys = 5 days.

There are many approved tylosin products for addition to feed or water for use in beef cattle, swine, and poultry. Many of these products have other active ingredients included in their formulations.

HUMAN-LABELED PRODUCTS: None.

URSODIOL

(ur-soe-***dye***-ole) Actigall®, Ursodeoxycholic acid

BILE ACID

Prescriber Highlights

- Bile acid that may be useful for treatment of hepatobiliary disease in dogs/cats. May also be used for cholesterol containing gallstones
- Contraindications: Rabbits & other hindgut fermenters. Caution: Complications associated with gallstones (*e.g.*, biliary obstruction, biliary fistulas, cholecystitis, pancreatitis, cholangitis)
- Adverse Effects: Appears to be well tolerated in dogs/cats

Uses/Indications

In small animals, ursodiol may be useful as adjunctive therapy for the medical management of cholesterol-containing gallstones and/or in patients with chronic liver disease, particularly where cholestasis (bile toxicity) plays an important role. Ursodiol's benefit in treating canine or feline hepatobiliary disease is unknown at the time of writing (studies are ongoing), but it may be of help in slowing the progression of inflammatory hepatic disorders, particularly autoimmune hepatitis and acute hepatotoxicity.

Pharmacology/Actions

After oral administration, ursodiol suppresses hepatic synthesis and secretion of cholesterol. Ursodiol also decreases intestinal absorption of cholesterol. By reducing cholesterol saturation in the bile, it is thought that ursodiol allows solubilization of cholesterol-containing gallstones. Ursodiol also increases bile flow and in patients with chronic liver disease, it apparently reduces the hepatocyte toxic effects of bile salts by decreasing their detergent action, and may protect hepatic cells from toxic bile acids (*e.g.*, lithocholate, deoxycholate, and chenodeoxycholate).

Pharmacokinetics

Ursodiol is well absorbed from the small intestine after oral administration. In humans, up to 90% of dose is absorbed. After absorption, it enters the portal circulation. In the liver, it is extracted and combined (conjugated) with either taurine or glycine and secreted into the bile. Only very small quantities enter the systemic circulation and very little is detected in the urine. After each entero-hepatic cycle, some quantity of conjugated and free drug undergoes bacterial degradation; eventually most of the drug is eliminated in the feces after being oxidized or reduced to less soluble compounds. Ursodiol detected in the systemic circulation is highly bound to plasma proteins.

Contraindications/Precautions/Warnings

Ursodiol is contraindicated in rabbits and other hindgut fermenters as it is converted into lithocholic acid (toxic). Patients sensitive to other bile acid products may also be sensitive to ursodiol. The benefits of using ursodiol should be weighed against its risks in patients with complications associated with gallstones (*e.g.*, biliary obstruction, biliary fistulas, cholecystitis, pancreatitis, cholangitis). While ursodiol may be useful in treating patients with chronic liver disease, some patients may experience further impairment of bile acid metabolism.

Adverse Effects

While ursodiol use in animals has been limited, it appears to be well tolerated in dogs and cats. Although hepatotoxicity has not been associated with ursodiol therapy, some human patients have an inability to sulfate lithocholic acid (a naturally occurring bile acid and also a metabolite of ursodiol). Lithocholic acid is a known hepatotoxin; veterinary significance is unclear. Diarrhea and other GI effects have rarely been noted in humans taking ursodiol. Ursodiol will not dissolve calcified radiopaque stones or radiolucent bile pigment stones.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*)

It is not known whether ursodiol is excreted in breast milk.

Overdosage/Acute Toxicity

Overdosage of ursodiol would most likely cause diarrhea. Treatment, if required, could include supportive therapy; oral administration of an aluminum-containing antacid (*e.g.*, aluminum hydroxide suspension); gastric emptying (if large overdose) with concurrent administration of activated charcoal or cholestyramine suspension.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving ursodiol and may be of significance in veterinary patients:

- **ALUMINUM-CONTAINING ANTACIDS:** May bind to ursodiol, thereby reducing its efficacy
- **CHOLESTYRAMINE RESIN:** May bind to ursodiol, thereby reducing its efficacy

Laboratory Considerations

- As ursodiol is detected by many **serum bile acid** tests, bile acids may remain falsely elevated. One study in normal dogs did not show any effects, however.

Doses

- **DOGS:**

For adjunctive treatment of chronic hepatitis:

a) 5–15 mg/kg PO divided q12h, with immunosuppressive therapy. (**Note:** Use of this drug at this dose is preliminary, but promising) (Johnson and Sherding 1994)

b) 10–15 mg/kg PO once daily (Leveille-Webster and Center 1995); (Twedt 1999)

c) For use in chronic active hepatitis, fibrosis and cirrhosis. May use as primary or adjunctive therapy. Dose: 11–15.4 mg/kg PO either once daily or divided twice daily (Tams 2000)