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)

■ **CATS:**

For adjunctive treatment of chronic hepatitis:

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

b) 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. Cats usually get 1/6th of a capsule mixed with a small amount of food. Cats may still eat their food even if drug is sprinkled on top. (Tams 2000)

c) 10 mg/kg/day PO (Zoran 2006b)

Monitoring

■ Efficacy (ultrasonography for gallstones; improved liver function tests for chronic hepatic disease)

■ Monitoring of SGPT/SGOT (AST/ALT) on a routine basis (in humans these tests are recommended to be performed at the initiation of therapy and at 1 and 3 months after starting therapy; then every 6 months).

Client Information

■ Because ursodiol dissolves more rapidly in the presence of bile or pancreatic juice, it should be given with food.

Chemistry/Synonyms

A naturally occurring bile acid, ursodiol, also known as ursodeoxycholic acid has a molecular weight of 392.6.

Ursodiol may also be known as: acidum ursodeoxycholicum, UDCA, ursodesoxycholic acid; many trade names are available.

Storage/Stability

Unless otherwise specified by the manufacturer, ursodiol capsules should be stored at room temperature (15–30°C) in tight containers.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Ursodiol Capsules: 300 mg; *Actigall®* & generic (Watson); (Rx)

Ursodiol Tablets: 250 mg & 500 mg; *URSO® 250* & *-Forte* (Axcan Pharma); (Rx)

VALPROIC ACID
VALPROATE SODIUM
DIVALPROEX SODIUM

(***val***-proe-***ik***; val-***proe***-ayte; die-val-proe-ex)

Depakene®, Depakote®, Depacon®

Prescriber Highlights

- **2nd to 4th line anticonvulsant that may be useful as adjunctive treatment in some dogs; most do not recommend its use in veterinary patients**
- **Contraindications: Significant hepatic disease or dysfunction, previous hypersensitivity**
- **Caution: Thrombocytopenia or altered platelet aggregation function**
- **Adverse Effects: GI effects (may be diminished by giving with food) most likely; hepatotoxicity, CNS (sedation, ataxia, behavioral changes, etc.), dermatologic reactions, (alopecia, rash, etc.), hematologic reactions, (thrombocytopenia, reduced platelet aggregation, leukopenias, anemias, etc.), pancreatitis, & edema are possible**
- **May be teratogenic**

Uses/Indications

Because of its cost, apparent unfavorable pharmacokinetic profile, and potential hepatotoxicity, valproic acid must be considered at best, a third or fourth line drug in the treatment of seizures in the dog. Some clinicians feel it is of benefit when added to phenobarbital in patients not adequately controlled with that drug alone. Additionally, it is less protein bound in dogs than in humans, so the human serum therapeutic range of the drug (40–100 mcg/mL) may be too high in dogs. The drug (free form) actually may concentrate in the CSF, and anticonvulsant effects may persist even after valproate levels are non-detectable in CSF, lending to the idea that serum levels do not accurately reflect clinical efficacy. Clearly, additional studies are needed to determine the clinical role, if any, for this drug.

Pharmacology/Actions

The mechanism of the anticonvulsant activity of valproic acid is not understood. Animal studies have demonstrated that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase causing increased CNS levels of GABA. Additionally, one study has demonstrated that valproic acid inhibits neuronal activity by increasing potassium conductance.

Pharmacokinetics

Sodium valproate is rapidly converted to valproic acid in the acidic environment of the stomach where it is rapidly absorbed from the GI tract. The bioavailability reported in dogs following oral administration is approximately 80%; peak levels occur in approximately 1-hour. Food may delay absorption, but does not alter the extent of it. Divalproex in its enteric-coated form has an approximately 1-hour delay in its oral absorption. Patients' who exhibit GI (nausea, vomiting) adverse effects may benefit from this dosage form.

Valproic acid is rapidly distributed throughout the extracellular water spaces and plasma. It is approximately 80–95% plasma protein bound in humans, and 78–80% plasma protein bound in