Drug Interactions

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

- **AMITRIPTYLINE:** Topiramate may increase levels
- **CARBONIC ANHYDRASE INHIBITORS (acetazolamide, dichlorphenamide,** etc.): Used concomitantly with topiramate, may increase the risk of renal stone formation
- **CNS DEPRESSANT DRUGS, OTHER:** Other CNS depressant drugs may exacerbate the adverse effects of topiramate
- **LAMOTRIGINE:** May increase topiramate levels
- **PHENYTOIN:** May decrease topiramate levels; phenytoin levels may increase
- **VALPROIC ACID:** May decrease topiramate and VPA levels

Laboratory Considerations

No specific laboratory interactions or considerations were noted. Plasma concentrations of topiramate are usually not monitored in human patients, but therapeutic levels are thought to range from 2–25 mg/L.

Doses

- **DOGS:**
  a) As an alternative second line anticonvulsant: 5–10 mg/kg PO q12h (Shell 2003c)
  b) As an alternative treatment for refractory generalized and focal seizures: 5–10 mg/kg PO twice daily (Smith 2002b)
  c) Initial dose of 2–10 mg/kg PO q12h. (Podell 2006a)
  d) 5–10 mg/kg PO twice daily; start at the lower dosage to reduce adverse effects. (Kortz 2005)
- **CATS:**
  a) 12.5–25 mg PO (total dose) q8–12h. (Podell 2006a)

Monitoring

- Efficacy
- Adverse effects

Client Information

- Clients must understand that the clinical use of this agent is relatively "investigational" in veterinary patients, that it must be dosed often in dogs, and the potential costs
- Caution clients not to stop therapy abruptly or "rebound" seizures may occur
- Have clients maintain a seizure diary to help determine efficacy

Chemistry/Synonyms

A sulfamate-substituted derivative of D-fructose antiepileptic, topiramate occurs as a white crystalline powder with a bitter taste. Its solubility in water is 9.8 mg/mL; it is freely soluble in alcohol.

Topiramate may also be known as: McN-4853, RWJ-17021, *Epitomax®, Topamac®, Topamax®*, or *Topimax®*.

Storage/Stability

Topiramate tablets should be stored in tight containers at room temperature (15–30°C; 59–86°F); protect from moisture. Topiramate sprinkle capsules should be stored in tight containers at temperatures below 25°C (76°F); protect from moisture.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 2 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Topiramate Tablets: 25 mg, 50 mg and 100 mg; Sprinkle Capsules: 15 mg & 25 mg; *Topamax®* (Ortho-McNeil); generic; (Rx)

TORSEMIDE

(*tor*-she-myde) Demadex®, Torasemide

LOOP DIURETIC

Prescriber Highlights

- **Potent loop diuretic potentially useful for adjunctive treatment of CHF in dogs & cats; very little information available on clinical use in veterinary medicine**
- **Approximately 10X more potent, longer diuretic action, & more potassium-sparing (in dogs) than furosemide**
- **May be more expensive than furosemide, but tablets are now available generically**

Uses/Indications

Torsemide is a loop diuretic similar to furosemide, but it is more potent, its diuretic effects persist for a longer period, and it does not cause as much potassium excretion (in dogs). While clinical use in dogs and cats thus far has been minimal, it potentially may be a useful adjunctive treatment for congestive heart failure in dogs and cats, particularly in patients that have become refractory to furosemide.

Pharmacology/Actions

Torsemide, like furosemide inhibits sodium and chloride reabsorption in the ascending loop of Henle via interference with the chloride-binding site of the 1Na+, 1K+, 2Cl- cotransport system.

Torsemide increases renal excretion of water, sodium, potassium, chloride, calcium, magnesium, hydrogen, ammonium, and bicarbonate. In dogs, excretion of potassium is affected much less so than is sodium (20:1); this is approximately twice the ratio of Na:K excreted than with furosemide. In cats, torsemide's effects on potassium excretion appear to be similar to that of furosemide. In dogs, torsemide appears to have differing effects on aldosterone than furosemide. When compared to furosemide, torsemide increases plasma aldosterone levels and inhibits the amount of receptor-bound aldosterone, however, additional research must be performed to determine the clinical significance of these effects.

Pharmacokinetics/Pharmacodynamics

Limited information is available. Oral bioavailability has been reported to be between 80–100% in dogs and cats. Elimination half-life in dogs is about 8 hours which is longer than furosemide. In dogs, diuretic activity begins within one hour of dosing, peaks at about 2 hours and persists for approximately 12 hours.

In cats, peak diuresis occurs about 4 hours post-dose and persists for 12 hours.

Contraindications/Precautions/Warnings

Torsemide should not be used in patients with known hypersensitivity to it or other sulfonylureas, or in anuric patients.

Use torsemide cautiously in patients with significant hepatic dysfunction, hyperuricemia (may increase serum uric acid), or diabetes mellitus (may increase serum glucose).

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance when used in horses.

The injection should be administered IV slowly over a period of 2 minutes. Ototoxicity has occurred in human patients receiving rapid IV administration of other loop diuretics.

Adverse Effects

Adverse effect profiles for dogs and cats have not been established due to the limited use of this drug in veterinary medicine. Furosemide, a related drug, can induce fluid and electrolyte abnormalities. Patients should be monitored for hydration status and electrolyte imbalances (especially potassium, calcium, magnesium and sodium). Prerenal azotemia may result if moderate to severe dehydration occurs. Hyponatremia is probably the greatest concern, but hypocalcemia, hypokalemia, and hypomagnesemia may all occur. Animals with normal food and water intake are much less likely to develop water and electrolyte imbalances than those that do not.

Other potential adverse effects include gastrointestinal disturbances, hematologic effects (anemia, leukopenia), weakness, and restlessness. Torsemide, unlike furosemide, apparently only rarely causes significant ototoxic effects in humans; very high doses in laboratory animals have induced ototoxicity.

Reproductive/Nursing Safety

No effects on fertility were noted when female and male rats were administered up to 25 mg/kg/day.

No adverse teratogenic effects were seen when pregnant rats and rabbits were administered up to 15X (human dose) and 5X (human dose), respectively. Larger doses did increase fetal resorptions, decreased average body weight, and delayed fetal ossification. In humans, the FDA categorizes torsemide 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 unknown if torsemide enters milk, but furosemide is distributed in milk. Clinical significance for nursing offspring is unknown.

Overdosage/Acute Toxicity

In dogs, the oral LD50 is >2 grams/kg. Fluid and electrolyte imbalance is the most likely risk associated with an overdose. Consider gut emptying protocols for very large or quantity unknown ingestions. Acute overdoses should generally be managed by observation with fluid, electrolyte and acid-base monitoring; supportive treatment should be initiated if required.

Drug Interactions

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

- **ACE INHIBITORS** (*e.g.,* **enalapril, benazepril**): Increased risks for hypotension, particularly in patients who are volume or sodium depleted secondary to diuretics
- **AMINOGLYCOSIDES** (**gentamicin, amikacin,** etc.): Other diuretics have been associated with increasing the ototoxic or nephrotoxic risks of aminoglycosides. It is unknown if torsemide can also have these effects and if so, what the clinical significance may be.
- **AMPHOTERICIN B:** Loop diuretics may increase the risk for nephrotoxicity development
- **DIGOXIN:** Can increase the area under the curve of torsemide by 50%, but is unlikely to be of significance clinically; torsemide-induced hypokalemia may increase the potential for digoxin toxicity
- **LITHIUM:** Torsemide may reduce lithium clearance
- **NSAIDs:** Some NSAIDs may reduce the natriuretic effects of torsemide
- **PROBENECID:** Can reduce the diuretic efficacy of torsemide
- **SALICYLATES:** Torsemide can reduce the excretion of salicylates

Laboratory Considerations

- Torsemide can affect **serum electrolytes, glucose, uric acid,** and **BUN** concentrations.

Doses

- **DOGS/CATS:**

  While no referenced dosages were located, torsemide could be considered for use as an alternative to furosemide particularly in those patients that have become refractory to furosemide therapy. Torsemide is approximately 10 times more potent than furosemide, so a starting dose of 10% of furosemide could be considered. As torsemide has a more persistent diuretic effect (approximately 12 hours), dosing frequency may also be reduced.

Monitoring

- Serum electrolytes, BUN, creatinine, glucose (if diabetic)
- Hydration status
- Blood pressure, if indicated
- Clinical signs of edema, patient weight, if indicated

Client Information

- Contact veterinarian if clinical signs of water or electrolyte imbalance occur. Signs such as excessive thirst, lethargy, restlessness, increased urination, GI distress or rapid heart rate may indicate electrolyte or water balance problems.

Chemistry/Synonyms

Torsemide is a pyridyl sulfonylurea loop diuretic that occurs as white to off-white, crystalline powder. It is practically insoluble in water and slightly soluble in alcohol. The injection has a pH >8.3.

Torsemide may also be known as torasemide, AC-3525, AC 4464, BM-02.015, JDL-464, and *Demadex*®. International trade names include *Torem*® and *Unat*®.

Storage/Stability/Compatibility

Torsemide tablets and injectable solution should be stored below 40°C; preferably between 15–30°C (59–86°F). Protect from freezing.

Torsemide injection is stable in NaCl 0.9%, NaCl 0.45%, or D5W. When given IV undiluted, the manufacturer recommends flushing the line to avoid incompatibilities with other drugs secondary to torsemide's high pH.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance.

HUMAN-LABELED PRODUCTS:

Torsemide Tablets: 5 mg, 10 mg, 20 mg, & 100 mg; *Demadex*® (Roche), generic; (Rx)

Torsemide Injection: 10 mg/mL in 2 and 5 mL amps; *Demadex*® (Roche)

TRAMADOL HCL

(***tram***-ah-doll) Ultram®

OPIATE (mu-RECEPTOR) AGONIST

Prescriber Highlights

- Synthetic *mu*-receptor opiate agonist that also inhibits reuptake of serotonin & norepinephrine
- May be useful as an analgesic or antitussive
- Not a controlled drug in USA, but has some potential for human abuse
- Appears well tolerated in dogs; sedation most likely adverse effect
- Avoid use with SSRIs (*e.g.*, fluoxetine) or MAOIs (*e.g.*, selegiline)
- Relatively inexpensive

Uses/Indications

Tramadol may be a useful alternative or adjunct for the treatment of pain or cough in dogs and, potentially, cats. When used in combination with NSAIDs, it may be particularly useful for chronic pain conditions in dogs. Epidurally administered tramadol may also be useful as an analgesic in horses, but no appropriate commercial dosage forms are presently available in the USA.

Pharmacology/Actions

Tramadol is a centrally acting opiate agonist that has primarily *mu*-receptor activity, but also inhibits reuptake of serotonin and norepinephrine. These pharmacologic actions all contribute to its analgesic properties. At least one metabolite (O-desmethyltramadol; ODT; M1) has activity. When compared to tramadol in lab animal studies, M1 is 6 times more potent an analgesic and has 20 times more potency in binding to *mu*-receptors. Naloxone only partially antagonizes the analgesic effects of tramadol.

Pharmacokinetics

In dogs after oral administration, bioavailability is about 65%, but there is significant interpatient variability. Volume of distribution is approximately 3.8 L/kg. Total body clearance and half-life are about 55 mL/kg/min and 1.7 hours, respectively. Tramadol is extensively metabolized via several metabolic pathways. At least one metabolite (M1) has agonist activity, but is a minor metabolite in dogs; M1 has a half-life of about 2 hours after oral tramadol administration in dogs.

One study in 8 cats using the immediate release oral tablet, showed high interpatient variability in absorption (with two cats there was not enough data to analyze). The elimination half-life for the parent compound was about 2.5 hours; for the M1 metabolite, 4.5 hours. Neurologic effects (mydriasis, dysphoria) were seen in 25% of cats (2 of 4 females) in the study group and the drug was observed to be unpalatable to cats. (Papich and Bledsoe 2007)

In neonatal and weaned foals, tramadol has different pharmacokinetics. After oral administration, higher bioavailability (53% vs. 20%), shorter time to peak concentration (1 hr. vs. 1.25 hr.), and peak levels occurred with neonatal (2 week old) versus weaned foals (4 months old). Elimination half-life did not significantly differ (approx. 2 hours). The active metabolite (M1; ODT) remained above the reported therapeutic concentration for humans for 3 hours in neonatal foals and 8 hours in weaned foals. (Stewart, Boothe et al. 2006)

Contraindications/Precautions/Warnings

Tramadol is contraindicated in patients hypersensitive to it or other opioids. The combination product containing acetaminophen is contraindicated in cats.

Use with caution in conjunction with other drugs that can cause CNS or respiratory depression. Because tramadol has caused seizures in humans, it should be used with caution in animals with preexisting seizure disorders or receiving other drugs that may reduce the seizure threshold. Like other opiates, tramadol should be used with caution in geriatric or severely debilitated animals. Patients with impaired renal or hepatic function may need dosage adjustments.

While the risk of physical dependence occurring is less than that of several other opiates, it has been reported in humans. The drug should be withdrawn gradually in animals that have received it chronically. While not a controlled substance in the USA, humans can potentially abuse tramadol and significant diversion of the drug reportedly occurs. Veterinarians should be alert to "clients" seeking tramadol for their animals.

Adverse Effects

Tramadol appears to be well tolerated in dogs. Potentially, it could cause a variety of adverse effects associated with its pharmacologic actions, including: CNS effects (excessive sedation, agitation, anxiety, tremor, dizziness), or GI (inappetence, vomiting, constipation to diarrhea).

Very limited information is available on the adverse effects in cats. Dysphoria, mydriasis, and dose avoidance (unpalatability) have been reported.

Approximately 10% of humans receiving the drug develop pruritus. Injectable tramadol may cause respiratory and cardiac depression.

Reproductive/Nursing Safety

In humans, the FDA categorizes tramadol as a category ***C*** drug for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*) At dosages 3–15 times usual, tramadol was embryotoxic and fetotoxic in laboratory animals. Tramadol and its active metabolite enter maternal milk in very low levels, but the drug's safety in neonates has not been established.

Overdosage/Acute Toxicity

Acute oral overdosage may cause respiratory depression, lethargy, coma, seizure, cardiac arrest and death.

There were 11 exposures to tramadol reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases all 11 were dogs with 1 showing clinical signs (subdued).

Treatment is primarily supportive (maintaining respiration, treating seizures with benzodiazepines or barbiturates, etc.). Naloxone may NOT be useful in tramadol overdoses as it may only partially reverse some of the effects of the drug and may, in fact, increase the risk of seizures. Naloxone did not decrease the drug's lethality in tramadol overdoses given to mice.

Drug Interactions

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

- **DIGOXIN**: In humans, tramadol has been rarely linked to digoxin toxicity
- **MAO INHIBITORS** (including **amitraz** and **possibly, selegiline**): Potential for serotonin syndrome; use together should be avoided