Reproductive/Nursing Safety
There is limited information on the reproductive safety of tiopronin. Skeletal defects, cleft palates and increased resorptions were noted when rats were given 10 times the human dose of penicillamine and, therefore, may also be of concern with tiopronin. Other animal studies have suggested that tiopronin may affect fetus viability at high doses. In humans, the FDA categorizes this drug as category ***C*** 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.*)

Because tiopronin may be excreted in milk, at present it is not recommended for use in nursing animals.

Overdosage/Acute Toxicity
There is little information available. It is suggested to contact an animal poison control center for further information in the event of an overdose situation.

Drug Interactions
Potentially use of tiopronin with **other drugs causing nephrotoxicity, hepatotoxicity, or bone marrow depression** could cause additive toxic effects. Clinical significance is not clear.

Doses
- **DOGS:**

  For treatment or prevention of recurrence of cystine urinary calculi:

  a) In conjunction with an alkalinizing, protein and sodium restricted diet (*e.g.*, *u/d*®), 30–40 mg/kg PO divided into two daily doses. (Cowan 1994)

  b) Treatment: 20 mg/kg PO twice daily for 1–3 months; relatively high incidence of adverse effects;

  Prevention: 15 mg/kg PO twice daily. (Adams and Syme 2005)

Monitoring
- Efficacy (stone size)
- CBC with platelets
- Liver enzymes
- Urinalyses including urine pH

Client Information
- Clients should be counseled on the importance of adequate compliance with this drug to maximize efficacy and detailed on the clinical signs to watch for regarding adverse effects.

Chemistry/Synonyms
A sulfhydryl compound related to penicillamine, tiopronin has a molecular weight of 163.2. It occurs as a white crystalline powder which is freely soluble in water.

Tiopronin may also be known as: SF 522, N-(2-Mercaptopropionyl)-glycine (MPG), 2-MPG, thiopronine, *Acadione*®, *Captimer*®, *Epatiol*®, *Mucolysin*®, *Mucosyt*®, *Sutilan*®, *Thiola*®, *Thiosol*®, or *Tioglis*®.

Storage/Stability
Store tablets at room temperature in tight containers.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Tiopronin Tablets: 100 mg; *Thiola*® (Mission); (Rx)

TOBRAMYCIN SULFATE

(toe-bra-*mye*-sin) Nebcin®, TOBI®

AMINOGLYCOSIDE ANTIBIOTIC

Prescriber Highlights
- Parenteral aminoglycoside antibiotic that has "good" activity against a variety of bacteria, predominantly gram-negative aerobic bacilli, also in ophthalmic preps
- Because of potential adverse effects usually reserved for serious infections when given systemically, may be less nephrotoxic than gentamicin
- Adverse Effects: Nephrotoxicity, ototoxicity, neuromuscular blockade
- Cats may be more sensitive to toxic effects
- Risk factors for nephrotoxicity: Preexisting renal disease, age (both neonatal & geriatric), fever, sepsis, & dehydration

Uses/Indications
While most veterinarians use gentamicin or amikacin and there are no approved veterinary tobramycin products in the U.S., tobramycin can be useful clinically to treat serious gram-negative infections in most species. It is often used in settings where gentamicin-resistant bacteria are a clinical problem. The inherent toxicity of the aminoglycosides limit their systemic use to serious infections when there is either a documented lack of susceptibility to other less toxic antibiotics or when the clinical situation dictates immediate treatment of a presumed gram-negative infection before culture and susceptibility results are reported.

Whether tobramycin is less nephrotoxic than either gentamicin or amikacin when used clinically is controversial. Laboratory studies indicate that in a controlled setting in laboratory animals, it may indeed be so.

Pharmacology/Actions
Tobramycin, like the other aminoglycoside antibiotics, act on susceptible bacteria presumably by irreversibly binding to the 30S ribosomal subunit thereby inhibiting protein synthesis. It is considered a bactericidal antibiotic.

Tobramycin's spectrum of activity includes coverage against many aerobic gram-negative and some aerobic gram-positive bacteria, including most species of *E. coli*, Klebsiella, Proteus, *Pseudomonas, Salmonella*, Enterobacter, Serratia, Shigella, Mycoplasma, and Staphylococcus.

Antimicrobial activity of the aminoglycosides is enhanced in an alkaline environment.

The aminoglycoside antibiotics are inactive against fungi, viruses and most anaerobic bacteria.

Pharmacokinetics
Tobramycin, like the other aminoglycosides, is not appreciably absorbed after oral or intrauterine administration, but it is absorbed from topical administration (not skin or urinary bladder) when used in irrigations during surgical procedures. Patients receiving oral aminoglycosides with hemorrhagic or necrotic enteritises may absorb appreciable quantities of the drug. Subcutaneous injection results in slightly delayed peak levels and more variability than after IM injection. Bioavailability from extravascular injection (IM or SC) is greater than 90%.

After absorption, aminoglycosides are distributed primarily in the extracellular fluid. They are found in ascitic, pleural, pericardial, peritoneal, synovial and abscess fluids, and high levels are found in sputum, bronchial secretions and bile. Aminoglycosides (other than streptomycin) are minimally protein bound (<20%) to plasma proteins. Aminoglycosides do not readily cross the blood-brain barrier nor penetrate ocular tissue. CSF levels are unpredictable and range from 0–50% those found in the serum. Therapeutic levels are found in bone, heart, gallbladder and lung tissues after parenteral dosing. Aminoglycosides tend to accumulate in certain tissues such as the inner ear and kidneys, which may help explain their toxicity. Aminoglycosides cross the placenta and fetal concentrations range from 15–50% those found in maternal serum.

Elimination of aminoglycosides after parenteral administration occurs almost entirely by glomerular filtration. Patients with decreased renal function can have significantly prolonged half-lives. In humans with normal renal function, elimination rates can be highly variable with the aminoglycoside antibiotics.

Contraindications/Precautions/Warnings

Aminoglycosides are contraindicated in patients who are hypersensitive to them. Because these drugs are often the only effective agents in severe gram-negative infections, there are no other absolute contraindications to their use; however, they should be used with extreme caution in patients with preexisting renal disease with concomitant monitoring and dosage interval adjustments made. Other risk factors for the development of toxicity include age (both neonatal and geriatric patients), fever, sepsis, and dehydration.

Because aminoglycosides can cause irreversible ototoxicity, they should be used with caution in "working" dogs (*e.g.*, "seeing-eye", herding, dogs for the hearing impaired, etc.).

Aminoglycosides should be used with caution in patients with neuromuscular disorders (*e.g.*, myasthenia gravis) due to their neuromuscular blocking activity.

Because aminoglycosides are eliminated primarily through renal mechanisms, they should be used cautiously, preferably with serum monitoring and dosage adjustment in neonatal or geriatric animals.

Aminoglycosides are generally considered contraindicated in rabbits/hares as they adversely affect the GI flora balance in these animals.

Adverse Effects

The aminoglycosides are infamous for their nephrotoxic and ototoxic effects. The nephrotoxic (tubular necrosis) mechanisms of these drugs are not completely understood, but are probably related to interference with phospholipid metabolism in the lysosomes of proximal renal tubular cells, resulting in leakage of proteolytic enzymes into the cytoplasm. Nephrotoxicity normally manifests by increases in BUN, creatinine, nonprotein nitrogen in the serum and decreases in urine specific gravity and creatinine clearance. Proteinuria and cells or casts may also be seen in the urine. Nephrotoxicity is usually reversible once the drug is discontinued. While gentamicin may be more nephrotoxic than the other aminoglycosides, the incidences of nephrotoxicity with all of these agents require equal caution and monitoring.

Ototoxicity (8th cranial nerve toxicity) of the aminoglycosides can manifest with either auditory and/or vestibular clinical signs and may be irreversible. Vestibular clinical signs are more frequent with streptomycin, gentamicin, or tobramycin. Auditory clinical signs are more frequent with amikacin, neomycin, or kanamycin, but either form can occur with any of the drugs. Cats are apparently very sensitive to the vestibular effects of the aminoglycosides.

The aminoglycosides can also cause neuromuscular blockade, facial edema, pain or inflammation at the injection site, peripheral neuropathy, and hypersensitivity reactions. Rarely, GI clinical signs, hematologic, and hepatic effects have been reported.

Reproductive/Nursing Safety

Tobramycin can cross the placenta and concentrate in fetal kidneys and while rare, cause 8th cranial nerve toxicity or nephrotoxicity in fetuses. Total irreversible deafness has been reported in some human babies whose mothers received tobramycin during pregnancy. Because the drug should only be used in serious infections, the benefits of therapy may exceed the potential risks. In humans, the FDA categorizes this drug as category ***D*** for use during pregnancy (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***C*** (*These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks.*)

Small amounts of aminoglycoside antibiotics are excreted in milk, but are unlikely to cause clinically significant effects in nursing offspring.

Overdosage/Acute Toxicity

Should an inadvertent overdosage be administered, three treatments have been recommended: 1) Hemodialysis is very effective in reducing serum levels of the drug, but is not a viable option for most veterinary patients; 2) Peritoneal dialysis also will reduce serum levels, but is much less efficacious; 3) Complexation of drug with either carbenicillin or ticarcillin (12–20 g/day in humans) is reportedly nearly as effective as hemodialysis.

Drug Interactions

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

- **BETA-LACTAM ANTIBIOTICS** (**penicillins**, **cephalosporins**): May have synergistic effects against some bacteria; some potential for inactivation of aminoglycosides *in vitro* (do not mix together) and *in vivo* (patients in renal failure)
- **CEPHALOSPORINS:** The concurrent use of aminoglycosides with cephalosporins is somewhat controversial. Potentially, cephalosporins could cause additive nephrotoxicity when used with aminoglycosides, but this interaction has only been well documented with cephaloridine and cephalothin (both no longer marketed).
- **DIURETICS, LOOP** (*e.g.,* **furosemide**, **torsemide**) or **OSMOTIC** (*e.g.,* **mannitol**): Concurrent use with loop or osmotic diuretics may increase the nephrotoxic or ototoxic potential of the aminoglycosides
- **NEPHROTOXIC DRUGS, OTHER** (*e.g.*, **cisplatin, amphotericin B, polymyxin B**, or **vancomycin**): Potential for increased risk for nephrotoxicity
- **NEUROMUSCULAR BLOCKING AGENTS & ANESTHETICS, GENERAL:** Concomitant use with general anesthetics or neuromuscular blocking agents could potentiate neuromuscular blockade

Laboratory Considerations

- Tobramycin serum concentrations may be falsely decreased if the patient is also receiving **beta-lactam antibiotics** and the serum is stored prior analysis. It is recommended that if assay is delayed, samples be frozen and, if possible, drawn at times when the beta-lactam antibiotic is at a trough level.

Doses

Note: There is significant inter-patient variability with aminoglycoside pharmacokinetic parameters. To insure therapeutic levels and to minimize the risks for toxicity development, consider monitoring serum levels for this drug. Like other aminoglycosides, most now recommend dosing mammals once daily; consider giving the total daily dose as a single dose (*e.g.,* if dose listed is 2 mg/kg q8h, give 6 mg/kg once daily).

■ **DOGS & CATS:**

For small animals, one pair of authors (Aronson and Aucoin 1989) make the following recommendations with regard to minimizing risks of toxicity, yet maximizing efficacy:

1) Dose according to animal size. The larger the animal, the smaller the dose (on a mg/kg basis).
2) The more risk factors (age, fever, sepsis, renal disease, dehydration) the smaller the dose.
3) In old patients or those suspected of renal disease, increase dosing interval from q8h to q16–24h.
4) Determine serum creatinine prior to therapy and adjust by changes in level even if it remains in "normal range."
5) Monitor urine for changes in sediment (*e.g.*, casts) or concentrating ability. Not very useful in patients with UTI.
6) Therapeutic drug monitoring is recommended when possible.
   a) 2 mg/kg IV, IM, or SC q8h (avoid use or reduce dosage in patients with renal failure; recommend therapeutic drug monitoring, particularly in young animals) (Vaden and Papich 1995)
   b) For susceptible UTI: 1–2 mg/kg SC q8h (Brovida 2003)
   c) For sepsis: 2–4 mg/kg IV three times daily (q8h) (Tello 2003b)
   d) Dogs:
      For soft tissue, systemic infections: 1–1.7 mg/kg IV q8h or 3–5.1 mg/kg IV q24h for less than 7 days;
      For systemic infections: 2 mg/kg SC q8–12h or 4–6 mg/kg SC q24h for less than 7 days;
      For persistent bacteremia: 3–5 mg/kg IV, IM, SC q8h or 9–15 mg/kg IV, IM or SC q24h for 7 days or less. (Greene, Hartmannn et al. 2006)
   e) Cats:
      For soft tissue, systemic infections: 2 mg/kg IV, IM or SC q12h or 4 mg/kg IV, IM, SC q24h for 5 days or less;
      For persistent bacteremia: 2 mg/kg IV, IM, SC q8h or 6 mg/kg IV, IM or SC q24h for 5 days or less.
      (Greene, Hartmannn et al. 2006)

■ **HORSES:**

For susceptible infections:

a) 1–1.7 mg/kg q8h IV (slowly) or IM (**Note**: This is a human dose and should be used as a general guideline only) (Walker 1992)

■ **LLAMAS:**

For susceptible infections:

a) 4 mg/kg IV q24h; 0.75 mg/kg IV q8h (Baird 2003)

■ **BIRDS:**

For susceptible infections:

a) 5 mg/kg IM every 12 hours (Bauck and Hoefer 1993)
b) 2.5–5 mg/kg/day; must be given parenterally (Flammer 2003b)

■ **REPTILES:**

For susceptible infections:

a) 2.5 mg/kg once daily IM (Gauvin 1993)

Monitoring

- Efficacy (cultures, clinical signs associated with infection)
- Renal toxicity; baseline urinalysis, and serum creatinine/BUN. Casts in the urine are often the initial sign of impending nephrotoxicity. Frequency of monitoring during therapy is controversial, but daily urinalysis and serum creatinine may not be too frequent.
- Gross monitoring of vestibular or auditory toxicity is recommended
- Serum levels if possible

Client Information

- With appropriate training, owners may give subcutaneous injections at home, but routine monitoring of therapy for efficacy and toxicity must still be done
- Clients should understand that the potential exists for severe toxicity (nephrotoxicity, ototoxicity) developing from this medication

Chemistry/Synonyms

An aminoglycoside derived from Streptomyces tenebrarius, tobramycin occurs as a white to off-white, hygroscopic powder that is freely soluble in water and very slightly soluble in alcohol. The sulfate salt is formed during the manufacturing process. The commercial injection is a clear, colorless solution and the pH is adjusted to 6–8 with sulfuric acid and/or sodium hydroxide.

Tobramycin Sulfate may also be known as: tobramycin sulphate, *Brulamycin®, Gernebcin®, Mytobrin®, Nebcina®, Nebcine®, Nebicina®, Obracin®, Tobra®, Tobra Gobens®, TOBI®, Tobra Laf®, Tobra-cell®, Tobracil®, Tobradistin®, Tobramina®, Tobraneg®, Tobrasix®, Tobrex®, Tomycin®,* or *Trazil®*.

Storage/Stability/Compatibility

Tobramycin sulfate for injection should be stored at room temperature (15–30°C); avoid freezing and temperatures above 40°C. Do not use the product if discolored.

While the manufacturers state that tobramycin should not be mixed with other drugs, it is reportedly physically **compatible** and stable in most commonly used intravenous solutions (not compatible with dextrose and alcohol solutions, Polysal, Polysal M, or Isolyte E, M or P) and **compatible** with the following drugs: aztreonam, bleomycin sulfate, calcium gluconate, cefoxitin sodium, ciprofloxacin lactate, clindamycin phosphate (not in syringes), floxacillin sodium, metronidazole (with or without sodium bicarbonate), ranitidine HCl, and verapamil HCl.

The following drugs or solutions are reportedly physically **incompatible** or only compatible in specific situations with tobramycin: cefamandole naftate, furosemide and heparin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references or a hospital pharmacist for more specific information.

In vitro inactivation of aminoglycoside antibiotics by beta-lactam antibiotics is well documented; see the information in the Drug Interaction and Laboratory Consideration sections.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Tobramycin Sulfate Injection: 0.8 mg/mL and 1.2 mg/mL (as sulfate) in 100 mL & 50 mL single-dose containers; 10 mg/mL in 2 mL vials; and 40 mg/mL in 1.5 mL and 2 mL syringes, 2 mL and 30 mL vials; Tobramycin in 0.9% Sodium Chloride (Hospira); generic (various); (Rx)

Tobramycin Sulfate Powder for Injection: 1.2 g vials (40 mg/mL after reconstitution), preservative free in 50 mL bulk package vial; generic (American Pharmaceutical Partners); (Rx)

Tobramycin Nebulizer Solution: 60 mg/mL in 5 mL amps; *TOBI*® (PathoGenesis); (Rx)

Also available in ophthalmic preparations.

TOCAINIDE HCL

(***toe***-kay-nide) **Tonocard®**

ORAL ANTIARRHYTHMIC

Prescriber Highlights

- **Oral antiarrhythmic with similar activity as lidocaine; not commonly used in veterinary medicine**
- **Contraindications: Hypersensitivity reactions to it or amide-type local anesthetics, 2nd or 3rd degree AV block & not being artificially paced. Caution: Heart failure, hematologic abnormalities, or preexisting bone marrow failure.**
- **Adverse Effects: CNS effects (depression, ataxia, muscle tremors, etc.), nausea & vomiting (usually transient), cardiovascular effects (hypotension, bradycardia, tachycardia, other arrhythmias, & exacerbation of CHF)**
- **Case reports of dogs on long-term therapy (>3 mos.) developing ocular & renal toxicity**

Uses/Indications

Veterinary experience with tocainide is limited. At this time, dogs are the only veterinary species where enough clinical experience has been garnered to recommend its use. It is indicated for the oral therapy of ventricular arrhythmias, principally ventricular tachycardia and ventricular premature complexes. In humans, response to lidocaine can usually predict whether tocainide might be effective.

Pharmacology/Actions

Tocainide is considered a class I_B (membrane-stabilizing) antidysrhythmic agent that demonstrates rapid rates of attachment and dissociation to sodium channels. Like lidocaine, tocainide produces a dose-dependent decrease in potassium and sodium conductance that results in decreased excitability of myocardial cells. Automaticity, conduction velocity, and effective refractory periods are decreased at therapeutic levels. Little or no increases in PR intervals, QRS complexes, or QT intervals are seen at therapeutic levels. Like lidocaine, tocainide has little, if any effect, on autonomic tone.

Pharmacokinetics

Following oral administration, tocainide is rapidly and almost completely absorbed. The presence of food in the stomach may alter the rate, but not the extent, of absorption. Unlike lidocaine, the hepatic first-pass effect is minimal with tocainide. In humans, peak plasma levels occur between 0.5–2 hours when administered on an empty stomach.

The distribution aspects of tocainide have not been fully described. In humans, the volume of distribution ranges from 1.5–4 L/kg and has been reported to be 1.7 L/kg in dogs. Tocainide is minimally bound to plasma proteins. It is unknown if it crosses the placenta or enters into the milk.

Tocainide is metabolized by the liver, but up to 50% of a dose is excreted unchanged by the kidneys into the urine. Alkalinization of the urine may result in a substantial decrease in the amount of tocainide that is excreted unchanged into the urine, but acidification of the urine reportedly does not enhance the excretion rate. Elimination half-life is dose-dependent and at the clinical doses used for dogs, not well-described.

Contraindications/Precautions/Warnings

Tocainide is contraindicated in patients who have demonstrated previous hypersensitivity reactions to it or amide-type local anesthetics, or who have 2nd or 3rd degree AV block and are not being artificially paced.

Use tocainide cautiously in patients with heart failure as it has the potential to aggravate the condition. Use with caution in patients with hematologic abnormalities or preexisting bone marrow failure.

Adverse Effects

It is expected that tocainide would exhibit a similar adverse reaction profile as lidocaine with anorexia, and vomiting being most likely. In dogs, tocainide serum concentrations of greater than 12 mcg/mL have been associated with neurotoxicity (ataxia, head tremor). There are case reports of dogs receiving tocainide for more than 3 months developing ocular (corneal dystrophy) and renal toxicity.

Although side effects are common in human patients, they are usually dose related, mild, and reversible upon discontinuation of the drug. CNS effects can include drowsiness, depression, ataxia, muscle tremors, etc. Nausea and vomiting may occur, but are usually transient. Cardiovascular effects reported include hypotension, bradycardia, tachycardia, other arrhythmias, and exacerbation of CHF. Rarely (<1% incidence), clinical signs of bone marrow depression or pulmonary effects (pulmonary fibrosis, pneumonia, respiratory arrest, pulmonary edema, etc.) have been reported in humans.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***C*** 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.*)

Tocainide enters milk in significant quantities and may potentially cause adverse effects in nursing offspring.

Overdosage/Acute Toxicity

Dogs tend to be rather resistant to the acute toxic effects of the drug. In one study, dogs were administered 750 mg/kg over 6 hours and emesis was the only frequent effect seen, but ECG changes were also seen in some animals.

There is no specific antidote for tocainide overdose and treatment tends to be supportive and symptomatic. For more information, see the Lidocaine monograph. Tocainide can be removed with hemodialysis.