rate of benign and malignant liver tumors when doses were approximately 1.3X of the human dose.

Reproductive/Nursing Safety
Gemfibrozil administered to female rats prior to and during gestation at 0.6–2X the human dose, showed decreased fertility rates and their offspring had an increased incidence of skeletal abnormalities. When given to pregnant rabbits at 1–3X the human dose, litter sizes were decreased and at the highest dose (3X), parietal bone variations were noted. In humans, the FDA categorizes gemfibrozil 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.*)

It is not known if gemfibrozil enters milk and safe use during nursing cannot be assured.

Overdosage/Acute Toxicity
Limited information is available. One 7-year-old child ingested up to 9 grams and recovered with supportive treatment. The reported LD50 (oral) in rats is 1414 mg/kg. Consider gut-emptying protocols for recent large oral ingestions and support as required. Monitor for dehydration and electrolyte imbalance if vomiting and/or diarrhea is severe or persists. Monitor liver function tests.

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

- **THIAZIDE DIURETICS**, **BETA-BLOCKERS**, **ESTROGENS**: May possibly increase triglyceride concentrations
- **URSODIOL**: May reduce effectiveness of gemfibrozil
- **WARFARIN**: Gemfibrozil may potentiate anticoagulant effects

Laboratory Considerations
No specific concerns associated with gemfibrozil; see Monitoring

Doses
- **DOGS/CATS:**

  For hypertriglyceridemia that has not been controlled with diet alone:

  a) Dogs: 150 mg–300 mg (total dose) PO q12h; Cats: 7.5–10 mg/kg PO q12h (Jones 2003)

  b) Dogs: 200 mg (total dose) PO once daily; Cats: 10 mg/kg PO q12h (Elliott 2005)

Monitoring
- Plasma triglycerides; realistic goal for therapy is 400 mg/dL or less
- Baseline and periodic: CBC, liver function tests
- Adverse effects
- If treatment is less effective than hoped, assure that clients have adhered to prescribed diet and dosing schedule before altering dosage

Client Information
- Clients must understand the use of this drug in animals is "investigational"; although approved for use in people, little information is known about it for use in dogs or cats
- Gemfibrozil is used in conjunction with diet modification; lack of adherence to dietary recommendations will likely negate the benefits of using this medication
- Report any significant adverse effects to the veterinarian, including changes in behavior, activity level, gastrointestinal effects (vomiting, diarrhea, lack of appetite), yellowish eyes or mucous membranes, etc.

Chemistry/Synonyms
Gemfibrozil is a fibric acid derivative that occurs as a waxy, crystalline solid that is practically insoluble in water, but soluble in alcohol.

Gemfibrozil may also be known as: CI-719, gemfibrozilo, or gemfibrozilium; many international trade names are available.

Storage/Stability
Gemfibrozil tablets or capsules should be stored below 30°C in tight containers.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Gemfibrozil Tablets: 600 mg; *Lopid*® (Parke-Davis), generic; (Rx)
Note: 300 mg capsules are available in Canada

GENTAMICIN SULFATE

(jen-ta-*mye*-sin) Gentocin®, Garamycin®

AMINOGLYCOSIDE ANTIBIOTIC

Prescriber Highlights
- **Parenteral-aminoglycoside antibiotic that has "good" activity against a variety of bacteria, predominantly gram-negative aerobic bacilli, but also many staphylococci strains**
- **Because of potential adverse effects, usually reserved for serious infections when given systemically**
- **Adverse effect profile: 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**
- **Usually dosed once daily**

Uses/Indications
The inherent toxicity of the aminoglycosides limit their systemic (parenteral) use to the treatment of serious gram-negative 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.

Various gentamicin products are approved for parenteral use in dogs, cats, chickens, turkeys, and swine, although the injectable small animal products appear to be no longer marketed. Although routinely used parenterally in horses, gentamicin is only approved for intrauterine infusion in this species. Oral products are approved for gastrointestinal infections in swine and turkeys. For more information, refer to the Dosage section below.

Pharmacology/Actions
Gentamicin has a mechanism of action and spectrum of activity (primarily gram-negative aerobes) similar to the other aminoglycosides. Like the other aminoglycoside antibiotics, it acts on suscep-

tible bacteria presumably by irreversibly binding to the 30S ribosomal subunit thereby inhibiting protein synthesis. It is considered a bactericidal concentration-dependent antibiotic.

Gentamicin'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, and Shigella, Mycoplasma, and Staphylococcus. Several strains of *Pseudomonas aeruginosa*, Proteus, and Serratia that are resistant to gentamicin may still be treated with amikacin.

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

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

Pharmacokinetics

Gentamicin, like other aminoglycosides, is not appreciably absorbed after oral or intrauterine administration, but 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. After IM administration to dogs and cats, peak levels occur from ½ to 1 hour later. Subcutaneous injection results in slightly delayed peak levels and with 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 are minimally protein bound (<20%, streptomycin 35%) to plasma proteins. Aminoglycosides do not readily cross the blood-brain barrier or penetrate ocular tissue. CSF levels are unpredictable and range from 0–50% of 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. Volumes of distribution have been reported to be 0.15–0.3 L/kg in adult cats and dogs, and 0.26–0.58 L/kg in horses. Volumes of distribution may be significantly larger in neonates and juvenile animals due to their higher extracellular fluid fractions. Aminoglycosides cross the placenta, but one study showed no detectable levels in foals when gentamicin was administered to mares at term. In other species, fetal concentrations range from 15–50% of those found in maternal serum.

Elimination of aminoglycosides after parenteral administration occurs almost entirely by glomerular filtration. The elimination half-lives for gentamicin have been reported to be 1.82–3.25 hours in horses, 2.2–2.7 hours in calves, 2.4 hours in sheep, 1.8 hours in cows, 1.9 hours in swine, 1 hour in rabbits, and 0.5–1.5 hours in dogs and cats. 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 often considered contraindicated in rabbits as they adversely affect the GI flora balance in these animals, but dosages are listed below. Use with caution.

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 is usually manifested by increases in: BUN, creatinine, non-protein 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 by 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 other forms 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/inflammation at injection site, peripheral neuropathy, and hypersensitivity reactions. Rarely, GI clinical signs, hematologic and hepatic effects have been reported.

Reproductive/Nursing Safety

Aminoglycosides can cross the placenta and, while rare, may cause 8th cranial nerve toxicity or nephrotoxicity in fetuses. 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.*)

While small amounts of gentamicin may be excreted into milk, the risk to nursing offspring appears minimal.

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 effective. **3**) Complexation of drug with 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 gentamicin 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

- **Gentamicin 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.

Doses

Note: Most infectious disease clinicians now agree that aminoglycosides should be dosed once a day in most patients (mammals). This dosing regimen yields higher peak levels with resultant greater bacterial kill, and as aminoglycosides exhibit a "post-antibiotic effect", surviving susceptible bacteria generally do not replicate as rapidly even when antibiotic concentrations are below MIC. Periods where levels are low may decrease the "adaptive resistance" (bacteria take up less drug in the presence of continuous exposure) that can occur. Once daily dosing may also decrease the toxicity of aminoglycosides as lower urinary concentrations may mean less-uptake into renal tubular cells. However, patients who are neutropenic (or otherwise immunosuppressed) may benefit from more frequent dosing (q8h).

- **DOGS:**

  For susceptible infections:

  a) For sepsis: 6 mg/kg IV once daily (Hardie 2000)

  b) 6–8 mg/kg (route not specified) once daily (q24h). Neutropenic or immunocompromised patients may still need to be dosed q8h (dose divided). (Trepanier 1999)

  c) 8 mg/kg once daily or 2–4 mg/kg q8h IV, IM or SC (Aucoin 2002b)

  d) For localized, urinary infections: First dose of 4.4 mg/kg IM, SC and then 2.2 mg/kg IM, SC once daily (q24h) for 7–10 days;

  For orthopedic and soft tissue infections: 4.4–6.6 mg/kg IV, IM, SC once daily (q24h) for <7 days.

  For bacteremia, sepsis: 6.6 mg/kg IV, IM, SC once daily (q24h) for <7 days.

  Monitor renal function by urine sediment examination and serum urea nitrogen levels. (Greene, Hartmannn et al. 2006)

  e) For Brucellosis: Gentamicin 5 mg/kg SC once daily (q24h) for 7 days; 2-courses of treatment, treating on weeks one and four; plus Minocycline at 25 mg/kg PO once daily (q24h) for 4 weeks. Eventually, doxycycline can be substituted for minocycline at the same dosage to lower cost. Infected animals may need to be treated for two or more 4-week courses. Sequential antibody tests at 3 to 6 monthly intervals are recommended to monitor treatment. Monitor renal function secondary to gentamicin therapy. (Hartmannn and Greene 2005)

- **CATS:**

  For susceptible infections:

  a) For sepsis: 6 mg/kg IV once daily (Hardie 2000)

  b) 6–8 mg/kg (route not specified) once daily (q24h). Neutropenic or immunocompromised patients may still need to be dosed q8h (dose divided). (Trepanier 1999)

  c) 8 mg/kg once daily or 2–4 mg/kg q8h IV, IM or SC (Aucoin 2002b)

  d) For localized, urinary infections: 2.2 mg/kg IV, IM, SC once daily (q24h) for <7 days;

  For bacteremia, sepsis: 4.4 mg/kg IV, IM, SC once daily (q24h) for <7 days.

  Monitor renal function by urine sediment examination and serum urea nitrogen levels. (Greene, Hartmannn et al. 2006)

- **FERRETS:**

  For susceptible infections:

  a) 5 mg/kg SC, IM q24h; use with caution or avoid use. (Morrisey and Carpenter 2004)

  b) 4–8 mg/kg IM, SC, IV divided and given 2–3 times daily. Use only when culture and sensitivity dictates. (Williams 2000)

- **RABBITS/RODENTS/SMALL MAMMALS:**

  a) Rabbits: 5–8 mg/kg daily dose (may divide into q8h–q24h) SC, IM or IV. Increased efficacy and decreased toxicity if given once daily. If given IV, dilute into 4 mL/kg of saline and give over 20 minutes (Ivey and Morrisey 2000)

  b) Chinchillas, Gerbils, Guinea pigs, Hamsters, Mice, Rats: 2–4 mg/kg SC or IM q8–24h (Adamcak and Otten 2000)

  c) Chinchillas: 2–4 mg/kg SC, IM q8–24h (Hayes 2000)

- **CATTLE:**

  For susceptible infections:

  a) 4.4–6.6 mg/kg/day IM divided three times daily (Upson 1988)

  b) Intramammary: 100–150 mg q12h (Schultz 1986)

- **HORSES:**

  For susceptible infections:

  a) Foals: 8–10 mg/kg q18–24 hours. Monitor levels to adjust dosage or dosing interval. (Furr 1999)

  b) Adults: 6.6 mg/kg IV or IM once daily (q24h) (Foreman 1999), (Chaffin 2006a)

  c) For intrauterine infusion: 0.5–2 grams. Little science is available for recommending doses, volume infused, frequency, diluents, etc. Most intrauterine treatments are commonly performed every day or every other day for 3–7 days. (Perkins 1999)

  d) Foals: 7 mg/kg IV or IM once daily (q24h) (Giguere 2003a)

- **SWINE:**

  For susceptible infections:

  a) For colibacillosis in neonates: 5 mg PO or IM once (Label directions; *Garacin® Pig Pump* and *Piglet Injection*—Schering)

b) For weanlings and other swine:
Colibacillosis: 1.1 mg/kg/day in drinking water (concentration of 25 mg/gallon) for 3 days.
Swine dysentery (*Treponema hyodysenteriae*): 2.2 mg/kg/day in drinking water (concentration of 50 mg/gallon) for 3 days (Label directions; *Garacin® Soluble Powder* and *Oral Solution*—Schering)

■ **BIRDS:**

For susceptible infections:
a) For Pheasants and Cranes: 5 mg/kg IM three times daily for 5–10 days. For Quail, African Grey Parrots: 10 mg/kg IM three times daily. Blue and Gold Macaws: 10 mg/kg IM twice daily. Once or twice daily dosing may be effective in less serious infections. (Clubb 1986)
b) For gut sterilization/gut infections: 40 mg/kg PO 1–3 times a day for 2–3 days. (Clubb 1986)
c) For pneumonia (with carbenicillin or tylosin given IM): 5–10 mg/kg intratracheally once daily (Clubb 1986)
d) Ratites: 5 mg/kg IM once daily; **Note:** use only as a last resort as it causes visceral gout (Jenson 1998)

■ **REPTILES:**

For susceptible infections:
a) For bacterial gastritis in snakes: gentamicin 2.5 mg/kg IM every 72 hours with oral neomycin 15 mg/kg plus oral live lactobacillus. (Burke 1986)
b) For bacterial shell diseases in turtles: 5–10 mg/kg daily in water turtles, every other day in land turtles and tortoises for 7–10 days. Used commonly with a beta-lactam antibiotic. Recommend beginning therapy with 20 mL/kg fluid injection. Maintain hydration and monitor uric acid levels when possible. (Rosskopf 1986)

Monitoring (Parenteral use)

- Efficacy (cultures, clinical signs associated with infection)
- Renal toxicity; baseline urinalysis, serum creatinine/BUN. Casts in the urine are often the initial sign of impending nephrotoxicity. Frequency of monitoring during therapy is controversial. 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. Draw levels at 1, 2, and 4 hours post dose. Peak should be at least 20 mcg/mL and 4 hour sample should be less than 10 mcg/mL (Papich 2003c).

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 obtained from cultures of *Micromonaspora purpurea*, gentamicin sulfate occurs as a white to buff powder that is soluble in water and insoluble in alcohol. The commercial product is actually a combination of gentamicin sulfate C_1, C_2, and C_3, but all these compounds apparently have similar antimicrobial activities. Commercially available injections have a pH from 3–5.5.

Gentamicin may also be known as: gentamicin sulphate, gentamicini sulfas, NSC-82261, and Sch-9724; many trade names are available.

Storage/Stability/Compatibility

Gentamicin sulfate for injection and the oral solution should be stored at room temperature (15–30°C); freezing or temperatures above 40°C should be avoided. The soluble powder should be stored from 2–30°C. Do not store or offer medicated-drinking water in rusty containers or the drug may be destroyed.

While the manufacturer does not recommend that gentamicin be mixed with other drugs, it is reportedly physically **compatible** and stable in all commonly used intravenous solutions and with the following drugs: bleomycin sulfate, cefoxitin sodium, cimetidine HCl, clindamycin phosphate, methicillin sodium, metronidazole (with and without sodium bicarbonate), penicillin G sodium, and verapamil HCl.

The following drugs or solutions are reportedly physically **incompatible** or only compatible in specific situations with gentamicin: amphotericin B, ampicillin sodium, carbenicillin disodium, cefamandole naftate, cephalothin sodium, cephapirin sodium, dopamine HCl, 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. Gentamicin is very susceptible to this effect and it is recommended to avoid mixing these compounds together.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Gentamicin Sulfate Injection: 100 mg/mL in 100 mL and 250 mL vials; *Amtech® Gentamax 100* (IVX), *Gentafuse®* (Butler), *Gentamax® 100* (Phoenix Pharmaceutical), *Gentaved® 100* (Vedco), *Gentozen®* (Schering-Plough), *Legacy®* (AgriLabs); generic; (Rx). Approved for horses.

Gentamicin Sulfate Injection: 100 mg/mL (poultry only) in 100 mL vials; *Garasol® Injection* (Schering-Plough); *Amtech® Gentapoult* (IVX); (OTC) For use in day-old chickens (slaughter withdrawal = 5 weeks) and 1–3 day-old turkeys (slaughter withdrawal=9 weeks) only.

Gentamicin Sulfate Injection: 5 mg/mL in 250 mL vials; *Garacin® Piglet Injection* (Schering-Plough); (OTC). Approved for use in piglets up to 3 days of age. Slaughter (when used as labeled) = 40 days.

Gentamicin Sulfate Oral Solution: 5 mg/mL in 118 mL bottles with pump applicator; *Amtech® Gentamicin Sulfate Pig Pump Oral Solution* (IVX); (Rx); Approved for use in neonatal swine only. Slaughter withdrawal = 14 days.

Gentamicin Soluble Powder: 333.33 mg/g in 360 gram jars. Approved for use in weanling swine. Slaughter withdrawal = 10 days. *Gen-Gard® Soluble Powder* (AgriLabs); (OTC)

Gentamicin Sulfate Soluble Powder: 2 g gentamicin/30 grams of powder in 360-gram jar; *Garacin® Soluble Powder* (Schering-Plough); (OTC). Approved for use in swine. Slaughter (when used as labeled) = 10 days.

Veterinary-approved injections for chickens and turkeys plus a water additive for egg dipping may also be available. Ophthalmic, otic, and topical preparations are available with veterinary labeling.

HUMAN-APPROVED PRODUCTS (partial listing):

Gentamicin Sulfate Injection: 40 mg/mL (as sulfate) in 2 mL and 20 mL vials and 1.5 mL and 2 mL cartridge-needle units; 10 mg/mL (as sulfate) in 2 mL vials & *ADD-Vantage* 60 mg, 80 mg & 100 mg vials; 0.8 mg/mL, 0.9 mg/mL, & 1 mg/mL (as gentamicin base) in 100 mL; 1.2 mg/mL, 1.4 mg/mL & 1.6 mg/mL (as gentamicin base) in 50 mL;

Pediatric Gentamicin Sulfate (Fujisawa); Gentamicin Sulfate in 0.9% Sodium Chloride (Hospira); generic; (Rx)

Topical, otic and ophthalmic labeled products are also available.

GLIMEPIRIDE

(glye-*meh*-per-ide) Amaryl®

SULFONYLUREA ANTIDIABETIC AGENT

Prescriber Highlights

- Oral, once-daily, anti-hyperglycemic agent; could be useful in the adjunctive treatment of non-insulin dependent diabetes mellitus (NIDDM) in cats
- Very limited experience in cats
- Contraindicated: Patients hypersensitive to it or with diabetic ketoacidosis
- Hypoglycemia may occur
- Potentially, significant drug interactions
- Do not confuse glipizide, glimepiride & glyburide

Uses/Indications

Glimepiride may potentially be a useful adjunct in the treatment of non-insulin dependent diabetes mellitus (NIDDM) in cats. Its duration of action in humans allows it to be dosed once daily, which could be of benefit in cats. It may also have fewer side effects than glipizide in cats.

Pharmacology/Actions

Glimepiride increases pancreatic release of insulin from functioning beta cells and, with continued use, may also increase peripheral tissue sensitivity to insulin. The exact mechanism for these effects is not well understood.

Pharmacokinetics

No pharmacokinetic data for cats was located. In humans, glimepiride is completely absorbed from the GI tract. Peak levels occur in 2–3 hours; food delays the peak somewhat and lowers AUC by about 9%. Volume of distribution is 0.11 L/kg; the drug is greater than 99% bound to plasma proteins. Glimepiride is hepatically metabolized to at least two major metabolites. One of these, M1, has activity at about ⅓ that of the parent compound; clearance is 48 mL/min and elimination half-life about 9 hours. Approximately 60% of the drug (as metabolites) are excreted into the urine and the remainder in the feces. The drug has a 24-hour duration of activity in humans.

Contraindications/Precautions/Warnings

Glimepiride is contraindicated in patients hypersensitive to it or with diabetic ketoacidosis.

Adverse Effects

Hypoglycemia has been reported in about 1% of human patients taking the drug. Dizziness and asthenia have been reported; rarely, liver function impairment, dermatologic reactions, or hematologic reactions have been reported in humans.

Reproductive/Nursing Safety

In humans, the FDA categorizes glimepiride 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*). In rabbits and rats, glimepiride did not cause teratogenic effects when given at high dosages. There were some intrauterine deaths when maternal hypoglycemia was induced by the drug.

Some glimepiride is excreted into maternal milk of rats. The manufacturer states to discontinue the drug in nursing, human mothers.

Overdosage/Acute Toxicity

Overdoses may result in hypoglycemia, ranging from mild to severe. Treatment consists of glucose administration and intensive monitoring. Because of the drug's long duration of activity, patients may need to be supported with glucose for a least 48 hours post-ingestion, even after apparent recovery.

Drug Interactions

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

- **ANTIFUNGALS, AZOLE** (**ketoconazole, itraconazole, fluconazole**): May increase plasma levels of glimepiride
- **BETA-BLOCKERS**: May potentiate hypoglycemic effect
- **CHLORAMPHENICOL**: May displace glimepiride from plasma proteins
- **CORTICOSTEROIDS**: May reduce efficacy
- **DIURETICS, THIAZIDE**: May reduce hypoglycemic efficacy
- **ISONIAZID**: May reduce hypoglycemic efficacy
- **NIACIN**: May reduce hypoglycemic efficacy
- **PHENOTHIAZINES**: May reduce hypoglycemic efficacy
- **PHENYTOIN**: May reduce hypoglycemic efficacy
- **SULFONAMIDES**: May displace glimepiride from plasma proteins
- **SYMPATHOMIMETIC AGENTS**: May reduce hypoglycemic efficacy
- **WARFARIN**: May displace glimepiride from plasma proteins

Laboratory Considerations

No specific laboratory interactions or considerations were noted.

Doses

- **CATS:**

  For treatment of NIDDM:

  a) 2 mg (total dose) per cat once daily (Bruyette 2004)

  b) 1–2 mg (total dose per cat) PO once daily (Scherk 2005c)

Monitoring

- Efficacy: Standard methods of monitoring efficacy for diabetes treatment should be followed (*e.g.*, fasting blood glucose, appetite, attitude, body condition, PU/PD resolution and, perhaps, serum fructosamine and/or glycosylated hemoglobin levels)
- Adverse effects

Client Information

- Clients should understand the "investigational" nature of using this drug in cats and report any untoward effects to the veterinarian.

Chemistry/Synonyms

A sulfonylurea antidiabetic agent, glimepiride occurs as a white to yellowish-white, crystalline, odorless to practically odorless powder. It is practically insoluble in water.

Glimepiride may also be known as: HOE-490, *Amarel®*, *Amaryl®*, *Amarylle®*, *Euglim®*, *Glimepil®*, *Solosa®*, and *Roname®*.