- Clients should contact the veterinarian if the patient exhibits any symptoms of profound depression, severe diarrhea, abnormal bleeding (including bloody diarrhea) and/or bruising

Chemistry/Synonyms

Asparaginase is an enzyme derived from *E. coli* and occurs as a white or almost white, slightly hygroscopic powder that is soluble in water. The commercially available product is a lyophilized powder that also contains mannitol that after reconstituting has a pH of about 7.4. Activity of asparaginase is expressed in terms of International Units (I.U.).

Asparaginase may also be known as: coloaspase, A-ase, ASNase, L-asparaginase, L-asparagine amidohydrolase, MK-965 NSC-109229, Re-82-TAD-15, *Crasnitin®*, *Crasnitine®*, *Elspar®*, *Erwinase®*, *Kidrolase®*, *L-Asp®*, *Laspar®*, *Leucogen®*, *Leunase®*, *Paronal®*, or *Serasa®*.

Storage/Stability/Compatibility

Asparaginase powder for injection should be stored at temperatures less than 8°C, but it is stable for at least 48 hours at room temperature. After reconstituting, the manufacturer states that the drug is stable when refrigerated for up to 8 hours, but other sources state that it is stable for up to 14 days.

Solutions should be used only if clear; turbid solutions should be discarded. Upon standing, gelatinous fibers may be noted in the solution occasionally. These may be removed without loss of potency with a 5 micron filter. Some loss of potency may occur if a 0.2 micron filter is used.

The solution may be shaken while reconstituting, but vigorous shaking should be avoided as the solution may become foamy and difficult to withdraw from the vial and some loss of potency can occur. Recommended intravenous diluents for asparaginase include D_5W and sodium chloride 0.9%.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Asparaginase Powder for Injection: 10,000 IU in 10 mL vials (with 80 mg mannitol, preservative-free); Reconstitute vial with 5 mL Sodium Chloride Injection or Sterile Water for Injection for IV use. For IM use, add 2 mL Sodium Chloride Injection. See Storage/Stability section for more information. *Elspar®* (Merck); (Rx)

ASPIRIN

(*ass*-pir-in) ASA, Acetylsalicylic Acid

ANALGESIC; ANTIPYRETIC; PLATELET AGGREGATION REDUCER; ANTIINFLAMMATORY

Prescriber Highlights

- NSAID used for analgesic, antiinflammatory & antiplatelet effects in a variety of species
- Contraindicated in patients hypersensitive to it or with active GI bleeds; Relatively contraindicated in patients with bleeding disorders, asthma, or renal insufficiency (but has been used to treat glomerular disease)
- Cats relatively sensitive to salicylates (dose carefully); dogs relatively sensitive to GI effects (bleeding)
- Low grade teratogen & may delay labor; avoid use in pregnancy
- Many drug & lab interactions

Uses/Indications

Aspirin is used in all species for its analgesic and antipyretic effects. It is one of the few nonsteroidal antiinflammatory agents that is relatively safe to use in both dogs and cats, although it can cause significant GI bleeding in dogs. Besides its analgesic, antiinflammatory and antipyretic effects, aspirin is used therapeutically for its effects on platelet aggregation in the treatment of DIC and pulmonary artery disease secondary to heartworm infestation in dogs. It is also used in cats with cardiomyopathy. Aspirin (at low doses) may be of benefit in the adjunctive treatment of glomerular disease due to its antiplatelet and antiinflammatory activity.

Pharmacology/Actions

Aspirin inhibits cyclooxygenase (prostaglandin synthetase) thereby reducing the synthesis of prostaglandins and thromboxanes. These effects are thought to be how aspirin produces analgesia, antipyrexia, and reduces platelet aggregation and inflammation. Most cells can synthesize new cyclooxygenase, but platelets cannot. Therefore, aspirin causes an irreversible effect on platelet aggregation. Aspirin has been shown to decrease the clinical signs of experimentally induced anaphylaxis in calves and ponies.

Pharmacokinetics

Aspirin is rapidly absorbed from the stomach and proximal small intestine in monogastric animals. The rate of absorption is dependent upon factors as stomach content, gastric emptying times, tablet disintegration rates and gastric pH. Absorption is slow from the GI tract in cattle, but approximately 70% of an oral dose will be absorbed.

During absorption, aspirin is partially hydrolyzed to salicylic acid where it is distributed widely throughout the body. Highest levels may be found in the liver, heart, lungs, renal cortex, and plasma. The amount of plasma protein binding is variable depending on species, serum salicylate and albumin concentrations. At lower salicylate concentrations it is 90% protein bound, but only 70% protein bound at higher concentrations. Salicylate is excreted into milk but levels appear to be very low. Salicylate will cross the placenta and fetal levels may actually exceed those found in the mother.

Salicylate is metabolized in the liver primarily by conjugation with glycine and glucuronic acid via glucuronyl transferase. Because cats are deficient in this enzymatic pathway, they have prolonged half-lives and are susceptible to accumulating the drug. Minor metabolites formed include gentisic acid, 2,3-dihydroxybenzoic acid, and 2,3,5-trihydroxybenzoic acid. Gentisic acid appears to be the only active metabolite, but because of its low concentrations appears to play an insignificant role therapeutically. The rate of metabolism is determined by both first order kinetics and dose-dependent kinetics depending on which metabolic pathway is looked at. Generally, steady-state serum levels will increase to levels higher (proportionally) than expected with dosage increases. These effects have not been well studied in domestic animals, however.

Salicylate and its metabolites are rapidly excreted by the kidneys by both filtration and renal tubular secretion. Significant tubular reabsorption occurs which is highly pH dependent. Salicylate excretion can be significantly increased by raising urine pH to 5–8. Salicylate and metabolites may be removed using peritoneal dialysis or more rapidly using hemodialysis.

Contraindications/Precautions/Warnings

Aspirin is contraindicated in patients demonstrating previous hypersensitivity reactions to it or in patients with bleeding ulcers. It is relatively contraindicated in patients with hemorrhagic disorders, asthma, or renal insufficiency.

Because aspirin is highly protein bound to plasma albumin, patients with hypoalbuminemia may require lower dosages to

prevent clinical signs of toxicity. Aspirin should be used cautiously with enhanced monitoring in patients with severe hepatic failure or diminished renal function. Because of its effects on platelets, aspirin therapy should be halted, if possible, one week prior to surgical procedures.

Aspirin must be used cautiously in cats because of their inability to rapidly metabolize and excrete salicylates. Clinical signs of toxicity may occur if dosed recklessly or without stringent monitoring. Aspirin should be used cautiously in neonatal animals; adult doses may lead to toxicity.

Adverse Effects

The most common adverse effect of aspirin at therapeutic doses is gastric or intestinal irritation with varying degrees of occult GI blood loss occurring. The resultant irritation may result in vomiting and/or anorexia. Severe blood loss may result in a secondary anemia or hypoproteinemia. In dogs, plain uncoated aspirin may be more irritating to the gastric mucosa than either buffered aspirin or enteric-coated tablets. Hypersensitivity reactions have been reported in dogs although they are thought to occur rarely. Cats may develop acidosis from aspirin therapy.

Reproductive/Nursing Safety

Salicylates are possible teratogens and have been shown to delay parturition; their use should be avoided during pregnancy, particularly during the later stages. 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.*)

Overdosage/Acute Toxicity

Clinical signs of acute overdosage in dogs and cats include: depression, vomiting (may be blood tinged), anorexia, hyperthermia, and increased respiratory rate. Initially, a respiratory alkalosis occurs with a compensatory hyperventilation response. A profound metabolic acidosis follows. If treatment is not provided, muscular weakness, pulmonary and cerebral edema, hypernatremia, hypokalemia, ataxia, and seizures may all develop with eventual coma and death.

There were 899 exposures to aspirin reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases 754 were dogs with 114 showing clinical signs and the remaining 132 cases were cats with 9 showing clinical signs. The remaining 12 cases were made up of 5 birds, 3 equine, 2 lagomorphs and 2 rodents that showed no clinical signs. Common findings in dogs recorded in decreasing frequency included: anorexia, vomiting, lethargy, bloody vomitus, diarrhea and hyperthermia. Common findings in cats recorded in decreasing frequency included vomiting, dyspnea, cyanosis and abnormal mucous membrane color.

Treatment of acute overdosage initially consists of emptying the gut if ingestion has occurred within 12 hours, giving activated charcoal and an oral cathartic, placing an intravenous line, beginning fluids and drawing appropriate lab work (*e.g.*, blood gases). Some clinicians suggest performing gastric lavage with a 3–5% solution of sodium bicarbonate to delay the absorption of aspirin. A reasonable choice for an intravenous solution to correct dehydration would be dextrose 5% in water. Acidosis treatment and forced alkaline diuresis with sodium bicarbonate should be performed for serious ingestions, but should only be attempted if acid-base status can be monitored. Diuresis may be enhanced by the administration of mannitol (1–2 gm/kg/hr). GI protectant medications should also be administered. Seizures may be controlled with IV diazepam. Treatment of hypoprothrombinemia may be attempted by using phytonadione (2.5 mg/kg divided q8–12h) and ascorbic acid (25 mg parenterally) but ascorbic acid may negate some of the urinary alkalinization effects of bicarbonate. Peritoneal dialysis or exchange transfusions may be attempted in very severe ingestions when heroic measures are desired.

Drug Interactions

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

- **DRUGS THAT ALKALINIZE THE URINE** (*e.g.*, **acetazolamide, sodium bicarbonate**) significantly increase the renal excretion of salicylates; because carbonic anhydrase inhibitors (*e.g.*, acetazolamide, dichlorphenamide) may cause systemic acidosis and increase CNS levels of salicylates, toxicity may occur
- **AMINOGLYCOSIDES:** Some clinicians feel that aspirin should not be given concomitantly with aminoglycoside antibiotics because of an increased likelihood of nephrotoxicity developing. The actual clinical significance of this interaction is not clear, and the risk versus benefits should be weighed when contemplating therapy
- **CORTICOSTEROIDS:** May increase the clearance of salicylates and decrease serum levels and increase the risks for GI bleeding
- **DIGOXIN:** In dogs, aspirin has been demonstrated to increase plasma levels of digoxin by decreasing the clearance of the drug
- **FUROSEMIDE:** May compete with the renal excretion of aspirin and delay its excretion; this may cause clinical signs of toxicity in animals receiving high aspirin doses
- **HEPARIN or ORAL ANTICOAGULANTS:** Aspirin may increase the risks for bleeding
- **METHOTREXATE:** Aspirin may displace MTX from plasma proteins increasing the risk for toxicity
- **NSAIDS:** Increased chances of developing GI ulceration exist
- **PHENOBARBITAL:** May increase the rate of metabolism of aspirin by inducing hepatic enzymes
- **PROBENECID, SULFINPYRAZONE:** At usual doses, aspirin may antagonize the uricosuric effects of probenicid or sulfinpyrazone
- **SPIRONOLACTONE:** Aspirin may inhibit the diuretic activity of spironolactone
- **TETRACYCLINE:** The antacids in buffered aspirin may chelate tetracycline products if given simultaneously; space doses apart by at least one hour
- **URINARY ACIDIFYING DRUGS** (**methionine, ammonium chloride, ascorbic acid**): Can decrease the urinary excretion of salicylates

Laboratory Considerations

- At high doses, aspirin may cause false-positive results for **urinary glucose** if using the cupric sulfate method (*Clinitest®*, Benedict's solution) and false-negative results if using the glucose oxidase method (*Clinistix®* or *Tes-Tape®*).
- **Urinary ketones** measured by the ferric chloride method (Gerhardt) may be affected if salicylates are in the urine (reddish-color produced). **5-HIAA** determinations by fluorescent methods may be interfered by salicylates in the urine. Falsely elevated **VMA** (vanillylmandelic acid) may be seen with most methods used if salicylates are in the urine. Falsely lowered **VMA** levels may be seen if using the Pisano method.

- Urinary excretion of **xylose** may be decreased if aspirin is given concurrently. Falsely elevated **serum uric acid** values may be measured if using colorimetric methods.
- Aspirin can decrease serum concentrations of **T3, T4** and **free T4** in dogs.

Doses

- **DOGS:**

Note: Recommend using buffered varieties of aspirin in dogs

For analgesia:

a) 10–25 mg/kg PO q8–12h (Morgan 1988); (McLaughlin 2000)
b) 10–20 mg/kg PO q12h (Jenkins 1987), (Holland and Chastain 1995)
c) 10–25 mg/kg PO q12h in food (Hardie 2000)
d) 10 mg/kg PO q12h (Lascelles 2003)

As an antiinflammatory/antirheumatic:

a) 25 mg/kg PO q8h (Holland and Chastain 1995)

For antipyrexia:

a) 10 mg/kg PO twice daily (Morgan 1988); (Holland and Chastain 1995)

Post-Adulticide therapy for heartworm disease:

a) 7–10 mg/kg PO once a day (Calvert 1987)

To decrease platelet aggregation; as an antithrombotic:

a) 0.5 mg/kg PO twice daily (Rackear et al. 1988); (Holland and Chastain 1995)
b) For adjunctive therapy of glomerular disease: 0.5 mg/kg PO q12–24h (Grauer and DiBartola 2000)
c) For adjunctive therapy of glomerular disease: 0.5 mg/kg PO q24h (DiBartola and Chew 2006b)
d) For adjunctive therapy with azathioprine and glucocorticoids for immune-mediated hemolytic anemia: 0.5 mg/kg PO once daily (Weinkle, Center et al. 2004)

For Disseminated Intravascular Coagulation (DIC):

a) 150–300 mg/20kg animal PO once a day to once every other day for 10 days (Morgan 1988)

As an analgesic/antiinflammatory prior to elective intraocular surgery:

a) 6.5 mg/kg two to three times daily (Wyman 1986)

- **CATS:**

For analgesia:

a) 10 mg/kg PO every other day (Jenkins 1987); (Holland and Chastain 1995)
b) 10 mg/kg PO q48–72h in food (Hardie 2000)
c) 11–22 mg/kg PO q48h (every other day) (Kelly 1995

For the treatment of arthritis as an antirheumatic/anti-inflammatory:

a) 10–20 mg/kg PO every other day (q48h) (Hardie 1997)
b) 25 mg/kg PO once daily (Chastain 1987); (Holland and Chastain 1995)

For antipyrexia:

a) 10 mg/kg PO q48h (every other day) (Holland and Chastain 1995)

As an antithrombotic agent:

a) For adjunctive treatment of hypertrophic feline cardiomyopathy or intermediate (restrictive) feline cardiomyopathy (as an anti-thrombogenic agent): 5 mg per cat PO q72h (every 3 days) (Tobias 2000)
b) For prophylaxis of arterial thromboembolism (ATE): 5 mg (total dose) per cat PO q72hours (every 3rd day) (Smith, Tobias et al. 2003)
c) For prophylaxis of arterial thromboembolism: 81 mg (total dose; one "baby" aspirin) q72hours (every 3rd day). Likely a weaker, but less expensive option than clopidogrel/LMWH. Generally, aspirin therapy is recommended in all cats with atrial enlargement and cardiomyopathy. (Meurs 2006d)
d) 25 mg/kg PO q56–84h (Holland and Chastain 1995)

As an analgesic/antiinflammatory prior to elective intraocular surgery:

a) 6.5 mg/kg two to three times daily (Wyman 1986)

To inhibit platelet function:

a) 25 mg/kg, (or ¼ of a 325 mg tablet) PO every 48–72 hours. Will inhibit platelet function for 3–5 days. (Fox 2000)

- **FERRETS:**

a) 10–20 mg/kg PO once daily (has short duration of activity) (Williams 2000)

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

a) Rabbits: 5–20 mg/kg PO once daily for low grade analgesia (Ivey and Morrisey 2000)
b) Mice, Rats, Gerbils, Hamsters: 100–150 mg/kg PO q4h. Guinea pigs: 87 mg/kg PO (Adamcak and Otten 2000)

- **CATTLE:**

For analgesia/antipyrexia:

a) 100 mg/kg PO q12h (Walz 2006b)
b) Mature Cattle: two to four 240 grain boluses PO; Calves: one to two 240 grain boluses, allow animals to drink water after administration (Label directions; Vedco Brand)

- **HORSES: (Note:** ARCI UCGFS Class 4 Drug)

For analgesia:

a) Mature Horses: two to four 240 grain boluses PO
b) Foals: one to two 240 grain boluses; allow animals to drink water after administration (Label directions–Vedco Brand)
c) 25 mg/kg PO q12h initially, then 10 mg/kg once daily (Jenkins 1987)
d) 15–100 mg/kg PO once daily (Robinson 1987)

For anti-platelet activity as an adjunctive treatment of laminitis:

a) 5–10 mg/kg PO q24–48 hours or 20 mg/kg PO every 4–5 days (Brumbaugh, Lopez et al.)

- **SWINE:**

For analgesia:

a) 10 mg/kg q4h PO (Jenkins 1987), (Koritz 1986)
b) 10 mg/kg q6h PO (Davis 1979)

- **AVIAN:**

a) 5 grams in 250 mL of water as sole water source (Clubb 1986)
Note: Because of the significant hydrolysis that will occur, this solution should be freshly prepared every 12 hours if stored at room temperature or every 4 days if kept refrigerated at 5° C.

Monitoring

- Analgesic effect &/or antipyretic effect
- Bleeding times if indicated
- PCV and stool guaiac tests if indicated

Client Information

- Contact veterinarian if symptoms of GI bleeding or distress occur (black, tarry feces; anorexia or vomiting, etc.).
- Because aspirin is a very old drug, formal approvals from the FDA for its use in animals have not been required. There is no listed meat or milk withdrawal times listed for food-producing animals but because there are salicylate-sensitive people, in the interest of public health, this author suggests a minimum of 1 day withdrawal time for either milk or meat.

Chemistry/Synonyms

Aspirin, sometimes known as acetylsalicylic acid or ASA, is the salicylate ester of acetic acid. The compound occurs as a white, crystalline powder or tabular or needle-like crystals. It is a weak acid with a pK_a of 3.5. Aspirin is slightly soluble in water and is freely soluble in alcohol. Each gram of aspirin contains approximately 760 mg of salicylate.

Aspirin may also be known as: ASA, acetylsal acid, acetylsalicylic acid, acidum acetylsalicylicum, polopiryna, or salicylic acid acetate; many trade names are available.

Storage/Stability/Compatibility

Aspirin tablets should be stored in tight, moisture resistant containers. Do not use products past the expiration date or if a strong vinegar-like odor is noted emitting from the bottle.

Aspirin is stable in dry air, but readily hydrolyzes to acetate and salicylate when exposed to water or moist air; it will then exude a strong vinegar-like odor. The addition of heat will speed the rate of hydrolysis. In aqueous solutions, aspirin is most stable at pH's of 2–3 and least stable at pH's below 2 or greater than 8. Should an aqueous solution be desirable as a dosage form, the commercial product *Alka-Seltzer®* will remain stable for 10 hours at room temperature in solution.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Aspirin Tablets (Enteric-Coated): 81 mg; (Hartz); (OTC) Labeled for use in dogs.

Aspirin Tablets (Buffered, Microencapsulated, Chewable for dogs): 150 mg & 450 mg; *Canine Aspirin Chewable Tablets for Small & Medium* (150 mg) or *Large Dogs®* (450 mg) (Pala-Tech); (OTC) Labeled for use in dogs.

Aspirin Tablets 60 grain (3.9 g): Aspirin 60 Grain (Butler); (OTC) and (Vedco); (Rx); Rx is labeled for use in horses, cattle, sheep and swine; not for use in horses intended for food or in lactating dairy animals.

Aspirin Boluses 240 grain (15.6 g): Labeled for use in horses, foals, cattle and calves; not for use in lactating animals. Aspirin 240 Grain Boluses, Aspirin Bolus (various); (OTC)

Aspirin Boluses 480 grain (31.2 g). Labeled for use in mature horses, & cattle. Aspirin 480 Grain Boluses (various); (OTC)

Oral Aspirin Gel: 250 mg/mL in 30 mL: *Aspir-Flex® Aspirin Gel for Small and Medium Dogs* (Durvet); 500 mg/1 mL in 30 mL: *Aspir-Flex® Aspirin Gel for Large Dogs* (Durvet); (OTC) Labeled for use in dogs.

Aspirin Powder: l lb. (various); (OTC); Aspirin Powder Molasses-Flavored 50% acetylsalicylic acid in base (Butler); Aspirin USP 204 g/lb (apple flavored) (Neogen); Acetylsalicylic acid; (OTC)

Aspirin Granules: 2.5 gram per 39 mL scoop (apple and molasses flavor); *Arthri-Eze Aspirin Granules®* (Durvet); (OTC); Labeled for use in horses

Aspirin Liquid Concentrate (equiv to 12% aspirin) for Dilution in Drinking Water in 32 oz btls. (AgriPharm, First Priority); (OTC); Labeled for addition to drinking water for swine, poultry, beef and dairy cattle

There are no listed meat or milk withdrawal times listed for food-producing animals, but because there are salicylate-sensitive people, in the interest of public health, this author suggests a minimum of 1 day withdrawal time for either milk or meat. For further guidance with determining use and withdrawal times, contact FARAD (see Phone Numbers & Websites in the appendix for contact information).

The ARCI (Racing Commissioners International) has designated this drug as a class 4 substance. See the appendix for more information.

■ HUMAN-LABELED PRODUCTS:

Note: Many dosage forms and brand names are commercially available; the following is an abbreviated list of some products that have been used for veterinary indications:

Aspirin, Chewable Tablets: 81 mg (1.25 grains); *Bayer® Children's Aspirin* (Bayer); *St. Joseph® Adult Chewable Aspirin* (Schering-Plough); (OTC)

Aspirin, Tablets; plain uncoated; 325 mg (5 grain), & 500 mg (7.8 grain); *Genuine* and *Maximum Bayer® Aspirin Tablets* and *Caplets* (Bayer); *Empirin®* (GlaxoWellcome); *Arthritis Foundation® Pain Reliever* (McNeil-CPC); *Norwich® Regular Strength* (Lee); *Norwich Extra-Strength®* (Procter & Gamble); generic; (OTC)

Aspirin Tablets, enteric coated: 81 mg, 165 mg, 325 mg, 500 mg, 650 mg, & 800 mg; *Ecotrin® Adult Low Strength* (GlaxoSmithKline Consumer Healthcare); *Halfprin 81®* and *½ Halfprin®* (Kramer), *Heartline®* (BDI), *Ecotrin® Tablets & Caplets* and *Ecotrin® Maximum Strength Caplets* (SmithKline Beecham); *Extra Strength Bayer® Enteric 500 Aspirin* (Bayer); generic; (OTC)

Aspirin Extended-controlled Release Tablets: 81 mg, 650 mg, 800 mg & 975 mg; *Extended Release Bayer® 8-hour Caplets* (Bayer); (OTC), *ZORprin®* (PAR); (Rx), *Bayer® Low Adult Strength* (Bayer); generic; (OTC)

Aspirin, Tablets; buffered uncoated; 325 mg (5 grain), with aluminum &/or magnesium salts; *Tri-Buffered Bufferin Tablets* and *Caplets®* (Bristol-Myers Squibb); *Bayer® Buffered Aspirin* (Bayer); *Asprimox®* and *Asprimox® Extra Protection for Arthritis* (Invamed); 500 mg with calcium carbonate, magnesium carbonate, & magnesium oxide; *Extra Strength Bayer® Plus Caplets* (Bayer); *Bufferin®* (Bristol-Myers); 500 mg with 237 mg calcium carbonate, 33 mg magnesium hydroxide, 33 mg aluminum hydroxide; *Ascriptin® Maximum Strength* (Novartis); 500 mg with 100 mg magnesium hydroxide and 27 mg aluminum hydroxide; *Arthritis Pain Formula®* (Whitehall); 325 mg with 75 mg aluminum hydroxide, 75 mg magnesium hydroxide and calcium carbonate; *Asprimox Extra Protection* for *Arthritis Pain®* (Invamed); generic; (OTC)

Aspirin Tablets: buffered coated: 325 mg & 500 mg. *Adprin-B®* (Pfeiffer); *Asprimox®* (Invamed); *Magnaprin®* and *Magnaprin® Arthritis Strength Captabs®* (Rugby); *Ascriptin®* and *Ascriptin® Extra Strength* (Rhone-Poulenc Rorer), *Bufferin®* (Bristol Myers); generic; (OTC)

Rectal suppositories, chewing gum and effervescent oral dosage forms are also available commercially for human use.

ATENOLOL

(a-*ten*-oh-lol) Tenormin®

BETA-ADRENERGIC BLOCKER

Prescriber Highlights

- Beta-blocker that is used primarily for hypertension & tachyarrhythmias in small animals
- Has minimal beta-2 activity at usual doses; comparatively safe to use in asthmatic patients
- Contraindicated in patients with bradycardic arrhythmias, or hypersensitivity to it
- Negative inotrope so must be used with caution in patients with CHF; use with caution in renal failure patients & those with sinus node dysfunction
- Higher dosages may mask clinical signs of hyperthyroidism or hypoglycemia; may cause hyper- or hypoglycemia—use with caution in brittle diabetics
- Primary adverse effects are lethargy, hypotension, or diarrhea
- If discontinuing, recommend withdrawing gradually

Uses/Indications

Atenolol may be useful in the treatment of supraventricular tachyarrhythmias, premature ventricular contractions (PVC's, VPC's), systemic hypertension and in treating cats with hypertrophic cardiomyopathy. Atenolol is relatively safe to use in animals with bronchospastic disease.

Pharmacology/Actions

Atenolol is a relatively specific $Beta_1$-blocker. At higher dosages, this specificity may be lost and $Beta_2$ blockade can occur. Atenolol does not possess any intrinsic sympathomimetic activity like pindolol nor does it possess membrane-stabilizing activity like pindolol or propranolol. Cardiovascular effects secondary to atenolol's negative inotropic and chronotropic actions include: decreased sinus heart rate, slowed AV conduction, diminished cardiac output at rest and during exercise, decreased myocardial oxygen demand, reduced blood pressure, and inhibition of isoproterenol-induced tachycardia.

Pharmacokinetics

Only about 50–60% of an oral dose is absorbed in humans, but is absorbed rapidly. In cats, it is reported to have a bioavailability of approximately 90%. The drug has very low protein binding characteristics (5–15%) and is distributed well into most tissues. Atenolol has low lipid solubility and unlike propranolol, only small amounts of atenolol are distributed into the CNS. Atenolol crosses the placenta and levels in milk are higher than those found in plasma. Atenolol is minimally biotransformed in the liver; 40–50% is excreted unchanged in the urine and the bulk of the remainder is excreted in the feces unchanged (unabsorbed drug). Reported half-lives: dogs = 3.2 hours; cats = 3.7 hours; humans = 6–7 hours. Duration of beta blockade effect in cats persists for about 12 hours.

Contraindications/Precautions/Warnings

Atenolol is contraindicated in patients with overt heart failure, hypersensitivity to this class of agents, greater than first-degree heart block, or sinus bradycardia. Non-specific beta-blockers are generally contraindicated in patients with CHF unless secondary to a tachyarrhythmia responsive to beta-blocker therapy. They are also relatively contraindicated in patients with bronchospastic lung disease.

Atenolol should be used cautiously in patients with significant renal insufficiency or sinus node dysfunction.

Atenolol (at high dosages) can mask the clinical signs associated with hypoglycemia. It can also cause hypoglycemia or hyperglycemia and, therefore, should be used cautiously in labile diabetic patients.

Atenolol can mask the clinical signs associated with thyrotoxicosis, however, it may be used clinically to treat the clinical signs associated with this condition.

Adverse Effects

It is reported that adverse effects most commonly occur in geriatric animals or those that have acute decompensating heart disease. Adverse effects considered clinically relevant include: bradycardia, inappetance, lethargy and depression, impaired AV conduction, CHF or worsening of heart failure, hypotension, hypoglycemia, and bronchoconstriction (less so with $Beta_1$ specific drugs like atenolol). Syncope and diarrhea have also been reported in canine patients with beta-blockers. Lethargy and hypotension may be noted within 1 hour of administration.

Exacerbation of symptoms has been reported following abrupt cessation of beta-blockers in humans. It is recommended to withdraw therapy gradually in patients who have been receiving the drug chronically.

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.*)

Overdosage/Acute Toxicity

There were 208 exposures to atenolol reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases 145 were dogs with 11 showing clinical signs, 62 cases were cats with 4 showing clinical signs and the remaining reported case was a bird that showed no clinical signs. Common findings in dogs recorded in decreasing frequency included bradycardia, lethargy and arrhythmia. Common findings in cats recorded in decreasing frequency included: coma, lethargy, protrusion of the third eyelid, subdued, and vomiting.

Humans have apparently survived dosages of up to 5 grams. The most predominant clinical signs expected would be extensions of the drug's pharmacologic effects: hypotension, bradycardia, bronchospasm, cardiac failure and hypoglycemia.

If overdose is secondary to a recent oral ingestion, emptying the gut and charcoal administration may be considered. Monitor: ECG, blood glucose, potassium and, if possible, blood pressure. Treatment of the cardiovascular effects is symptomatic. Use fluids and pressor agents to treat hypotension. Bradycardia may be treated with atropine. If atropine fails, isoproterenol given cautiously has been recommended. Use of a transvenous pacemaker may be necessary. Cardiac failure can be treated with a digitalis glycoside, diuretics and oxygen. Glucagon (5–10 mg IV; human dose) may increase heart rate and blood pressure and reduce the cardiodepressant effects of atenolol.

Drug Interactions

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