ALLOPURINOL

(al-oh-*pyoor*-i-nol) Zyloprim®

XANTHINE OXIDASE INHIBITOR; PURINE ANALOG

Prescriber Highlights

- Used as a uric acid reducer in dogs, cats, reptiles & birds & as an alternative treatment Leishmaniasis & Trypanosomiasis in dogs
- Use with caution (dosage adjustment may be required) in patients with renal or hepatic dysfunction
- Contraindicated in red-tailed hawks & should be used with caution, if at all, in other raptors
- Diet may need to be adjusted to lower purine
- GI effects are most likely adverse effects, but hypersensitivity, hepatic & renal effects can occur
- Many potential drug interactions

Uses/Indications

The principle veterinary uses for allopurinol are for the prophylactic treatment of recurrent uric acid uroliths and hyperuricosuric calcium oxalate uroliths in small animals. It has also been used in an attempt to treat gout in pet birds and reptiles.

Allopurinol has been recommended as an alternative treatment for canine Leishmaniasis. Although it appears to have clinical efficacy, it does not apparently clear the parasite in most dogs at usual dosages. Allopurinol may also be useful for American Trypanosomiasis.

Pharmacology/Actions

Allopurinol and its metabolite, oxypurinol, inhibit the enzyme xanthine oxidase. Xanthine oxidase is responsible for the conversion of oxypurines (*e.g.*, hypoxanthine, xanthine) to uric acid. Hepatic microsomal enzymes may also be inhibited by allopurinol. It does not increase the renal excretion of uric acid nor does it possess any antiinflammatory or analgesic activity.

Allopurinol is metabolized by *Leishmania* into an inactive form of inosine that is incorporated into the organism's RNA leading to faulty protein and RNA synthesis.

Allopurinol, by inhibiting xanthine oxidase, can inhibit the formation of superoxide anion radicals, thereby providing protection against hemorrhagic shock and myocardial ischemia in laboratory conditions. The clinical use of the drug for these indications requires further study.

Pharmacokinetics

In Dalmatians, absorption rates were variable between subjects. Peak levels occur within 1–3 hours after oral dosing. Elimination half-life is about 2.7 hours. In dogs (not necessarily Dalmatians), the serum half-life of allopurinol is approximately 2 hours and for oxipurinol, 4 hours. Food does not appear to alter the absorption of allopurinol in dogs.

In horses, oral bioavailability of allopurinol is low (approximately 15%). Allopurinol is rapidly converted to oxypurinol in the horse as the elimination half-life of allopurinol is approximately 5–6 minutes. Oxypurinol has an elimination half-life of about 1.1 hours in the horse.

In humans, allopurinol is approximately 90% absorbed from the GI tract after oral dosing. Peak levels after oral allopurinol administration occur 1.5 and 4.5 hours later, for allopurinol and oxypurinol, respectively.

Allopurinol is distributed in total body tissue water but levels in the CNS are only about 50% of those found elsewhere. Neither allopurinol nor oxypurinol are bound to plasma proteins, but both drugs are excreted into milk.

Xanthine oxidase metabolizes allopurinol to oxypurinol. In humans, the serum half-life for allopurinol is 1–3 hours and for oxypurinol, 18–30 hours. Half-lives are increased in patients with diminished renal function. Both allopurinol and oxypurinol are dialyzable.

Contraindications/Precautions/Warnings

Allopurinol is contraindicated in patients who are hypersensitive to it or have previously developed a severe reaction to it. It should be used cautiously and with intensified monitoring in patients with impaired hepatic or renal function. When used in patients with renal insufficiency, dosage reductions and increased monitoring are usually warranted.

Red-tailed hawks appear to be sensitive to the effects of allopurinol. Doses at 50 mg/kg PO once daily caused clinical signs of vomiting and hyperuricemia with renal dysfunction. Doses of 25 mg/kg PO once daily were safe but not effective in reducing plasma uric acid.

Adverse Effects

Adverse effects in dogs are apparently uncommon with allopurinol when fed low purine diets. There has been one report of a dog developing hemolytic anemia and trigeminal neuropathy while receiving allopurinol. Xanthine coatings have formed around ammonium urate uroliths in dogs that have been fed diets containing purine. If the drug is required for chronic therapy, reduction of purine precursors in the diet with dosage reduction should be considered.

Several adverse effects have been reported in humans including GI distress, bone marrow suppression, skin rashes, hepatitis, and vasculitis. Human patients with renal dysfunction are at risk for further decreases in renal function and other severe adverse effects unless dosages are reduced. Until further studies are performed in dogs with decreased renal function, the drug should be used with caution and at reduced dosages.

Reproductive/Nursing Safety

While the safe use of allopurinol during pregnancy has not been established, dosages of up to 20 times normal in rodents have not demonstrated decreases in fertility. Infertility in males (humans) has been reported with the drug, but a causal effect has not been firmly established. 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.*)

Allopurinol and oxypurinol may be excreted into milk; use caution when allopurinol is administered to a nursing dam.

Overdosage/Acute Toxicity

Vomiting is common in dogs at doses >100 mg/kg per the APCC database. A human ingesting 22.5 grams did not develop serious toxicity. The oral LD50 in mice is 78 mg/kg.

There were 27 exposures to allopurinol reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases 25 were dogs with 2 showing clinical signs; the remaining 2 reported cases were cats that showed no clinical signs. Common findings recorded in decreasing frequency included vomiting and tachycardia.

Drug Interactions

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

- **AMINOPHYLLINE** or **THEOPHYLLINE**: Large doses of allopurinol may decrease metabolism thereby increasing their serum levels
- **AMOXICILLIN** or **AMPICILLIN**: In humans, concomitant use with allopurinol has been implicated in increased occurrences of skin rashes; the veterinary significance of this interaction is unknown
- **AZATHIOPRINE** or **MERCAPTOPURINE**: Allopurinol may inhibit metabolism and increase toxicity; if concurrent use is necessary, dosages of the antineoplastic/immunosuppressive agent should be reduced initially to 25–33% of their usual dose and then adjusted, dependent upon patient's response
- **CHLORPROPAMIDE**: Allopurinol may increase risks for hypoglycemia and hepato-renal reactions
- **CYCLOPHOSPHAMIDE**: Increased bone marrow depression may occur in patients receiving both allopurinol and cyclophosphamide
- **CYCLOSPORINE**: Allopurinol may increase cyclosporine levels
- **DIURETICS** (**Furosemide, Thiazides, Diazoxide, and Alcohol**): Can increase uric acid levels
- **ORAL ANTICOAGULANTS** (*e.g.*, **Warfarin**): Allopurinol may reduce the metabolism of warfarin thereby increasing effect
- **TRIMETHOPRIM/SULFAMETHOXAZOLE**: In a few human patients, thrombocytopenia has occurred when used with allopurinol
- **URICOSURIC AGENTS** (*e.g.*, **Probenecid, Sulfinpyrazone**): May increase the renal excretion of oxypurinol and thereby reduce xanthine oxidase inhibition; in treating hyperuricemia the additive effects on blood uric acid may, in fact, be beneficial to the patient
- **URINARY ACIDIFIERS** (*e.g.*, **Methionine, Ammonium Chloride**) May reduce the solubility of uric acid in the urine and induce urolithiasis

Doses

- **DOGS:**

  For urate uroliths:

  a) 7–10 mg/kg PO three times daily for both dissolution and prevention. Goal is to reduce urine urate:creatinine ratio by 50%. (Senior 1989)

  b) For dissolution: 15 mg/kg PO q12h; only in conjunction with low purine foods.

  For prevention: 10–20 mg/kg/day; because prolonged high doses of allopurinol may result in xanthine uroliths, it may be preferable to minimize recurrence with dietary therapy, with the option of treating infrequent episodes of urate urolith formation with dissolution protocols. (Osborne, Lulich et al. 2003a)

  c) Alkalinize urine to a pH of 6.5–7 (see sodium bicarbonate monograph), give low purine diet and eliminate any UTI. Allopurinol at 10 mg/kg three times daily for the first month, then 10 mg/kg once daily thereafter. Reduce dose in patients with renal failure. (Polzin and Osborne 1985), (Lage, Polzin, and Zenoble 1988)

  For Leishmaniasis:

  a) 15 mg/kg PO twice daily for months (Lappin 2000)

  b) If possible use with meglumine antimoniate, if not, use allopurinol alone at 10 mg/kg PO twice daily. If animal has renal insufficiency, use at 5 mg/kg PO twice daily. (Font 1999)

  c) Meglumine antimoniate (100 mg/kg/day SQ) until resolution, with allopurinol at 20 mg/kg PO q12h for 9 months.

  An alternate protocol using allopurinol alone: allopurinol 10 mg/kg PO q8h or 10–20 mg/kg PO q12h for 1–4 months. (Brosey 2005)

- **CATS:**

  For urate uroliths:

  a) 9 mg/kg PO per day (Schultz 1986)

- **BIRDS:**

  For gout:

  a) In budgies and cockatiels: Crush one 100 mg tablet into 10 mL of water. Add 20 drops of this solution to one ounce of drinking water. (McDonald 1989)

  b) For parakeets: Crush one 100 mg tablet into 10 mL of water. Add 20 drops of this solution to one ounce of drinking water or give 1 drop 4 times daily. (Clubb 1986)

- **REPTILES:**

  a) For elevated uric acid levels in renal disease in lizards: 20 mg/kg PO once daily (de la Navarre 2003a)

  b) For gout: 20 mg/kg PO once daily. Suggested dosage based upon human data as dose is not established for reptiles. (Johnson-Delaney 2005d)

Monitoring

- Urine uric acid (for urolithiasis)
- Adverse effects
- Periodic CBC, liver and renal function tests (*e.g.*, BUN, Creatinine, liver enzymes); especially early in therapy

Client Information

- Unless otherwise directed, administer after meals (usually 1 hour or so). Notify veterinarian if animal develops a rash, becomes lethargic or ill.

Chemistry/Synonyms

A xanthine oxidase inhibitor, allopurinol occurs as a tasteless, fluffy white to off-white powder with a slight odor. It melts above 300° with decomposition and has an apparent pK_a of 9.4. Oxypurinol (aka oxipurinol, alloxanthine), its active metabolite, has a pK_a of 7.7. Allopurinol is only very slightly soluble in both water and alcohol.

Allopurinol may also be known as: allopurinolum, BW-56-158, HPP, or NSC-1390; many trade names are available.

Storage/Stability/Compatibility

Allopurinol tablets should be stored at room temperature in well-closed containers. The drug is stated to be stable in both light and air. The powder for injection should be stored at 25°C; may be exposed to 15–30°C. Once diluted to a concentration ≤ 6 mg/mL, store at room temperature and use within 10 hours; do not refrigerate. **Compatible** IV solutions include D5W and normal saline.

An extemporaneously prepared suspension containing 20 mg/mL allopurinol for oral use can be prepared from the commercially available tablets. Tablets are crushed and mixed with an amount of *Cologel*® suspending agent equal to ⅓ the final volume. A mixture of simple syrup and wild cherry syrup at a ratio of 2:1 is added to produce the final volume. This preparation has been reported to be stable for at least 14 days when stored in an amber bottle at either room temperature or when refrigerated.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Allopurinol Tablets: 100 mg & 300 mg; *Zyloprim*® (GlaxoWellcome); generic; (Rx)

Allopurinol Powder for Injection: 500 mg preservative-free in 30 mL vials; *Aloprim*® (Nabi); Allopurinol Sodium (Bedford Labs); (Rx)

ALPRAZOLAM

(al-*prah*-zoe-lam) Xanax®

BENZODIAZEPINE SEDATIVE/TRANQUILIZER

Prescriber Highlights

- Oral benzodiazepine that may be useful for unwanted behaviors in dogs or cats
- Contraindications: Aggressive animals (controversial), benzodiazepine hypersensitivity
- Caution: Hepatic or renal disease
- Adverse Effects: Sedation, behavior changes, & contradictory responses; physical dependence is a possibility; may impede training
- C-IV controlled substance

Uses/Indications

Alprazolam may be useful for adjunctive therapy in anxious, aggressive dogs or in those demonstrating panic reactions. (**Note:** Some clinicians believe that benzodiazepines are contraindicated in aggressive dogs as anxiety may actually restrain the animal from aggressive tendencies). It may be useful in cats to treat anxiety disorders.

Alprazolam may have less effect on motor function at low doses than does diazepam.

Pharmacology/Actions

Subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS are depressed by alprazolam and other benzodiazepines thus producing the anxiolytic, sedative, skeletal muscle relaxant, and anticonvulsant effects seen. The exact mechanism of action is unknown, but postulated mechanisms include: antagonism of serotonin, increased release of and/or facilitation of gamma-aminobutyric acid (GABA) activity, and diminished release or turnover of acetylcholine in the CNS. Benzodiazepine specific receptors have been located in the mammalian brain, kidney, liver, lung, and heart. In all species studied, receptors are lacking in the white matter.

Pharmacokinetics

The pharmacokinetics of alprazolam have not been described for either dogs or cats. In humans, alprazolam is well absorbed and is characterized as having an intermediate onset of action. Peak plasma levels occur in 1–2 hours.

Alprazolam is highly lipid soluble and widely distributed throughout the body. It readily crosses the blood-brain barrier and is somewhat bound to plasma proteins (80%).

Alprazolam is metabolized in the liver to at least two metabolites, including alpha-hydroxy-alprazolam which is pharmacologically active. Elimination half-lives range from 6–27 hours in people.

Contraindications/Precautions/Warnings

Some clinicians believe that benzodiazepines are contraindicated in aggressive dogs as anxiety may actually restrain the animal from aggressive tendencies. This remains controversial. Alprazolam is contraindicated in patients with known hypersensitivity to the drug. Use cautiously in patients with hepatic or renal disease, narrow angle glaucoma and debilitated or geriatric patients. Benzodiazepines may impair the abilities of working animals.

Adverse Effects

Benzodiazepines can cause sedation, increased appetite, and transient ataxia. Cats may exhibit changes in behavior (irritability, increased affection, depression, aberrant demeanor) after receiving benzodiazepines.

Dogs may rarely exhibit a contradictory response (CNS excitement) following administration of benzodiazepines.

Chronic usage of benzodiazepines may induce physical dependence. Animals appear to be less likely than humans to develop physical dependence.

Benzodiazepines may impede the ability of the animal to learn and may retard training.

Reproductive/Nursing Safety

Diazepam and other benzodiazepines have been implicated in causing congenital abnormalities in humans if administered during the first trimester of pregnancy. Infants born of mothers receiving large doses of benzodiazepines shortly before delivery have been reported to suffer from apnea, impaired metabolic response to cold stress, difficulty in feeding, hyperbilirubinemia, hypotonia, etc. Withdrawal symptoms have occurred in infants whose mothers chronically took benzodiazepines during pregnancy. The veterinary significance of these effects is unclear, but the use of these agents during the first trimester of pregnancy should only occur when the benefits clearly outweigh the risks associated with their use. 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.*)

Overdosage/Acute Toxicity

When administered alone, alprazolam overdoses are generally limited to significant CNS depression (confusion, coma, decreased reflexes, etc.). Hypotension, respiratory depression, and cardiac arrest have been reported in human patients but apparently, are quite rare. The reported LD50 in rats for alprazolam is >330 mg/kg, but cardiac arrest occurred at doses as low as 195 mg/kg.

There were 935 exposures to alprazolam reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases 863 were dogs with 208 showing clinical signs, 63 were cats with 20 showing clinical signs, 3 were rodents with 1 reported as having clinical signs, and 2 cases were rabbits with 1 reported as having clinical signs. Common findings in dogs recorded in decreasing frequency included ataxia, lethargy, hyperactivity, disorientation, depression. Common findings in cats recorded in decreasing frequency included ataxia disorientation, sedation, hyperactivity and restlessness. Common findings in rodents recorded in decreasing frequency included ataxia, somnolence and vomiting. Common findings in lagomorphs recorded in decreasing frequency included ataxia and lethargy.

Treatment of acute toxicity consists of standard protocols for removing and/or binding the drug in the gut if taken orally and supportive systemic measures. Flumazenil (see separate monograph) may be employed to reverse the sedative effects of alprazolam, but only if the patient has significant CNS or respiratory depression. Seizures may be precipitated in patients physically dependent. The use of analeptic agents (CNS stimulants such as caffeine) is generally not recommended.

Drug Interactions

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