ATIPAMEZOLE HCL

(at-i-*pam*-a-zole) Antisedan®

ALPHA-2 ADRENERGIC ANTAGONIST

Prescriber Highlights

- Alpha$_2$ adrenergic antagonist; antagonizes agonists such as medetomidine or xylazine
- No safety data on use in pregnant or lactating animals
- May reverse effects rapidly, including analgesia; animals should be observed & protected from self-harm or causing harm to others
- Adverse Effects may include vomiting, diarrhea, hypersalivation, tremors, or excitation

Uses/Indications

Atipamezole is labeled for use as a reversal agent for medetomidine and dexmedetomidine. It potentially could be useful for reversal of other alpha$_2$-adrenergic agonists as well (*e.g.*, amitraz, xylazine, clonidine, tizanidine, brimonidine).

Pharmacology/Actions

Atipamezole competitively inhibits alpha$_2$-adrenergic receptors, thereby acting as a reversal agent for alpha$_2$-adrenergic agonists (*e.g.*, medetomidine). Net pharmacologic effects are to reduce sedation, decrease blood pressure, increase heart and respiratory rates, and reduce the analgesic effects of alpha$_2$-adrenergic agonists.

Pharmacokinetics

After IM administration in the dog, peak plasma levels occur in about 10 minutes. Atipamezole is apparently metabolized in the liver to compounds that are eliminated in the urine. The drug has an average plasma elimination half-life of about 2–3 hours.

Contraindications/Precautions/Warnings

While the manufacturer lists no absolute contraindications to the use of atipamezole, the drug is not recommended in pregnant or lactating animals due to the lack of data establishing safety. Caution should be used in administration of anesthetic agents to elderly or debilitated animals.

When used as a reversal agent (antidote) for alpha$_2$-agonist toxicity, atipamezole's effects may subside before non-toxic levels of the offending agent are reached; repeat dosing may be necessary.

Adverse Effects

Potential adverse effects include occasional vomiting, diarrhea, hypersalivation, tremors, and brief excitation or apprehensiveness.

Because reversal can occur rapidly, care should be exercised as animals emerging from sedation and analgesia may exhibit apprehensive or aggressive behaviors. After reversal, animals should be protected from falling. Additional analgesia (*e.g.*, butorphanol) should be considered, particularly after painful procedures.

Reproductive/Nursing Safety

The manufacturer states that the drug is not recommended in pregnant or lactating animals, or in animals intended for breeding due to lack of data establishing safety in these animals. No other data was noted.

Overdosage/Acute Toxicity

Dogs receiving up to 10X the listed dosage apparently tolerated the drug without major effects. When overdosed, dose related effects seen included panting, excitement, trembling, vomiting, soft or liquid feces, vasodilatation of sclera and some muscle injury at the IM injection site. Specific overdose therapy should generally not be necessary.

Drug Interactions

The manufacturer states that information on the use of atipamezole with other drugs is lacking, therefore, caution should be taken when using with other drugs (other than medetomidine). The following drug interactions have either been reported or are theoretical in humans or animals receiving atipamezole and may be of significance in veterinary patients:

- **ALPHA1-ADRENERGIC BLOCKERS** (*e.g.*, **prazosin**): Atipamezole is a relatively specific alpha-2 blocker it can also partially block alpha1 receptors and reduce the effects of prazosin
- **ALPHA2-ADRENERGICS AGONISTS** (*e.g.*, **detomidine, clonidine, brimonidine, xylazine, amitraz,** etc.): Atipamezole can reduce the effects (toxic or therapeutic) of these agents

Doses

- **DOGS:**

  For reversal of medetomidine:

  a) Give IM an equal volume of *Antisedan*® and *Domitor*® is administered (mL per mL). The actual concentration of *Antisedan*® will be 5X that of *Domitor*®, as *Antisedan*® is 5 mg/mL versus *Domitor*®'s 1 mg/mL. (Package Insert; *Antisedan*®—Pfizer)

  b) As above, but may give IV as well as IM. If it has been at least 45 minutes since medetomidine was given, may give atipamezole at half the volume of medetomidine if administered IV. If after 10–15 minutes an IM dose of atipamezole has not seemed to reverse the effects of medetomidine, an additional dose of atipamezole at ½ the volume of the medetomidine dose may be given. (McGrath and Ko 1997)

  For treatment of amitraz toxicity:

  a) 50 mcg/kg IM (Hugnet, Buronrosse et al. 1996)

- **CATS:**

  For reversal of medetomidine as part of a medetomidine/ butorphanol or buprenorphine/ketamine/carprofen or meloxicam anesthesia/analgesia injectable combination:

  a) Use an equal volume IM of atipamezole as medetomidine was used in the combination. (Ko 2005)

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

  a) Rabbits: For medetomidine reversal: 1 mcg/kg SC, IV or IP. Will reverse analgesia as well. (Ivey and Morrisey 2000)

  b) Mice, Rats, Gerbils, Hamsters, Guinea pigs: To reverse xylazine or medetomidine: 0.1–1 mg/kg IM, IP, IV or SC (Adamcak and Otten 2000)

- **RUMINANTS:**

  a) For reversal of alpha$_2$-adrenergic agonists in bovine, new world camelids, ovine and caprine species: 0.02–0.1 mg/kg IV to effect (Haskell 2005b)

- **BIRDS:**

  a) As a reversal agent for alpha$_2$-adrenergic agonists (*e.g.*, xylazine, detomidine, etc.): 0.5 mg/kg IM (Clyde and Paul-Murphy 2000)

- **REPTILES:**
  a) Reversal of all dosages ketamine/medetomidine combination (see ketamine or medetomidine monographs) with atipamezole is 4–5 times the medetomidine dose (Heard 1999)

Monitoring
- Level of sedation and analgesia
- Heart rate
- Body temperature

Client Information
- Atipamezole should be administered by veterinary professionals only. Clients should be informed that occasionally vomiting, diarrhea, hypersalivation, excitation and tremors may be seen after atipamezole administration. Should these be severe or persist after leaving the clinic, clients should contact the veterinarian.

Chemistry/Synonyms
Atipamezole is an imidazole alpha$_2$-adrenergic antagonist. The injection is a clear, colorless solution.

Atipamezole HCl may also be known as MPV-1248 or *Antisedan*®.

Storage/Stability/Compatibility
Atipamezole HCl injection should be stored at room temperature (15°–30°C) and protected from light.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS:

Atipamezole HCl for Injection: 5 mg/mL in 10 mL multidose vials; *Antisedan*® (Pfizer); (Rx). Approved for use in dogs.

HUMAN-LABELED PRODUCTS: None

ATOVAQUONE

(ah-***toe***-va-kwone) Mepron®

ORAL ANTIPROTOZOAL AGENT

Prescriber Highlights
- Atovaquone (with azithromycin) appears effective in treating dogs with *Babesia gibsoni* infections. Alone, it is a second-line agent (after trimethoprim/sulfa) for pneumocystosis in dogs.
- Limited use thus far; appears well-tolerated by dogs
- Treatment may be quite expensive

Uses/Indications
Atovaquone (with azithromycin) appears effective in treating dogs with *Babesia gibsoni* (Asian genotype) infections, particularly in dogs not immunosuppressed or splenectomized. Atovaquone may be of benefit for treating pneumocystosis in dogs, but it is considered second line therapy after potentiated sulfonamides.

Atovaquone (with azithromycin) may be of benefit in treating *Cytauxzoon felis* infections in cats (research is in progress at the time of writing).

Pharmacology/Actions
Atovaquone's antiprotozoal mechanism of action is not completely understood. It is believed that the hydroxynaphthoquinones, like atovaquone, selectively inhibit protozoan mitochondrial electron transport causing inhibition of *de novo* pyrimidine synthesis. Unlike mammalian cells, certain protozoa cannot salvage preformed pyrimidines.

Pharmacokinetics
Pharmacokinetic data for dogs was not located. In humans after oral administration, bioavailability ranges from 23–47%. The presence of food, particularly high in fat, can increase bioavailability significantly (2+ fold over fasted administration). The drug is highly bound to human plasma proteins (99.9%) and levels in the CSF are approximately 1% of those found in plasma. Elimination half-life in people is about 70 hours presumably due to enterohepatic recycling. There may be limited hepatic metabolism, but the bulk of absorbed drug is eventually eliminated unchanged in the feces.

Contraindications/Precautions/Warnings
No absolute contraindications for using atovaquone in dogs have been documented. Dogs with malabsorption syndromes or that cannot take the drug with food should have alternate therapies considered.

The drug is contraindicated in human patients that develop or have a prior history of hypersensitivity reactions to the drug.

Reproductive/Nursing Safety
Studies in pregnant rats with atovaquone plasma levels approximately 2–3 times those found in humans receiving therapeutic dosages revealed no increase in teratogenicity. Similar studies in rabbits showed increased maternal and fetal toxicity (decreased fetal growth and increased early fetal resorption). In humans, the FDA categorizes atovaquone 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.*)

Little information is available on the safety of this drug during lactation. In rats, milk levels were approximately ⅓ those found in maternal plasma. It is unlikely atovaquone in milk poses much risk to nursing puppies.

Adverse Effects
Atovaquone use in dogs has been limited and the adverse effect profile is not well known. One study (Birkenheuer, Levy et al. 2004) using atovaquone and azithromycin for treating *Babesia gibsoni* infections in 10 dogs reported that no adverse effects were noted. The combination product containing atovaquone and proguanil (*Malarone*®) reportedly causes severe gastrointestinal effects in dogs.

In humans treated with atovaquone, rashes (up to 39% of treated patients) and gastrointestinal effects (nausea, vomiting, diarrhea) are the most frequently reported adverse effects. Rashes or diarrhea may necessitate discontinuation of therapy. Other adverse effects reported in humans include hypersensitivity reactions, increased liver enzymes, CNS effects (headache, dizziness, insomnia), hyperglycemia, hyponatremia, fever, neutropenia, and anemia.

Overdosage/Acute Toxicity
Limited information is available for any species. Minimum toxic doses have not been established; laboratory animals have tolerated doses up to 31.5 grams. The current recommendation for treating overdoses is basically symptomatic and supportive.

Drug Interactions
The following drug interactions have either been reported or are theoretical in humans or animals receiving atovaquone and may be of significance in veterinary patients:
- **METOCLOPRAMIDE:** Can decrease atovaquone plasma concentrations
- **TETRACYCLINE:** Can decrease atovaquone plasma concentrations
- **RIFAMPIN:** Can decrease atovaquone plasma concentrations