MIDAZOLAM HCL

(mid-*ay*-zoe-lam) Versed®

PARENTERAL BENZODIAZEPINE

Prescriber Highlights

- Injectable benzodiazepine used primarily as a pre-op med; unlike diazepam may be given IM
- Contraindications: Hypersensitivity to benzodiazepines; acute narrow-angle glaucoma. Caution: Hepatic or renal disease, debilitated or geriatric patients, & those in coma, shock, or with significant respiratory depression.
- Adverse Effects: Potential for respiratory depression is of most concern
- Avoid intra-carotid injection
- Drug interactions

Uses/Indications

In veterinary patients, midazolam is used principally as a premedicant for general anesthesia. Alone, it does not appear to provide predictable sedation in animals. Animals may become sedated or dysphoric and excited. Cats may be more prone to develop the "excited" effect more than dogs. When used in combination with other drugs (*i.e.*, opioids or ketamine), midazolam does provide more predictable sedation.

Midazolam may also be of benefit to treat status epilepticus when given either IV or IM (not rectally).

In humans, midazolam has been suggested for use as a premedicant before surgery, and as a conscious sedative when combined with potent analgesic/anesthetic drugs (*e.g.*, ketamine or fentanyl). In humans, midazolam reduces the incidences of "dreamlike" emergence reactions and increases in blood pressure and cardiac rate caused by ketamine.

When compared to the thiobarbiturate induction agents (*e.g.*, thiamylal, thiopental), midazolam has less cardiopulmonary depressant effects, is water-soluble, can be mixed with several other agents, and does not tend to accumulate in the body after repeated doses.

Pharmacology/Actions

Midazolam exhibits similar pharmacologic actions as other benzodiazepines. The subcortical levels (primarily limbic, thalamic, and hypothalamic), of the CNS are depressed by the 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.

Midazolam's unique solubility characteristics (water soluble injection but lipid soluble at body pH) give it a very rapid onset of action after injection. When compared to diazepam, midazolam has approximately twice the affinity for benzodiazepine receptors, is nearly 3 times as potent, and has a faster onset of action and a shorter duration of effect.

Pharmacokinetics

Following IM injection, midazolam is rapidly and nearly completely (91%) absorbed. Midazolam is well absorbed after oral administration (no oral products are marketed), but because of a rapid first-pass effect, bioavailabilities suffer (31–72%). The onset of action following IV administration is very rapid due to the high lipophilicity of the agent. In humans, the loss of the lash reflex or counting occurs within 30–97 seconds of administration.

The drug is highly protein bound (94–97%) and rapidly crosses the blood-brain barrier. Because only unbound drug will cross into the CNS, changes in plasma protein concentrations and resultant protein binding may significantly alter the response to a given dose.

Midazolam is metabolized in the liver, principally by microsomal oxidation. An active metabolite (alpha-hydroxymidazolam) is formed, but because of its very short half-life and lower pharmacologic activity, it probably has negligible clinical effects. The serum half-life and duration of activity of midazolam in humans is considerably shorter than that of diazepam. Elimination half-lives in dogs average 77 minutes; in humans, approximately 2 hours (vs. approx. 30 hrs for diazepam).

In dogs, rectal bioavailability of midazolam is very low and this route is not useful clinically.

Contraindications/Precautions/Warnings

The manufacturer lists the following contraindications for use in humans: hypersensitivity to benzodiazepines, or acute narrow-angle glaucoma. Additionally, intra-carotid artery injections must be avoided.

Use cautiously in patients with hepatic or renal disease, and in debilitated or geriatric patients. Patients with congestive heart failure may eliminate the drug more slowly. The drug should be administered to patients in coma, shock, or with significant respiratory depression very cautiously.

When used alone, midazolam does not possess significant effects on cardiorespiratory function, but in combination with other agents, cardiorespiratory effects may be noted. Increased heart rate and blood pressure may be noted when used with ketamine. If this combination is used after an opioid has been administered, these effects may be diminished. If isoflurane will be used as the general anesthetic, use ketamine/midazolam with caution as bradycardia, hypotension and reduced cardiac output are possible.

Midazolam/opioid combinations can cause less cardiovascular depression, but greater respiratory depression, than acepromazine/opioid.

Midazolam and butorphanol used during isoflurane anesthesia can cause decreased blood pressure, heart rate and enhanced respiratory depression.

Adverse Effects

Few adverse effects have been reported in human patients receiving midazolam. Most frequently, effects on respiratory rate, cardiac rate and blood pressure have been reported. Respiratory depression has been reported in patients who have received narcotics or have COPD. The following adverse effects have been reported in more than 1%, but less than 5% of patients receiving midazolam: pain on injection, local irritation, headache, nausea, vomiting, and hiccups.

The principle concern in veterinary patients is the possibility of respiratory depression.

Reproductive/Nursing Safety

Although midazolam has not been demonstrated to cause fetal abnormalities, in humans, other benzodiazepines have been implicated in causing congenital abnormalities 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.*)

Midazolam is excreted in milk and may cause CNS effects in nursing neonates. Exercise caution when administering to a nursing mother.

Overdosage/Acute Toxicity

Very limited information is currently available. The IV LD_{50} in mice has been reported to be 86 mg/kg. It is suggested that accidental overdoses be managed in a supportive manner, similar to diazepam. Flumazenil could be used to antagonize midazolam effects, but because of midazolam's short duration of effect and flumazenil's high cost, supportive therapy may be more suitable in all but the largest overdoses.

Drug Interactions

See the precautions noted above (Contraindications/Precautions) when using midazolam with other agents for preoperative use in small animals. The following drug interactions have either been reported or are theoretical in humans or animals receiving midazolam and may be of significance in veterinary patients:

- **ANESTHETICS, INHALATIONAL**: Midazolam may decrease the dosages required
- **AZOLE ANTIFUNGALS** (**ketoconazole, itraconazole**, **fluconazole**): May increase midazolam levels
- **CALCIUM CHANNEL BLOCKERS** (**diltiazem, verapamil**): May increase midazolam levels
- **CIMETIDINE**: May increase midazolam levels
- **CNS DEPRESSANTS, OTHER**: May increase the risk of respiratory depression
- **MACROLIDES** (**erythromycin, clarithromycin**): May increase midazolam levels
- **OPIATES**: May increase the hypnotic effects of midazolam and hypotension has been reported when used with meperidine.
- **PHENOBARBITAL**: May decrease peak levels and AUC of midazolam
- **RIFAMPIN**: May decrease peak levels and AUC of midazolam
- **THIOPENTAL**: Midazolam may decrease the dosages required

Doses

- **DOGS:**

  As a preoperative agent:
  a) 0.2–0.4 mg/kg IV or IM with an opioid such as hydromorphone (0.1 mg/kg IV or 0.2 mg/kg IM) (Day 2002)
  b) 0.1–0.3 mg/kg; may be used in combination with ketamine in a 50:50 mixture (volume/volume) at a dose of 1 mL/9.1 kg (1 mL/20 lb), this equates to a dose of 0.28 mg/kg of midazolam and 5.5 mg/kg of ketamine (Reed 2002)
  c) 0.1–0.5 mg/kg IV (Hellyer 2005b)

  For status epilepticus:
  a) 0.25 mg/kg IV (Knipe 2006b)
  b) 0.2–0.4 mg/kg IV or IM (not per rectum); may repeat once. (Hopper 2006a)

- **CATS:**

  As a preoperative agent:
  a) 0.2–0.4 mg/kg IV or IM with an opioid such as hydromorphone (0.1 mg/kg IV or 0.2 mg/kg IM) (Day 2002)
  b) 0.05–0.5 mg/kg; a dose of 0.3 mg/kg being the most effective when mixed with ketamine to allow for intubation. May be used in combination with ketamine in a 50:50 mixture (volume/volume) at a dose of 1 mL/9.1 kg (1 mL/20 lb), this equates to a dose of 0.28 mg/kg of midazolam and 5.5 mg/kg of ketamine. (Reed 2002)
  c) 0.1–0.5 mg/kg IV (Hellyer 2005b)

- **RABBITS, RODENTS, SMALL MAMMALS:**
  a) Rabbits: As a tranquilizer (to increase relaxation of lightly anesthetized animals and permit ET intubation): 1 mg/kg IV as needed (Huerkamp 1995)
  b) Rabbits**:** 1–2 mg/kg IM, IV. (Ivey and Morrisey 2000)
  c) Hamsters**,** Gerbils, Mice, Rats, Guinea pigs, Chinchillas: 1–2 mg/kg IM (Adamcak and Otten 2000)
  d) Rodents: 5 mg/kg IV (in combination with fentanyl/droperidol or fentanyl-fluanisone for neuroleptanesthesia) (Huerkamp 1995)

- **HORSES:**

  As a preoperative agent:
  a) 0.011–0.0.44 mg/kg IV (Mandsager 1988)

  For seizure control in foals:
  a) 2–5 mg (total dose) for a 50kg foal given IV; rapid IV administration may result in apnea and hypotension. A CRI may be used at a dose of 1–3 mg/hour for a 50kg foal. (Bentz 2006b)
  b) 2–5 mg (total dose) for a 50kg foal given IV or IM; may be repeated to effect. (Toppin 2007)

- **BIRDS:**

  For adjunctive use (with an analgesic) for pain control:
  a) 1–2 mg/kg IM or IV (Clyde and Paul-Murphy 2000)

Monitoring

- Level of sedation
- Respiratory and cardiac signs

Client Information

- This agent should be used in an inpatient setting only or with direct professional supervision where cardiorespiratory support services are available.

Chemistry/Synonyms

Midazolam HCL is a benzodiazepine that occurs as a white or yellowish crystalline powder. Solubility in water is dependent upon pH. At a pH of 3.4 (approximately the pH of commercial injection), 10.3 mg are soluble in one mL of water.

Midazolam HCl may also be known as Ro-21-3981/003, *Versed®*, *Dormicum®*, *Dormonid®*, *Fulsed®*, *Hypnovel®*, *Midaselect®*, and *Zolamid®*.

Storage/Stability/Compatibility

It is recommended to store midazolam injection at room temperature (15°–30°C) and protected from light. After being frozen for 3 days and allowed to thaw at room temperature, the injectable product was physically stable. Midazolam is stable at a pH from 3–3.6.

Midazolam is reportedly physically **compatible** when mixed with the following products: D_5W, normal saline, lactated Ringer's, atropine sulfate, fentanyl citrate, glycopyrrolate, hydroxyzine HCl, ketamine HCl, meperidine HCl, morphine sulfate, nalbuphine HCl, promethazine HCl, sufentanil citrate, and scopolamine HBr. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 2 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Midazolam HCl Injection: 1 mg (as HCl)/mL in 1 mL, 2 mL, 5 mL vials and *Carpuject* vials, 10 mL vials; 5 mg (as HCl)/mL in 1 mL, 2 mL, 5 mL vials and *Carpuject* vials, 10 mL vials, 2 mL syringes; generic; (Rx, C-IV)

Midazolam HCl Syrup: 2 mg/mL in 118 mL; generic; (Roxane); (Rx, C-IV)

MILBEMYCIN OXIME

(mil-beh-*my*-sin) Interceptor®, Sentinel®

MACROLIDE ANTIPARASITIC

For information on the combination product with lufenuron (Sentinel®), see the lufenuron monograph

Prescriber Highlights

- **GABA inhibitor in invertebrates used for heartworm prophylaxis, microfilaricide, & treat demodicosis, etc.**
- **Contraindications: No absolute contraindications**
- **Adverse Effects: Animals with circulating microfilaria may develop a transient shock-like syndrome; at higher doses, neuro signs become more likely**

Uses/Indications

Milbemycin tablets are labeled as a once-a-month heartworm preventative (*Dirofilaria immitis)* and for hookworm control (*Ancylostoma caninum*). It has activity against a variety of other parasites, including adult hookworms (*A. caninum*), adult roundworms (*T. canis, T. leonina*) and whipworms (*Trichuris vulpis*). In cats, milbemycin has been used successfully to prevent larval infection of *Dirofilaria immitis*.

Milbemycin, like ivermectin can be used for treatment of generalized demodicosis in dogs, but treatment can be significantly more expensive. It is likely safer to use in breeds susceptible to mdr1 genetic mutation (Collies, Shelties, Australian shepherds, etc.) at the doses used for this indication, but neuro toxicity is possible. Older dogs, those that have had a long duration of disease prior to treatment, and dogs with pododemodicosis appear have a lower success rate with milbemycin treatment.

Pharmacology/Actions

Milbemycin is thought to act by disrupting the transmission of the neurotransmitter gamma amino butyric acid (GABA) in invertebrates.

Pharmacokinetics

No specific information was located. At labeled doses, milbemycin is considered effective for at least 45 days after infection by *D. immitis* larva.

Contraindications/Precautions/Warnings

Because some dogs with a high number of circulating microfilaria will develop a transient, shock-like syndrome after receiving milbemycin, the manufacturer recommends testing for preexisting heartworm infections.

The manufacturer states to not use the product (*Interceptor*®) in puppies less than 4 weeks of age or less than 2 lbs. of body weight or in kittens less than 6 weeks of age or less than 1.5 lbs. of body weight.

Adverse Effects

At labeled doses, adverse effects appear to be negligible in microfilaria-free dogs, including breeds susceptible to neurologic toxicity (see Overdosage below). At higher dosages (*e.g.*, used for treating demodicosis) neurologic effects may be more likely particularly in dog breeds (Collies, etc.) with the genetic mutation that affects P-glycoprotein.

Eight week old puppies receiving 2.5 mg/kg (5X label) for 3 consecutive days showed no clinical signs after the first day, but after the second or third consecutive dose, showed some ataxia and trembling.

Reproductive/Nursing Safety

The manufacturer states that safety in breeding, pregnant, and lactating queens and breeding toms has not been established.

Studies in pregnant dogs at daily doses 3X those labeled showed no adverse effects to offspring or bitch.

Milbemycin does enter maternal milk; at standard doses, no adverse effects have been noted in nursing puppies.

Overdosage/Acute Toxicity

Beagles have tolerated a single oral dose of 200 mg/kg (200 times monthly rate). Rough-coated collies have tolerated doses of 10 mg/kg (20 times labeled) without adversity. Toxic doses can cause mydriasis, hypersalivation, lethargy, ataxia, pyrexia, seizures, coma and death. There is no specific antidotal treatment and supportive therapy is recommended.

Drug Interactions

The manufacturer states that the drug was used safely during testing in dogs receiving other frequently used veterinary products, including vaccines, anthelmintics, antibiotics, steroids, flea collars, shampoos and dips.

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

- **BENZODIAZEPINES**: Effects may be potentiated by milbemycin; use together not advised in humans

Caution is advised if using other drugs that can inhibit **p-glycoprotein** particularly in those dogs at risk for MDR1-allele mutation (Collies, Australian Shepherds, Shelties, Long-haired Whippet, etc. "white feet"), unless tested "normal": Drugs and drug classes involved include: