Highly differentiated vials and cartons

Identification is ImperatIV™
- Available in 2 mg per 2 mL, 5 mg per 5 mL, 5 mg per 1 mL and 10 mg per 2 mL single-dose vials and 10 mg per 10 mL, 25 mg per 5 mL and 50 mg per 10 mL multi-dose vials

Packaging is InformatIV™
- Full-color cartons that coordinate with vial labels
- Easy-to-read drug name and strengths
- Distinct label and cap color for each strength
- AP rated, bar coded and not made with natural rubber latex

Every SAGENT Product Features...

MIDAZOLAM Injection, USP

Please see full prescribing information, including boxed warning, for MIDAZOLAM Injection, USP, enclosed.

PreventIV Measures™
Packaging and Labeling

SAGENT Pharmaceuticals™
Discover Injectables Excellence™
**INDICATIONS AND USAGE**

Midazolam hydrochloride injection is indicated:

- Intramuscularly or intravenously for preoperative sedation/analgesia/anesthesia;
- Intravenously as an agent for sedation/analgesia/anesthesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;
- Intravenously for induction of general anesthesia, before administration of other anesthetic agents. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia);
- Continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

**PRECAUTIONS**

- Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.
- Midazolam hydrochloride should only be administered intramuscularly or intravenously.

**CONTRAINDICATIONS**

Midazolam hydrochloride is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy.

- Multi-dose vials of SAGENT’s Midazolam Injection, USP are not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form.

**WARNING**

- In a neonatal study, midazolam hydrochloride was not used because of the risk of respiratory depression and failure to increase the heart rate in neonates under 1 mg/kg. In the event of severe respiratory depression, the patient should be supported by mechanical ventilation until recovery.

**ADVERSE REACTIONS**

- Serious cardiorespiratory adverse events have occurred after administration of midazolam. These include respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury.
- Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combative behavior have been reported in both adult and pediatric patients.
- Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hyperventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect.
- Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered.
- Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.
- Midazolam hydrochloride should not be administered intramuscularly or intravenously.

**OVERDOSAGE**

- Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults. These included decreased tidal volume and/or respiratory rate decrease and apnea, as well as variations in blood pressure and pulse rate.
- The majority of serious adverse events, particularly those associated with oxygenation and ventilation, have been reported when midazolam hydrochloride is administered with other medications capable of depressing the central nervous system.
- Other adverse events reported are local effects at the injection site, hiccoughs, nausea, vomiting, oversedation, headache, coughing and drowsiness.

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- Midazolam hydrochloride should only be administered intramuscularly or intravenously.

**IMPORTANT SAFETY INFORMATION**

- Midazolam hydrochloride may be used in only in hospital or ambulatory care settings, including physicians and dental offices, that provide for continuous monitoring of respiratory and cardiac function, i.e., pulse oximetry. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured (see WARNING). For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

- The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for elderly (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS) depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of 1 mg/ml formulation or dilution of the 5 mg/ml formulation is recommended to facilitate slower injection. Doses of sedative medications in all subsequent doses should always be titrated slowly.

- The initial pediatric dose of midazolam for sedation/analgesia/anesthesia is age, procedure, and route dependent (see DOSAGE AND ADMINISTRATION for complete dosing information).

- Neonates: Midazolam hydrochloride should not be administered by rapid injection in the neonatal population.

- Severe hypotension and/or severe hypoxia have been reported following rapid IV administration, particularly with concomitant use of fentanyl (see DOSAGE AND ADMINISTRATION for complete information).

- This SAGENT product meets stringent FDA requirements and is AP rated and not made with natural rubber latex.
Concentration-effect relationships (after an IV dose) have been demonstrated for a variety of CLINICAL administration in pediatric patients. Fentanyl alone.

studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope. In one study of at 15 to 30 minutes depending upon the dose administered. In pediatric patients, up to 85% had no recall of pictures shown after receiving absorbed as such.

structural formula:

DESC

At 15 to 30 minutes after a single IV dose of fentanyl. This was a single-blind study in which the duration of the period of analgesia was significantly longer than that produced by the placebo with a 10 mg/kg dose, peak effect when administered before surgical procedures caused by anticholinergic drugs. However, in some cases, these effects may become apparent in the postoperative period and should be avoided and, if necessary, should be treated with supportive care (e.g., intubation, ventilatory assistance, supplemental oxygen).

that produces satisfactory sedation. It is primarily due to the parent drug. Elimination of the parent drug, a decrease in the concentration of midazolam in plasma after an IV dose of midazolam, and time to peak (T

max)

In vitro studies in which midazolam was not found to be neuromuscular blocking agents (e.g., vecuronium, atracurium, rocuronium, pancuronium, and other nondepolarizing muscle relaxants). In this study, however, the incidence of neuromuscular blockade was not significantly different between the two groups.

For patients who are intubated, the adverse reaction of respiratory depression is, therefore, generally considered to be low risk. However, the potential for respiratory depression is increased in the presence of COPD, obesity, or increased intracranial pressure. Therefore, it is recommended that these patients and their caretakers be monitored for signs of respiratory depression.

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Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with induction of anesthesia. This decrease correlates with the dose of midazolam hydrochloride administered; no similar studies have been carried out with other benzodiazepines.

Intravenous induction doses of midazolam hydrochloride depress the ventilatory response to a clinically significant extent in adults. Intravenous induction doses of midazolam hydrochloride depress the ventilatory response to a clinically significant extent in adults.

In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, but no midazolam was found in the fetal venous serum of the human fetus. In the rat, the concentration of midazolam in maternal serum and amniotic fluid was significantly higher than that in the fetal serum. In the mouse, the concentration of midazolam in maternal serum and amniotic fluid was significantly higher than that in the fetal serum.

Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

The safety and efficacy of midazolam following nonintravenous and nonintramuscular routes of administration have not been established.

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In the absence of compelling evidence to the contrary, benzodiazepines are considered to produce a state of amnesia. Midazolam may be given for this purpose in the concentration of 3 to 5 mg/mL in 5 mL vials. For intravenous use, dilute 1 mL of midazolam injection with 4 mL of sterile water for injection to provide a concentration of 0.75 mg/mL. For intramuscular use, dilute 1 mL of midazolam injection with 1 mL of sterile water for injection to provide a concentration of 1 mg/mL.

Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.
Treatment of injectable midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. An initial dose of 0.025 to 0.05 mg/kg; total dose up to 0.4 mg/kg. If a loading dose is necessary to rapidly initiate sedation, 0.01 to 0.05 mg/kg should be given. Midazolam may be administered by rapid intravenous injection or by continuous intravenous infusion. Treatment should be supported by the administration of oxygen and other appropriate countermeasures. There is no information as to whether sedative agents including midazolam. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed.
Concentration-effect relationships (after an IV dose) have been demonstrated for a variety of midazolam products. Midazolam is a short-acting benzodiazepine. Peak plasma concentrations occur within 5 minutes of an IV injection. The volume of distribution varies depending on the route of administration. After IV administration, midazolam is extensively distributed and binds to plasma proteins. After oral administration, midazolam is less well absorbed due to presystemic metabolism. Midazolam is not significantly excreted in the urine, but is almost completely metabolized in the liver. Metabolism: Midazolam is predominantly metabolized in the liver by cytochrome P450 enzymes. The 1-hydroxymethyl midazolam conjugate is the major active metabolite, and the 1-hydroxy-midazolam glucuronide is a minor metabolite. The 1-hydroxymethyl midazolam conjugate is further metabolized to form 4-hydroxy- and dihydroxy-midazolam conjugates. The amount of midazolam excreted unchanged in the urine after a single IV dose is less than 1%. Metabolites are excreted in the urine and feces. In pediatric patients, the pharmacokinetics of midazolam following a single IV dose have been studied. The elimination half-life is longer in pediatric patients compared to adults. Midazolam hydrochloride is not metabolized by the renal system. The amount of unchanged midazolam and its metabolites in the urine is negligible.

In vitro and in vivo studies have shown that midazolam hydrochloride is reversibly bound to plasma proteins, primarily albumin. The extent of this binding is dependent on the concentration of midazolam. The plasma binding of midazolam is decreased in patients with renal failure and in those with liver disease. Midazolam hydrochloride is an anesthetic drug that is used as a sedative, hypnotic, or premedication agent. It is administered by IM, IV, or oral routes. The drug is rapidly absorbed after IM injection. Following an IM injection, it is distributed throughout the body within minutes. Peak plasma concentrations are reached within 30-60 minutes. The drug is rapidly redistributed from the plasma to the extravascular compartment, resulting in a decrease in the concentration of the drug in the plasma. The drug is mainly eliminated by metabolism. The elimination half-life of midazolam is shorter in patients with normal renal function compared to those with renal impairment. Midazolam hydrochloride should be used with caution in patients with impaired renal function. Midazolam hydrochloride is metabolized in the liver by cytochrome P450 enzymes. The major metabolites are the 1-hydroxymethyl midazolam conjugate and the 1-hydroxy-midazolam glucuronide. The 1-hydroxymethyl midazolam conjugate is further metabolized to form 4-hydroxy- and dihydroxy-midazolam conjugates. The amount of midazolam excreted unchanged in the urine after a single IV dose is less than 1%. Metabolites are excreted in the urine and feces. In pediatric patients, the pharmacokinetics of midazolam following a single IV dose have been studied. The elimination half-life is longer in pediatric patients compared to adults. Midazolam hydrochloride is not metabolized by the renal system. The amount of unchanged midazolam and its metabolites in the urine is negligible.

Midazolam hydrochloride is a white to off-white crystalline powder. It is soluble in water and freely soluble in alcohol. It is insoluble in ether and chloroform. Midazolam hydrochloride is an anesthetic drug that is used as a sedative, hypnotic, or premedication agent. It is administered by IM, IV, or oral routes. The drug is rapidly absorbed after IM injection. Following an IM injection, it is distributed throughout the body within minutes. Peak plasma concentrations are reached within 30-60 minutes. The drug is rapidly redistributed from the plasma to the extravascular compartment, resulting in a decrease in the concentration of the drug in the plasma. The drug is mainly eliminated by metabolism. The elimination half-life of midazolam is shorter in patients with normal renal function compared to those with renal impairment. Midazolam hydrochloride should be used with caution in patients with impaired renal function. Midazolam hydrochloride is metabolized in the liver by cytochrome P450 enzymes. The major metabolites are the 1-hydroxymethyl midazolam conjugate and the 1-hydroxy-midazolam glucuronide. The 1-hydroxymethyl midazolam conjugate is further metabolized to form 4-hydroxy- and dihydroxy-midazolam conjugates. The amount of midazolam excreted unchanged in the urine after a single IV dose is less than 1%. Metabolites are excreted in the urine and feces. In pediatric patients, the pharmacokinetics of midazolam following a single IV dose have been studied. The elimination half-life is longer in pediatric patients compared to adults. Midazolam hydrochloride is not metabolized by the renal system. The amount of unchanged midazolam and its metabolites in the urine is negligible.

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**WARNINGS**

**CNS EFFECTS**

CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE EVENTS IS RECOMMENDED. 

In the event of cardiorespiratory arrest, endotracheal intubation should be performed to secure the airway. Adequate ventilation should be maintained, as well as adequate perfusion and oxygenation. The administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate patient monitoring, see box below.

In addition, close monitoring of the patient's clinical condition must be maintained and other measures instituted to prevent further deterioration. There are no data available regarding the administration of flumazenil for cardiorespiratory arrest in the pediatric population.

**CONTRAINDICATIONS**

It is not recommended to use midazolam for sedation in patients with contraindications to or evidence of severe respiratory distress, airway obstruction, or recurrent aspiration who are at risk of aspiration.

**WARNINGS**

**PREGNANCY**

Midazolam is not indicated for use during labor and delivery.

**WARNINGS**

**PEDIATRIC PATIENTS**

Midazolam should not be used in pediatric patients for sedation, when possible alternatives exist. When the use of midazolam is necessary (e.g., for procedural sedation), the use of age-appropriate techniques, such as age-appropriate dosing and monitoring, should be considered.

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