PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

$^{C/T}$MIDAZOLAM INJECTION, USP

Midazolam injection

Sterile Solution, 1 mg / mL and 5 mg / mL, Intramuscular, Intravenous

USP

Benzodiazepine

Premedicant / Sedative / Anesthetic Agent

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Midazolam Injection, USP (midazolam) is indicated as:

- an intramuscular premedication prior to surgical or diagnostic procedures;
- an intravenous agent for patients requiring sedation/anxiolysis/amnesia prior to and during short endoscopic or short diagnostic procedures and direct-current cardioversion;
- an alternative intravenous agent for the induction of anesthesia;
- a continuous intravenous infusion in intubated, mechanically ventilated patients requiring sedation in the Intensive Care Unit (ICU).

1.1 Pediatrics

Pediatrics (<18 years old): Health Canada has authorized an indication for pediatric use of Midazolam Injection, USP for:

- sedation, anxiolysis, and/or amnesia for diagnostic or therapeutic procedures
- preanesthesia
- a component of anesthesia during surgical procedures, or during treatment in critical care settings.

(see 4.1 Dosing Considerations; 4.2 Recommended Dose and Dosage Adjustment; 7.1.3 Pediatrics)

1.2 Geriatrics

Geriatrics (>55 years old): Evidence suggests that use in the geriatric population is associated with differences in safety or effectiveness. Intravenous sedation with Midazolam Injection, USP is contraindicated in elderly or debilitated patients outside the ICU setting. With other uses, enhanced monitoring is recommended (see 2 CONTRAINDICATIONS; 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).

2 CONTRAINDICATIONS

Midazolam Injection, USP is contraindicated in patients with:

- a known hypersensitivity to this drug or to benzodiazepines, or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING
- acute pulmonary insufficiency
- severe chronic obstructive pulmonary disease (see 7 WARNINGS AND PRECAUTIONS, Respiratory)
- acute narrow angle glaucoma.

Midazolam Injection, USP is contraindicated for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form (see 4.4 Administration)

Intravenous sedation with Midazolam Injection, USP is contraindicated in:

- elderly or debilitated patients outside the ICU setting
- patients not sufficiently alert to respond appropriately to verbal requests

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Serious Cardiorespiratory Events

Serious cardiorespiratory events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Midazolam Injection, USP must never be used without individualization of dose. The immediate availability of oxygen and other appropriate medication, and the equipment necessary for resuscitation, the maintenance of a patent airway, support of ventilation and cardiac function, should be ensured prior to the use of intravenous midazolam in any dose.

Patients should be continuously monitored for early signs of hypoventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken. Vital signs should continue to be monitored during the recovery period. Opioid agonists and other sedatives add to the respiratory depression produced by midazolam.

Addiction, Abuse and Misuse

The use of benzodiazepines, including Midazolam Injection, USP, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing Midazolam Injection, USP
- Monitor all patients regularly for the development of these behaviours or conditions.
- Midazolam Injection, USP should be stored securely to avoid theft or misuse.

Withdrawal

Benzodiazepines, like Midazolam Injection, USP, can produce severe or life-threatening withdrawal symptoms with repeated or continuous administration:

- Avoid abrupt discontinuation or rapid dose reduction of Midazolam Injection, USP.
- Terminate treatment with Midazolam Injection, USP by gradually tapering the dosage schedule under close monitoring.

(see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

Risks from Concomitant use with Opioids

Concomitant use of Midazolam Injection, USP and opioids may result in profound sedation, respiratory depression, coma and death (see 7 WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General

- Midazolam Injection, USP should always be prescribed at the lowest effective dose for the shortest duration possible. Long-term use of Midazolam Injection, USP should be avoided.
- The dosage of midazolam must be carefully individualized.
- As with other sedative medications, there is wide interpatient variability in midazolam dosage requirements, and these requirements may change with time.
- Doses used for intravenous sedation should always be restricted to the special low levels recommended and careful attention should be given in the selection and exclusion of patients that might be especially susceptible to adverse cardiac and respiratory reactions.
- The dosage of midazolam should further be adjusted according to the type and amount of premedication used.
- Outside the ICU setting, midazolam should not be administered to patients in shock, coma, acute alcoholic intoxication, renal failure, or with severe depression of vital signs.
- Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. Should such reactions occur, the response to each dose of midazolam and all other drugs, including local anesthetics, should be evaluated before proceeding with the administration of the drug (see 7 WARNINGS AND PRECAUTIONS, Peri-Operative Considerations).

Geriatrics:

- Geriatric patients in particular may be more sensitive to benzodiazepines (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).
- In elderly patients, enhanced monitoring is recommended.
- Careful monitoring and slow administration is essential if the drug is used in elderly or debilitated patients.

- Geriatric patients are more susceptible to respiratory depression and/or arrest with excess doses or rapid or single bolus IV administration (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Respiratory; 9.1 Serious Drug Interactions).

Pediatrics:

- As a group, pediatric patients generally require higher doses of midazolam than do adults, and younger children may require higher doses than older children. (see 4.2 Recommended Dose and Dosage Adjustment)
- In obese pediatric patients, the dose should be calculated based on ideal body weight.
- Pediatric patients are more susceptible to respiratory depression/airway obstruction when Midazolam Injection, USP is given in conjunction with opioids or other sedatives. Enhanced monitoring is required (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Respiratory; 9.1 Serious Drug Interactions).
- Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid intravenous administration, particularly with concomitant use of fentanyl (see 4.2 Recommended Dose and Dosage Adjustment).

Intramuscular Premedication

- For intramuscular use, Midazolam Injection, USP should be injected deep in a large muscle mass. Intravenous midazolam should be administered as an induction agent only by a person trained in general anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintenance of a patent airway and support of ventilation. The necessary equipment and the appropriate medications must be immediately available to ensure the safety of the procedures involved and the maintenance of respiratory and cardiovascular functions (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Geriatrics:

- Midazolam can be administered concomitantly with atropine sulfate or scopolamine hydrobromide. When administered concomitantly with an opioid, the dose of midazolam should be reduced. (See 4.2 Recommended Dose and Dosage Adjustment)

Pediatrics:

- Midazolam and an opioid should not be mixed as a premedication; however, if required then constant monitoring is recommended. Should both be required, the initial dose of each must be reduced and the second agent of the two should be administered intravenously on arrival at the procedure area. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Respiratory; 9.1 Serious Drug Interactions)

Intravenous Sedation

- Midazolam Injection, USP for intravenous sedation, prior to and during short endoscopic or short diagnostic procedures and direct current cardioversion, should always be administered slowly (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 4.4 Administration). Rapid intravenous injection may cause respiratory depression or apnea requiring respiratory assistance or controlled ventilation.

- The initial dose and all subsequent doses should always be titrated slowly; administered over 2-3 minutes and allow about 2 minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection.
- Midazolam can be used either alone or combined with an opioid immediately before the procedure, with supplemental doses to maintain the desired level of sedation throughout the procedure. For peroral procedures, the use of an appropriate topical anesthetic is recommended. During routine diagnostic bronchoscopies, with no compromise of respiratory function, the use of opioid premedication is recommended.
- When used intravenously as an agent for sedation/anxiolysis/amnesia for short endoscopic or other short diagnostic procedures, the desired psychosedation can usually be attained within 3 to 6 minutes, depending on the dose administered and whether or not opioid premedication is used concomitantly.
- The dose of Midazolam Injection, USP must be reduced in patients premedicated with opioids or other sedative agents including midazolam. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Respiratory; 9.1 Serious Drug Interactions)

Pediatrics:

- Doses of sedative medications in pediatric patients must be calculated on a mg/kg basis, and initial doses and all subsequent doses should always be titrated slowly (see 4.2 Recommended Dose and Dosage Adjustment).

Intravenous Induction of Anesthesia

- For induction of general anesthesia in healthy patients, the initial dose should be administered over 20 to 30 seconds for optimal effect. About 2 minutes must pass to see the effect of the dose. Extreme care should be taken to avoid intra-arterial injection or extravasation.
- Induction of anesthesia with midazolam occurs in approximately 1.5 minutes when an opioid premedicant has been administered and in 2 or more minutes with or without a nonopioid premedicant. Duration of effect when used for induction of anesthesia is generally dose-dependent.

ICU Sedation

- Dosage and infusion rate should be individualized to achieve the required level of sedation according to the patient's age and clinical status.
- In patients who are still sedated and/or who received large doses of opioids, a bolus dose may not be necessary and the initial infusion rate should be substantially decreased.

4.2 Recommended Dose and Dosage Adjustment

Intramuscular Premedication

Adults: The recommended dose of Midazolam Injection, USP is 0.07 to 0.08 mg/kg intramuscularly (usual intramuscular dose is about 5 mg for an average adult) administered 30 to 60 minutes preoperatively.

Elderly and/or Debilitated Patients: Lower doses should be used in elderly or debilitated patients. In a study of patients 60 years or older who did not receive concomitant opioids, 2 to 3 mg of midazolam produced adequate sedation during the preoperative period. Some patients responded to doses as low as 1 mg. As with any potential respiratory depressant, these patients require observation for signs of cardiorespiratory depression after receiving intramuscular midazolam. Onset of action is within 15 minutes, with peak effect occurring 30 to 60 minutes following injection.

Pediatrics: For sedation prior to anesthesia or procedures (for longer and/or more stimulating procedures, intramuscular midazolam can be used to facilitate insertion of an intravenous catheter for titration of additional medication). Sedation with intramuscular midazolam is age- and dose-dependent; higher doses may result in deeper and more prolonged sedation. Doses of 0.1 to 0.15 mg/kg are usually effective and do not prolong emergence from general anesthesia. For more anxious patients, doses up to 0.5 mg/kg may be needed.

Intravenous Sedation

For short endoscopic or short diagnostic procedures and direct current cardioversion:

Midazolam Injection, USP 1 mg/mL formulation is recommended for intravenous sedation to facilitate slow injection. See Table 1.

Table 1 – Recommended Dose and Dosage Adjustment for Intravenous Sedation

Patient Type	Unpremedicated Patient		Premedicated Patient (Opioids or CNS Depressants, see 4.1 Dosing Considerations)
	Initial Dose	Total Dose	
Adults (18-55 years of age)	No more than 2 to 2.5 mg	• Some patients may respond to as little as a total dose of 1 mg; • More than a total dose of 5 mg is not usually necessary; • Do not exceed 0.1 mg/kg.	Reduce dosage by about 30%.
Elderly (>55 years of age); debilitated; chronically ill; limited pulmonary reserve	No more than 1 to 1.5 mg	• Patients may respond to as little as a total dose of 1 mg; • More than a total dose of 3.5 mg is not usually necessary; • Do not exceed 0.07 mg/kg.	Reduce dosage by about 30% (i.e., 60% less than for healthy young unpremedicated patients).

Pediatrics

Intermittent Injection, for sedation prior to and during procedures or prior to anesthesia:

The initial pediatric dose of midazolam for sedation/anxiolysis/amnesia is age, procedure, and route dependent. See Table 2.

Table 2 – Recommended Dose for Intravenous Sedation by Intermittent Injection for Pediatric Patients

Age of Patient	Initial Dose	Total Dose	Comments
6 months - 5 years	0.015 - 0.1 mg/kg	0.6 mg/kg	The initial dose should be administered over 2 - 3 minutes, wait for an additional 2 - 3 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved.
6 - 12 years	0.025 - 0.05 mg/kg	0.4 mg/kg	
12 - 17 years	Dose as Adults (see Table 1)		

Continuous intravenous infusion for sedation in critical care settings: To initiate sedation, an intravenous loading dose of 0.05 to 0.2 mg/kg administered over at least 2 to 3 minutes can be used to establish the desired clinical effect.

This loading dose may be followed by a continuous intravenous infusion to maintain the effect. Based on pharmacokinetic parameters and reported clinical experience, continuous intravenous infusions of midazolam should be initiated at a rate of 0.001 - 0.002 mg/kg/min (1 - 2 mcg/kg/min). The rate of infusion can be increased or decreased as required, or supplemental intravenous doses of midazolam can be administered to increase or maintain the desired effect. Frequent assessment using standard pain/sedation scales is recommended. Drug elimination may be delayed in patients receiving erythromycin and/or other P-450IIIa enzyme inhibitors (see 9.4 Drug-Drug Interactions) and in patients with liver dysfunction, renal dysfunction, low cardiac output (especially those requiring ionotropic support), and in neonates. Hypotension may be observed in patients who are critically ill, particularly those receiving opioids and/or when Midazolam Injection, USP is rapidly administered.

When initiating an infusion with Midazolam Injection, USP in hemodynamically compromised patients, the usual loading dose of Midazolam Injection, USP should be titrated in small increments, separated by 2 - 3 minutes, and the patient monitored for hemodynamic instability, e.g., hypotension, respiratory rate and oxygen saturation.

Neonates

Midazolam Injection, USP should not be administered as a rapid intravenous dose to preterm and term neonates.

Based on the pharmacokinetic parameters and reported clinical experience in preterm and term neonates, continuous intravenous infusion of midazolam should be initiated at a rate of 0.0005 - 0.001 mg/kg/min (0.5 - 1 mcg/kg/min). Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients in combination with regional anesthesia.

Intravenous Induction of Anesthesia

For induction of general anesthesia before administration of other anesthetic agents: Individual response to midazolam is variable, particularly when an opioid premedicant is not used. The dosage should be titrated according to the patient's age and clinical status. See Table 3. Doses are administered over 20 to 30 seconds, allowing 2 minutes for effect. The dosage should be lowered in the elderly and debilitated, and in patients with limited pulmonary reserve (see Table 3). Because the danger of underventilation or apnea is greatest in these patients, and because peak effect may take longer, increments should be smaller and the rate of injections slower.

Table 3 – Recommended Dose and Dosage Adjustment for Intravenous Induction of Anesthesia

Patient Type	Unpremedicated Patients		Premedicated Patients (Opioids or CNS Depressants, see 4.1 Dosing Considerations)	
	Initial Dose	Increments	Initial Dose	Increments
Adults (18-55 years of age)	0.3 - 0.35 mg/kg	If needed to complete induction, increments of approximately 25% of the initial dose may be used.	0.15 - 0.35 mg/kg 0.25 mg/kg will usually suffice.	If needed to complete induction, increments of approximately 25% of the initial dose may be used.
Elderly (>55 years of age); (ASA I or II surgical patients)	0.3 mg/kg		0.2 mg/kg	
Patients with severe systemic disease or other debilitation	0.2 - 0.25 mg/kg In some cases, as little as 0.15 mg/kg will suffice.	The need for increment doses to complete induction must be evaluated by the anesthesiologist.	0.15 - 0.2 mg/kg In some cases, as little as 0.15 mg/kg will suffice.	The need for increment doses to complete induction must be evaluated by the anesthesiologist.

ICU Sedation

For initiation and maintenance of ICU sedation in intubated, mechanically ventilated patients : see Table 4.

Table 4 – Recommended Dose and Dosage Adjustment for ICU Sedation

Patient Type	Bolus Dose	Initial Infusion Dose	Max. Dose	Increments
Unpremedicated	0.015 - 0.03 mg/kg	0.01 - 0.03 mg/kg/hr	0.07 - 0.15 mg/kg/hr	For optimal sedation, the maintenance infusion rate

Premedicated	0.015 - 0.03 mg/kg	0.01 - 0.03 mg/kg/hr	0.07 mg/kg/hr	may be increased or decreased by increments of 25% - 50% of the initial dose at intervals of 30 minutes.

4.3 Reconstitution

Midazolam Injection, USP is compatible with 5% dextrose injection and 0.9% sodium chloride injection. Both the 1 mg/mL and 5 mg/mL formulations may be diluted with 5% dextrose injection or 0.9% sodium chloride injection.

Midazolam Injection, USP is compatible and stable for 24 hours when diluted to 0.1 - 0.5 mg/mL with either 5% dextrose injection or 0.9% sodium chloride injection (see 11 STORAGE, STABILITY AND DISPOSAL).

4.4 Administration

Midazolam Injection, USP should only be administered intramuscularly or intravenously.

The safety and efficacy of midazolam following non-intravenous and non-intramuscular routes of administration have not been established.

Intramuscular: Midazolam Injection, USP should be injected deeply into the muscle.

Intravenous: Midazolam should be used for intravenous sedation only with caution and must not be administered by single bolus or rapid intravenous administration.

The hazards of intra-arterial injection of midazolam solutions in humans are unknown; therefore, precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

Midazolam Injection, USP is contraindicated for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form (see 2 CONTRAINDICATIONS).

Because intravenous midazolam depresses respiration and because opioid agonists and other sedatives can add to this depression, midazolam should be administered as an induction agent only by a person trained in general anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintenance of a patent airway and support of ventilation (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended. During routine diagnostic bronchoscopies, in patients with CO_2 retention, the use of opioid premedication is recommended. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 4.1 Dosing Considerations)

Midazolam should be administered immediately prior to the procedure in small increments and titrated slowly until the desired sedative effect is achieved. An initial titration with a small dose, such as 2 to 2.5 mg (see Table 3) administered over a 2- to 3-minute period is suggested for an average healthy adult. After waiting about 2 minutes, the dosage may be further titrated in small increments of the initial dose if necessary to achieve the desired sedative effect. Wait about 2 minutes after each increment to fully evaluate the sedative effect. Additional maintenance doses may be given in increments of 25% of the

initial dose to maintain the desired level of sedation, only by slow titration. The desired end point can usually be attained within 3 to 6 minutes, depending on the total dose administered and whether or not it is preceded by opioid premedication. Opioid premedication, when indicated, results in less variability of patient response.

Prior to the administration of midazolam for intravenous sedation, it is essential to ensure:

- experience in the administration of drugs for intravenous sedation
- continuous monitoring of patients to detect reversible adverse effects which may occur in individual patients
- the means and setting required for immediate management of these patients

Extreme care must be used in administering Midazolam Injection, USP, particularly by the intravenous route to the elderly, to very ill patients and to those with limited pulmonary reserve due to the possible occurrence of excessive sedation and/or of apnea or respiratory depression. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam (see 2 CONTRAINDICATIONS; 7.1.4 Geriatrics).

ICU Sedation

When administering Midazolam Injection, USP as a continuous infusion for ICU sedation, the changes in the rate of administration should be made slowly (at 30-minute intervals) in order to avoid hypotension and/or overdosage. The change in dose should be in increments of 25 to 50% of the original dose (see 4 DOSAGE AND ADMINISTRATION). Dosage should be titrated to a desired level of sedation; reliance on predicted kinetics may result in significant overdosage.

The elimination half-life of midazolam is variable and may be considerably longer. Recovery may be dependent upon the duration of infusion and is more prolonged if the infusion exceeds 24 hours.

4.5 Missed Dose

Discontinuation Following Repeated or Continuous Administration

- Midazolam Injection, USP can produce withdrawal symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.

5 OVERDOSAGE

Symptoms

The manifestations of midazolam overdosage are: sedation, somnolence, confusion, impaired coordination, diminished reflexes, untoward effects on vital signs, coma and possible cardiorespiratory arrest.

Treatment

Treatment of overdosage is the same as that followed for overdosage with other benzodiazepines. Continuous monitoring of vital signs including EKG, should be immediately instituted and general supportive measures should be employed. Immediate attention should be given to the maintenance of an adequate airway and support of ventilation. If not already present, an intravenous infusion line should be established and further measures should be taken to provide critical care. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, and other appropriate countermeasures. Cardiopulmonary resuscitation may be required. At present, there is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of value in the treatment of midazolam overdosage.

The benzodiazepine antagonist, flumazenil is a specific antidote in known or suspected overdose. (For conditions of use refer to the flumazenil Product Monograph). Caution should be observed with the use of flumazenil in cases of mixed drug overdosage and in patients with epilepsy treated with benzodiazepines.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intramuscular, Intravenous	Solution, 1 mg / mL, 5 mg / mL	Benzyl alcohol, disodium edetate, hydrochloric acid, sodium chloride, sodium hydroxide, water for injection

Midazolam Injection, USP 1 mg/mL contains midazolam hydrochloride equivalent to 1 mg midazolam/mL.

- 2 mL multiple-dose vials with flip-top seals in boxes of 10 vials.
- 5 mL multiple-dose vials with flip-top seals in boxes of 10 vials.
- 10 mL multiple-dose vials with flip-top seals in boxes of 10 vials.

Midazolam Injection, USP 5 mg/mL contains midazolam hydrochloride equivalent to 5 mg midazolam/mL.

- 1 mL multiple-dose vials with flip-top seals in boxes of 10 vials.
- 2 mL multiple-dose vials with flip-top seals in boxes of 10 vials.
- 10 mL multiple-dose vials with flip-top seals in boxes of 10 vials.

The vial stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Concomitant use with opioids: Concomitant use of benzodiazepines, including midazolam injection, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; 9.1 Serious Drug Interactions).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.

If a decision is made to prescribe Midazolam Injection, USP concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of Midazolam Injection, USP than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking Midazolam Injection, USP, prescribe a lower initial dose of the opioid analgesic andtitrate based on clinical response. Follow patients closely for signs and symptoms of respiratorydepression and sedation (see 5 OVERDOSAGE).

Advise both patients and caregivers about the risks of respiratory depression and sedation when Midazolam Injection, USP is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use ofthe opioid have been determined.

Carcinogenesis and Mutagenesis

Twenty-four months (lifetime) toxicity studies in mice and rats indicate carcinogenic activity. The significance of these findings relative to the infrequent use of midazolam in humans is, at present, unknown. The physician should therefore take these findings into consideration when using midazolam. See animal data in 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Doses used for intravenous sedation should always be restricted to the special low levels recommended (see 4.1 Dosing Considerations; 4.2 Recommended Dose and Dosage Adjustment) and careful attention should be given in the selection and exclusion of patients that might be especially susceptible to adverse cardiac and respiratory reactions. Older chronically ill patients and those with concomitant use of other cardiorespiratory depressant agents are also especially susceptible to adverse reactions. It should be borne in mind that a fall in oxygen saturation will increase the probability of arrhythmias and other

potentially fatal events in susceptible patients. Oxygen supplementation should be used in elderly patients with chronic respiratory or cardiac disease and patients who are seriously ill. Experience in the administration of drugs for intravenous sedation, continuous monitoring of patients to detect reversible adverse effects which may occur in individual patients, and the means and setting required for immediate management of these patients are essential prior to the administration of midazolam for intravenous sedation. (see 7 WARNINGS AND PRECAUTIONS, Respiratory; 7.1.4 Geriatrics).

Serious cardiorespiratory events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. Strict adherence to the cautions and warnings recommended in the use of this drug is therefore required in order to minimize the incidence of these reactions (see 8 ADVERSE REACTIONS).

Dependence/Tolerance

Use of benzodiazepines, such as midazolam injection, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur withshort-term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with Midazolam Injection, USP with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing Midazolam Injection, USP. In individuals prone to substance use disorder, Midazolam Injection, USP should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- Midazolam Injection, USP should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving opioids should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

Withdrawal: Benzodiazepines, such as midazolam injection, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use but can occur with short-term use at recommended therapeutic doses.

The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may be difficult todistinguish from a relapse of the patient's condition.

Severe or life-threatening symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behavior.

Other withdrawal signs and symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal signs and symptoms should seek immediate medical attention.

(See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal; 4.1 Dosing Considerations).

Driving and Operating Machinery

Patients receiving Midazolam Injection, USP on an outpatient basis should not engage in hazardous activities requiring complete mental alertness (i.e., operating machinery or driving a motor vehicle) until the effects of the drug, such as drowsiness, have subsided or until one full day after anesthesia and surgery, whichever is longer. Patients should also be cautioned about the ingestion of alcohol or other CNS depressant drugs until the effects of midazolam have subsided.

Falls and Fractures

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitantsedatives (including alcoholic beverages), the elderly or debilitated patients.

Hepatic/Biliary/Pancreatic

Patients with chronic severe alcoholic cirrhosis exhibit changes in elimination half-life, volume of distribution and total body clearance (see 10.3 Pharmacokinetics, Special Populations and Conditions). Caution should therefore be exercised in administering midazolam to these patients.

Musculoskeletal

Myasthenia: Myasthenic patients have the potential for respiratory decompensation if a substance with CNS-depressant and/or muscle-relaxant properties is administered. However, those myasthenic patients with established respiratory failure will need mechanical ventilation and for this sedation will be necessary. Careful monitoring of the patients is recommended should midazolam be used for sedation.

Neurologic

Midazolam has been shown to cause dose-related anterograde amnesia, an impairment or a lack of recall of events following administration of the drug.

Ophthalmologic

Benzodiazepines such as Midazolam Injection, USP are contraindicated in patients with acute narrow angle glaucoma (see 2 CONTRAINDICATIONS). Midazolam lowered the intraocular pressure in subjects without eye disease, but did not prevent the increases elicited by succinylcholine or endotracheal intubation. Patients with glaucoma have not been studied.

Peri-Operative Considerations

Higher risk surgical patients or debilitated patients require lower dosages, whether as a premedicant or for intravenous sedation or induction of anesthesia. (see 4.2 Recommended Dose and Dosage Adjustment)

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of midazolam and all other drugs, including local anesthetics, should be evaluated before proceeding.

Midazolam does not protect against the circulatory effects of succinylcholine administration or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Pediatrics: Pediatric patients should be discharged in the care of a responsible individual.

Renal

Patients with chronic renal failure exhibit changes in elimination half-life, volume of distribution and total body clearance (see 10.3 Pharmacokinetics, Special Populations and Conditions). Caution should therefore be exercised in administering midazolam to these patients.

Reproductive Health: Female and Male Potential

- **Teratogenic Risk:**

There are no adequate and well-controlled studies of midazolam in pregnant women. Animal studies with other anxiolytic-sedative agents have suggested increased risk of congenital malformations (see 7.1.1 Pregnant Women; 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Respiratory

Danger of respiratory disorders may increase when midazolam is administered with opioids. Therefore, the dosage of both agents should be reduced (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, General, Concomitant use with Opioids; 9.1 Serious Drug Interactions).

Apnea: Concomitant use of barbiturates, alcohol, opioids or other CNS depressants increases the risk of apnea and may contribute to excessive and/or prolonged drug effect. Midazolam should not be given with an opioid as an intramuscular combination for premedication due to the risk of apnea. If opioid premedication is given, the subsequent intravenous dose of midazolam should be reduced. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 4 DOSAGE AND ADMINISTRATION; 9.3 Drug-Behavioural Interactions; 9.4 Drug-Drug Interactions)

Respiratory depression: Intravenous midazolam injection has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some

cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam should be used only in hospital or ambulatory care settings 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX). For deeply sedated patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure. Marked hypoventilation is common if the patient is not responsive to verbal commands. Therefore, all patients receiving midazolam for intravenous sedation should remain sufficiently alert to respond appropriately to verbal requests (See 2 CONTRAINDICATIONS)

Chronic Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease may experience prolonged sedation and prolonged respiratory depression (see 2 CONTRAINDICATIONS).

7.1 Special Populations

7.1.1 Pregnant Women

Safety in pregnancy has not been established. Therefore, midazolam should not be used in women who may be pregnant. Several studies have suggested an increased risk of congenital malformations associated with the use of some of the benzodiazepines during the first trimester of pregnancy.

The use of midazolam has not been evaluated in obstetric studies; therefore, it is not recommended for obstetrical use.

Pregnant women in active labour reach significantly higher midazolam plasma levels, a smaller volume of distribution, and a lower clearance than pregnant women undergoing Cesarean section or nonpregnant gynecological patients. When given immediately before Cesarean section, midazolam can cause respiratory depression of the infant.

7.1.2 Breast-feeding

Midazolam is excreted in human milk. Therefore, Midazolam Injection, USP is not recommended for use in nursing mothers. (see 10.3 Pharmacokinetics, Special Populations and Conditions, Pregnancy and Breast-Feeding)

7.1.3 Pediatrics

Based upon published literature, pediatric patients generally require higher doses of midazolam than adults (see 4 DOSAGE AND ADMINISTRATION). Convulsions have occurred in children, most frequently in premature infants and neonates (8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics).

Preterm Infants and Neonates: Midazolam contains 1% v/v benzyl alcohol. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis) particularly in neonates and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including Midazolam Injection, USP) containing this preservative must take into account the total amount of benzyl alcohol administered. The

recommended dosage range of midazolam injection for preterm and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amounts of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages of other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

7.1.4 Geriatrics

Elderly or debilitated patients may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

Doses of Midazolam Injection, USP should be decreased for elderly and debilitated patients (see 4 DOSAGE AND ADMINISTRATION). Complete recovery after midazolam administration in such patients may take longer.

Older chronically ill patients and those with concomitant use of other cardiorespiratory depressant agents are also especially susceptible to adverse reactions. It should be borne in mind that a fall in oxygen saturation will increase the probability of arrhythmias and other potentially fatal events in susceptible patients. Oxygen supplementation should be used in elderly patients with chronic respiratory or cardiac disease and patients who are seriously ill. (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; Respiratory)

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Sedative effects and fluctuations in vital signs were the most frequent findings following parenteral administration of midazolam. These are affected by the lightening or deepening of anesthesia, instrumentation, intubation and use of concomitant drugs. The more frequently encountered fluctuations in vital signs included decreased tidal volume and/or decreased respiratory rate and apnea, as well as variations in blood pressure and pulse rate. When used in intravenous sedation, midazolam tends to produce a higher incidence of fall in mean arterial pressure than diazepam.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observedin the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The most frequently reported adverse reactions observed in association with the use of midazolam in clinical research programs are reported in Table 6. Although adverse reactions may not have been observed in all clinical research programs, the possibility of their occurrence with the different clinical uses of midazolam cannot be excluded.

Table 6 – Most Frequently Reported Treatment Emergent Adverse Events in Association with the use of Midazolam in Clinical Research Programs.

	IM Premedication n = 380 (%)	IV Sedation n = 512 (%)	IV Induction n = 1,073 (%)	IV ICU Sedation n = 115 (%)
Cardiovascular				
Increased Mean Arterial Pressure	2.6	8.0	16.7	6.9
Decreased Mean Arterial Pressure	6.3	29.9	30.8	17.0
Hypotension	7.1	29.9	36.0	26.0*
Increased Pulse Rate	9.5	16.8	12.6	
Decreased Pulse Rate				
Central Nervous System				
Headache	1.3	0.8	2.0	
Drowsiness		0.5	1.7	
Excessive Sedation		0.6	1.6	
Dizziness		0.2	1.2	
Hallucination				2.8
Agitation				1.8
Confusion	0.3	0.6	0.9	2.8
Gastrointestinal				
Hiccoughs	0.3	0.4[b]	6.0	0.9
Nausea	0.5	0.8[b]	4.0	
Emesis/Vomiting	0.5	0.6[b]	3.5	
Respiratory				
Increased Respiratory Rate/Tachypnea	11.5[a]	36.9	0.1	
Decreased Respiratory Rate	10.8[a]	25.6	0.1	
Apnea		1.0	22.9	
Coughing		0.2	2.0	
Respiratory Depression		0.2	25.0	
Airway Obstruction		0.2	1.0	

a: N = 130

b: N = 500

* Hypotension during ICU Sedation was defined as systolic blood pressure ≤ 90 mmHg or diastolic blood pressure ≤ 50 mmHg or a clinically significant fall in blood pressure.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Limited information is available from published literature regarding the use of midazolam in pediatric patients. However, based on information obtained from published literature and spontaneous adverse reaction reporting, the safety profile in children more than one month of age appears to be very similar to that observed in adults.

In pediatric patients similar observations as in adults have been made. Some of the most frequently reported findings include: rash, urticaria, erythema, hives, skin necrosis and wheals.

The most frequent acute events were airway compromise and hypoventilation. This most often occurred when used in conjunction with opioids or other anesthetic agents. The next most common adverse event with long-term use was withdrawal syndrome.

8.3 Less Common Clinical Trial Adverse Reactions

Other adverse reactions occurring at a lower incidence, usually less than 1%, are listed below:

Cardiac Disorders: premature ventricular contractions, bigeminy, vasovagal episode, bradycardia, tachycardia, and nodal rhythm.

Ear and Labyrinth Disorders: ears blocked and loss of balance.

Eye Disorders: blurred vision, diplopia, nystagmus, visual disturbance, difficulty focusing eyes, pinpoint pupils, cyclic movement of eyelids.

Gastrointestinal Disorders: acid taste, excessive salivation, retching and toothache.

Immune System Disorders: allergic reactions, including anaphylactic shock.

Injury, Poisoning and Procedural Complications: cold feeling when drug injected and cool sensation in arm during infusion.

Musculoskeletal and Connective Tissue Disorders: muscle stiffness.

Nervous System Disorders: nervousness, restlessness, anxiety, argumentativeness, aggression, insomnia, nightmares; deep sedation, prolonged sedation, oversedation, disorientation, slurred speech, emergence delirium, agitation during emergence, prolonged emergence from anesthesia, dreaming during emergence; dysphoria, euphoria, anterograde amnesia, lightheadedness, feeling faint; tremors, muscle contractions, twitches and abnormal spontaneous muscular activity, tonic/clonic movements, athetoid movements; ataxia.

Respiratory, Thoracic and Mediastinal Disorders: yawning, laryngospasm, bronchospasm, dyspnea, shallow respiration, hyperventilation, wheezing, respiratory arrest, respiratory failure, apnea, hypoxia, and oxygen desaturation.

Skin and Subcutaneous Tissue Disorders: erythema, rash, pruritus and hives.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

The following list shows the other reported side effects. This list is not exhaustive.

Cardiovascular: hypotension, bradycardia, cardiac/cardiopulmonary arrest.

General Disorders and Administration Site Conditions: lack of efficacy, paradoxical response, therapeutic response decreased.

Hepatobiliary Disorders: isolated elevations in certain parameters of liver function, e.g., AST (SGOT), ALT (SGPT), alkaline phosphatase and total bilirubin, as well as isolated changes in total protein and albumin, have been reported.

Injury, Poisoning and Procedural Complications: excessive sedation.

Nervous System Disorders: convulsions, tonic/clonic convulsions, cerebral convulsion, lethargy. Convulsions occurred primarily in neonates (under 4 months old) and/or children with history of seizures.

Psychiatric Disorders: withdrawal syndrome, combative reaction, agitation, hallucination.

Respiratory, Thoracic and Mediastinal Disorders: respiratory arrest, respiratory failure, apnea, hypoxia, oxygen desaturation.

The incidence of local and vein tolerance observed in the early experience with midazolam is listed in Table 7.

Table 7 – Incidence of Adverse Effects on Local and Vein Tolerance

	IM Premed n = 380	IV Sedation n = 512	IV Induction n = 1,073
LOCAL			
Pain at injection site	3.7	--	--
Pain during injection of drug	0.0	0.4	7.5
Induration at injection site	0.5	--	--
Swelling at injection site	0.0	0.0	0.2
Erythema at injection site	0.5	--	--
Hive-like elevation at injection site	--	--	0.2
Warmth at injection site	--	--	0.1
Burning at injection site	--	--	0.1
Hematoma at IV site	--	--	0.3
VEIN			
Tenderness of vein	0.0	1.4	8.0
Induration of vein	--	1.6	2.1
Redness of vein	0.0	1.4	3.4
Red wheal/flare along vein	--	--	0.1
Pain in vein after injection	--	--	0.1
Phlebitis	--	--	0.6
Thrombophlebitis	--	--	0.1

8.5 Post-Market Adverse Reactions

Injury, Poisoning and Procedural Complications

There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

Dependence/Withdrawal

Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as midazolam. Severe and life-threatening symptoms have been reported. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Concomitant use of Midazolam Injection, USP and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

(see 7 WARNINGS AND PRECAUTIONS, Concomitant use with Opioids)

9.2 Drug Interactions Overview

Concomitant use of barbiturates, alcohol, opioids or other CNS depressants increases the risk of apnea and may contribute to excessive and/or prolonged drug effect.

The hypnotic effect of intravenous midazolam and the risk of apnea is accentuated by premedication, particularly opioids (e.g., morphine, meperidine and fentanyl), secobarbital, and the droperidol-fentanyl combination. Consequently, the dosage of midazolam should be adjusted according to the type and amount of premedication administered.

A slight reduction in induction dosage requirements of thiopental (about 13%) has been noted following intramuscular use of midazolam for premedication.

The administration of midazolam has resulted in a dose dependent reduction of the minimum alveolar concentration of halothane required during maintenance of anesthesia.

Preliminary data, with a small number of subjects, reveal that midazolam appears to potentiate the effect of pancuronium.

Midazolam Injection, USP does not cause a clinically significant change in onset or duration of action of a single intubating dose of succinylcholine. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium.

Midazolam has been used as an induction agent in conjunction with commonly used premedicants or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, succinylcholine and d-tubocurarine, and other nondepolarizing muscle relaxants) or topical anesthetics (e.g., lidocaine).

The metabolism of midazolam is predominantly mediated by cytochrome P-450 3A4 (CYP3A4) isozyme. Approximately 25% of the total cytochrome P-450 system in the adult liver is from the CYP3A4 subfamily. Inhibitors and inducers of this isozyme may lead to drug interaction with midazolam. Data from spontaneous reports as well as kinetic studies in humans indicate that midazolam may interact with compounds, which affect or are also metabolized by the cytochrome P-450 3A4 hepatic enzymes. Data indicate that these compounds (cimetidine, erythromycin, diltiazem, verapamil, ketoconazole, fluconazole and itraconazole) influence the pharmacokinetics of midazolam (increased C_{max} and AUC)

and may lead to prolonged sedation (azithromycin has little or no effect on the pharmacokinetics of midazolam). Therefore, patients receiving the above compounds or others, which inhibit P-450 3A4 enzymes (including saquinavir), together with midazolam should be monitored for the first few hours after administration of midazolam. For further information see 9.4 Drug-Drug Interactions.

9.3 Drug-Behavioural Interactions

Concomitant use of alcohol increases the risk of apnea and may contribute to excessive and/or prolonged drug effect. (see 7 WARNINGS AND PRECAUTIONS, Respiratory).

9.4 Drug-Drug Interactions

The drugs listed in Table 8 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 8 – Established or Potential Drug-Drug Interactions

Proper/Common name	Effect	Clinical comment
Itraconazole and Fluconazole	Co-administration of midazolam and itraconazole or fluconazole prolonged the elimination half-life of midazolam from 2.9 to 7.0 hours (itraconazole) or 2.9 to 4.4 hours (fluconazole).	Bolus doses of midazolam given for short-term sedation did not enhance the effect of midazolam to a clinically significant degree by itraconazole and fluconazole, and dosage reduction is not required. However, administration of high doses of midazolam may require dosage adjustments. Long-term infusions of midazolam to patients receiving antimycotics, e.g., during intensive care treatment, may result in long-lasting hypnotic effects if the dose is not titrated according to the effect.
Erythromycin	Co-administration of midazolam and erythromycin prolonged the elimination half-life of midazolam from 3.5 to 6.2 hours.	Although only relatively minor pharmacodynamic changes were observed, it is advised to adjust doses of intravenous midazolam, especially if high doses are being administered.
Saquinavir	Co-administration of a single intravenous dose of 0.05 mg/kg midazolam after 3 or 5 days of saquinavir dosing (1200 mg t.i.d.) to 12 healthy volunteers decreased the midazolam clearance by 56% and increased the elimination half-life from 4.1 to 9.5 hours. Only the	Bolus doses of intravenous midazolam can be given in combination with saquinavir. During a prolonged midazolam infusion, an initial dose reduction of 50% is recommended.

Proper/Common name	Effect	Clinical comment
	subjective effects to midazolam (visual analogue scales with the item "overall drug effect") were intensified by saquinavir.	
Sodium Valproate	Displacement of midazolam from its plasma binding sites by sodium valproate may increase the response to midazolam.	Care should be taken to adjust the midazolam dosage in patients with epilepsy.
Cimetidine and Ranitidine	Cimetidine increased the steady-state plasma concentration of midazolam by 26%, whereas ranitidine had no effect. Co-administration of midazolam and cimetidine or ranitidine had no clinically significant effect on the pharmacokinetics and pharmacodynamics of midazolam.	These data indicate that intravenous midazolam can be used in usual doses with cimetidine and ranitidine and dosage adjustment is not required.
Cyclosporin	There is no pharmacokinetic and pharmacodynamic interaction between cyclosporin and midazolam.	The dosage of midazolam needs no adjustment when given concomitantly with cyclosporin.
Nitrendipine	Nitrendipine did not affect the pharmacokinetics and pharmacodynamics of midazolam.	Both drugs can be given concomitantly and no dosage adjustment of midazolam is required.
Oral Contraceptives	The pharmacokinetics of intramuscular midazolam was not affected by the use of oral contraceptives.	Both drugs can be given concomitantly and no dosage adjustment of midazolam is required.
Lidocaine	Midazolam had no effect on the plasma protein binding of lidocaine in patients undergoing antiarrhythmic therapy or regional anesthesia with lidocaine.	Both drugs can be given concomitantly and no dosage adjustment of midazolam is required.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Midazolam is a short-acting, water-soluble benzodiazepine, which has central nervous system (CNS) depressant effects. Midazolam possesses all the pharmacological effects of the benzodiazepines, namely it is a sedative, hypnotic, anticonvulsant, anxiolytic, muscle relaxant and amnestic agent. In addition, midazolam enhances GABAergic inhibition, decreases the firing rate of single neurons, decreases the cerebral metabolic rate for oxygen, decreases cerebral blood flow, enhances the survival time of mice in a hypoxic milieu and induces amnesia in the passive avoidance paradigm. Depending on the route of administration and dose used, midazolam can produce sedative-hypnotic effects or induce anesthesia. The administration of midazolam may often be followed by anterograde amnesia.

Midazolam binds in nanomolar concentrations to the high-affinity, stereospecific benzodiazepine receptor sites in the mammalian brain. These receptor sites are functionally coupled to GABA recognition sites and to sites related to chloride channels. Midazolam decreases the cyclic GMP level in the cerebellum. The CNS pharmacological effects of midazolam can be reversed with flumazenil (Ro 15-1788), a specific benzodiazepine antagonist.

In most tests, the potency of midazolam is comparable to that of diazepam or somewhat greater. However, in tests predicting sedation, amnesia, and attenuation of muscle tone and coordination, midazolam is considerably more potent than diazepam.

Clinical experience has shown midazolam to be more potent than diazepam on a mg per kg basis.

10.2 Pharmacodynamics

The onset of effect of midazolam is rapid and its duration of action short. Onset of sedative effects after intramuscular administration is about 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. Sedation (defined as drowsiness with the ability to respond to verbal commands) after intravenous injection is usually achieved within 3 to 6 minutes; the time of onset is affected by the dose administered, the concurrent administration of opioid premedications and the condition of the patient. When midazolam is used intravenously, induction of anesthesia can usually be achieved in 1.5 minutes when opioid premedication has been administered and in 2 to 2.5 minutes without opioid premedication. When used as directed, recovery after awakening from general anesthesia usually occurs within 2 hours, but recovery may take up to 6 hours in some cases. Recovery in patients receiving midazolam may be slightly slower than in patients who receive thiopental.

Intravenous doses of midazolam depress the ventilatory response to CO_2 stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental. The ventilatory response to CO_2 is markedly impaired in patients with chronic obstructive pulmonary disease. Intravenous sedation with midazolam in healthy volunteers does not adversely affect the mechanics of respiration (pulmonary resistance, static recoil, functional residual capacity or residual volume). However, total lung capacity (TLC) and peak expiratory flow decrease significantly, but static compliance and maximum expiratory flow at 50% of awake TLC (V_{max}) increase. In healthy volunteers, an

intramuscular premedicating dose of 0.07 mg/kg did not depress the ventilatory response to CO_2 stimulation to a clinically significant extent. The intravenous administration of midazolam decreases, in a dose-dependent manner, the minimum alveolar concentration (MAC) of halothane required for general anesthesia.

In cardiac hemodynamic studies, induction with midazolam was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume, and systemic vascular resistance. When used in intravenous sedation, midazolam produces a higher incidence of fall in mean arterial pressure than diazepam. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly while faster heart rates (e.g., 85/minute) tended to slow slightly.

In patients without any previous history of cerebrospinal diseases scheduled for elective surgery under lumbar spinal anesthesia, intravenous administration of midazolam at a dose of 0.15 mg/kg tended to reduce the cerebrospinal fluid pressure during induction of anesthesia to an extent similar to 3.9 mg/kg of intravenous thiopental. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam. Patients with glaucoma have not been studied. The increase in intraocular pressure after succinylcholine administration or endotracheal intubation is not prevented by midazolam, diazepam or thiopental.

10.3 Pharmacokinetics

Midazolam dosing should not be based on pharmacokinetic values; it should always be titrated to achieve a given clinical effect. This is especially important when used for long-term sedation in the Intensive Care Unit (ICU). The elimination half-life of midazolam is increased in congestive heart failure, hepatic cirrhosis, and chronic renal failure. It is markedly and unpredictably increased in critically ill patients with multiorgan failure. The following table summarizes the available data.

Table 9 – Summary of Midazolam Pharmacokinetic Parameters for Intramuscular and Intravenous Administration

Patient Type	Dose Range (mg/kg)	Elimination $t_{½}$[a] (hr)	Volume of Distribution; V_d (L/kg)	Total Body Clearance; TBC (L/hr/kg)
Normal Subjects 21 - 50 years	0.07 - 0.25	1.0[b] - 2.8	0.80 - 1.64	0.24 - 0.43
Surgical (Elective) 30 - 54 years	0.15 - 0.45	3.0 - 3.9	1.67 - 3.21	0.37 - 0.51
Congestive Heart Failure 33 - 67 years	0.1	6.5	2.50	0.27
Hepatic Dysfunction 21 - 59 years	0.07	2.4	1.77	0.50
Severe Alcoholic Cirrhosis 39 – 54 years	0.075	3.9	1.49	0.32
Chronic Renal Failure[c] 24 - 68 years	0.20	3.3	3.40	0.60
Volunteers:				

Patient Type	Dose Range (mg/kg)	Elimination $t_{½}$[a] (hr)	Volume of Distribution; V_d (L/kg)	Total Body Clearance; TBC (L/hr/kg)
Male:				
24 - 33 years	5 mg[d]	1.9	1.34	0.47
60 - 74 years	5 mg[d]	4.0	1.64	0.26
Female:				
23 - 37 years	5 mg[d]	2.3	2.00	0.56
64 - 79 years	5 mg[d]	3.0	2.11	0.45
Patients				
Male:				
30 years[e]	0.2	2.3	1.44	0.49
82 years[e]	0.2	8.5	3.63	0.34
Female:				
31 years[e]	0.2	2.9	1.36	0.36
86 years[e]	0.2	3.0	2.30	0.55
Obese volunteers				
22 - 62 years	5 mg[d]	6.5	2.66	0.25

[a] Harmonic mean (hr)

[b] Lower value of the range in the study (mean not reported)

[c] In two critically ill patients with impaired renal function and renal failure with impaired hepatic function, $t_{1/2}$ values of 18 hours and 21 hours, respectively, were reported (Shelly MP, *et al*. Anesthesia 1987;42:619-26).

[d] Absolute dose

[e] Mean age

Pharmacokinetics in Adult Intensive Care Unit (ICU) Patients

The pharmacokinetics of midazolam following continuous intravenous infusion were determined in intubated, mechanically ventilated patients although not critically ill. The kinetics in critically ill patients with multisystem dysfunction are unpredictable and it is recommended that midazolam be titrated to the desired effect. See table 10.

Table 10 – Summary of Midazolam Dosing and Pharmacokinetic Parameters for ICU Sedation

Patient Type	Dosing		Pharmacokinetic Values		
	Bolus* Doses (mg/kg)	Maintenance Infusion Rate (mg/kg/hr)	C_{ss} (ng/mL)	$t_{½}$ (hr)	Total Body Clearance (L/kg/hr)
Coronary artery bypass graft surgery (n = 30)	0.015 0.03 0.05	0.014 to 0.017	66	9.3	0.26

45 - 71 years					
Abdominal-aortic surgery	0.03	0.036	76	6.2	0.52
(n = 30)	0.06	0.054	132	6.2	0.40
50 - 76 years	0.10	0.080	205	6.5	0.41

* Bolus doses of 0.05, 0.06 and 0.10 mg/kg administered in these studies are not recommended in clinical practice (see 4 DOSAGE AND ADMINISTRATION).

Absorption, Distribution and Metabolism

Intramuscular

The mean relative bioavailability of midazolam following intramuscular administration is greater than 90%. Following intramuscular administration, the mean time to peak midazolam plasma concentrations is one half hour. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after intramuscular administration are about one-half of those achieved after equivalent intravenous doses. There is, however, no direct correlation between clinical effects and blood levels of midazolam.

Intravenous

Following intravenous administration, midazolam is rapidly metabolized to 1-hydroxymethyl midazolam, which is the major metabolite, and to 4-hydroxy and 1,4-dihydroxy midazolam, which are minor metabolites. Mean peak plasma concentration of midazolam is several fold greater than that of 1-hydroxymethyl midazolam. Midazolam is approximately 97% plasma protein-bound in normal subjects.

Elimination

Intramuscular

The elimination half-life of intramuscular administered midazolam is comparable to that observed following intravenous administration.

Intravenous

The half-life of elimination of this metabolite is similar to that of the parent compound. Less than 0.03% of the dose is excreted in the urine as intact midazolam, 45% to 81% of the dose is excreted in urine as the conjugates of the metabolites.

ICU Sedation

The elimination half-life of midazolam was longer following continuous infusion in ICU patients than following the injection of single intravenous doses. The data were derived from studies in which midazolam was infused for less than 24 hours. Steady-state plasma levels increased with increasing rates of infusion.

Special Populations and Conditions

- **Pediatrics:** In healthy children aged one year and older, the pharmacokinetic properties of midazolam are similar to those in adults. Weight-normalized clearance is similar to or higher than adult and elimination half-life is similar to or shorter than adult. As with adults, absolute bioavailability of intramuscular midazolam is greater than 80%.

  In seriously ill neonates and children the half-life of midazolam is substantially prolonged and the clearance reduced compared to healthy adults or other groups of children. It cannot be determined if these differences are due to age, immature organ function or immature metabolic pathways, underlying illness or debility.

In the literature, midazolam is reported to be administered orally and rectally in pediatric patients as well as via the recommended parenteral routes, intravenously andintramuscularly. When administered via the nonparenteral routes, the elimination half-life is similar to that of the parenteral administration, however, the bioavailability is lessthan 50% versus greater than 80% when administered intramuscularly. The following tables display pharmacokinetic data on midazolam in pediatric patients. This information was collected from published scientific literature. See tables 11 and 12.

Table 11 – Summary of Midazolam Pharmacokinetic Parameters for Intravenous Administration in Pediatric Patients After Single Intravenous Doses or Short Intravenous Infusions

Number of Patients	Age (years)	Dose (mg/kg)	V_d, area method (L/kg)	Elimination $t_{½}$ (hours)	Clearance (mL/min/kg)
18	12.8[a]	0.08	-	1.45	8.0
20	8 - 17[b]	up to 0.1	0.6	0.78	10.0
21	3.8 - 7.3[c]	0.075 - 0.6	1.4 - 1.7[c]	1.4 - 1.7[c]	4.8 - 11.2[c]
6	2.5[a]	0.2	2.4	2.4	13.3
8	1 - 10[b]	0.15	-	1.2	9.1
12	5 - 9[b]	0.5	2.2	1.8	15.4
17	1.3 - 5.2[c]	0.3	2.4 - 2.7[c]	2.8 - 3.3[c]	8.5 - 12.0[c]
9	2 - 9[b]	0.2	-	0.6	7.6
6	5 - 7	0.1	-	1.8	3.2
10	2 - 5 days	0.2	-	6.5	2.0

[a] Mean Value

[b] Actual Range

[c] Range of Mean Values for Subgroups

Table 12 – Summary of Midazolam Pharmacokinetic Parameters for Intravenous Administration in Pediatric Patients during and After Prolonged Intravenous Infusion

Number of Patients	Age (years)	Infusion Rate (mcg/kg/min)	Infusion Duration (hr)	Elimination $t_{½}$ (hours)	Clearance (mL/min/kg)
10	0.5 - 8.8[b]	2 - 5	21 - 114	4.0 (n = 5)	-
10	4.9[a]	0.8	16	3.1	9.6
15	1 - 5 days[b]	1.0	60	12.0	1.7
187	0 - 10 days[b]	1.15[a]	62[a]	-	1.17[a]

[a] Mean Value

[b] Actual Range

- **Pregnancy and Breast-Feeding:** In animals and humans, midazolam has been shown to cross the placenta and to enter the fetal circulation. Clinical data indicate that midazolam is excreted in human milk. Following oral intake, low concentrations of midazolam could be detected for short periods of time. Measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum, and amniotic fluid, indicating placental transfer of the drug in humans. Fifteen to 60 minutes following intramuscular administration of 0.05 mg/kg of midazolam, both

the umbilical venous and the umbilical arterial serum concentrations were lower than maternal venous concentrations.

- **Hepatic Insufficiency:** Patients with chronic severe alcoholic cirrhosis exhibit changes in elimination half-life, volume of distribution and total body clearance (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- **Renal Insufficiency:** In patients with chronic renal failure, the free fraction of drug in plasma can be significantly higher than in healthy subjects. In patients with acute renal failure (n = 6, mean age 48 years), total body clearance was lower (132 mL/min versus 198 mL/min), and the elimination half-life of midazolam was longer (13.2 hours versus 7.6 hours) than in patients with normal kidney function (n = 33, mean age 62 years). In patients with impaired kidney function, the excretion of 1-hydroxymethyl midazolam glucuronide, the major metabolite of midazolam, is impaired. The de-glucuronidation of this metabolite may increase its plasma concentration, which in turn may interfere with the hydroxylation of midazolam itself.
- **Obesity:** Patients with congestive heart failure and obese subjects have a substantially prolonged elimination half-life and an increased volume of distribution of midazolam.

11 STORAGE, STABILITY AND DISPOSAL

The recommended storage temperature for Midazolam Injection, USP is between 15 °C and 30 °C. Protect from light. Discard unused portion 28 days after initial puncture.

Midazolam Injection, USP is compatible and stable for 24 hours when diluted to 0.1 - 0.5 mg/mL with either 5% dextrose injection or 0.9% sodium chloride injection.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration, whenever solution and container permit.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

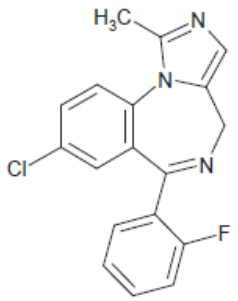
Proper Name: midazolam

Chemical Name: 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo [1,5a] [1,4] benzodiazepine

Molecular Formula: $C_{18}H_{13}ClFN_3$

Molecular Weight: 325.78 g/mol

Structural Formula:



Description: White to light yellow crystalline solid, insoluble in water. The hydrochloride salt of midazolam, which is formed *in situ*, is soluble in aqueous solutions. The melting point is 161 °C – 164 °C.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Subchronic Toxicity

LD_{50} Midazolam Hydrochloride

Species	Strain	Route	LD_{50} (mg/kg)	Observation Period
Mice	Charles River	IV	(M) 47 (F) 48	14 days
		IM	> 50	
Rats	Charles River	IV	> 50	14 days
		IM	> 10[a]	

[a] Highest dose administered

Signs and Symptoms

Decreased motor activity, muscle relaxation, ataxia, loss of righting reflex, hypnosis, respiratory depression.

- **Two-Week IM – Rats:** Midazolam base (5.0 mg/mL) was administered intramuscularly once a day for two weeks to rats (12/sex/group), at doses of 0 (saline control), 0 (vehicle control), 0.5, 1.6 or 5.0 mg/kg.

  The 5.0 mg/kg/day dose produced a significant decrease in food consumption and a slight decrease in body weight gain, in male rats. Transient, dose-related signs of CNS depression were observed in all midazolam-treated groups within five minutes of the injections. The duration of these pharmacological effects was 2.0, 1.0 and 0.5 hr in the high-, mid- and low-dose groups, respectively. In rats from all midazolam-treated groups, multifocal, extensive myositis, myodegeneration and myonecrosis were encountered at the injection sites. The lesions were characterized as chronic active myositis and were moderate to severe in all treatment groups. However, in the low-dose group, the lesions were less extensive with respect to the amount of tissue involved.

- **Five-Week IV – Rats:** Midazolam base (5.0 mg/mL) was administered intravenously once a day for five weeks to rats (12/sex/group) at doses of 1.0, 2.5 or 6.0 mg/kg. A control group received 1.2 mL/kg/day of saline. Local tolerance during the first four weeks was good in all treated groups;

however, during the last week of treatment, intraperitoneal injections were necessary in most members of the high-dose group because of swollen tails. All animals survived the five-week treatment period. Sedation and ataxia were noted in the high-dose group for several minutes after injection. Except for minimal decreases of 6 - 7 % in body weight in males receiving the mid and high doses, no effects on this parameter were observed. The only clinical laboratory finding was a slight reduction in total serum protein in males of the high-dose group.

- **Two-Week IM – Dogs:** Midazolam base (5.0 mg/mL) was administered intramuscularly, once a day for two weeks to dogs (three/sex/group) at doses of 0 (saline control), 0 (vehicle control), 0.3, 1.0 or 3.0 mg/kg.

  Administration of 3.0 and 1.0 mg/kg/day of midazolam was associated with dose-related and transient behavioural changes and central nervous system effects.

  Mean serum total creatine phosphokinase (CPK), alanine aminotransferase (SGPT) and aspartate aminotransferase (SGOT) were significantly elevated in the group treated with 3.0 mg/kg/day compared to the control group. However, the SGOT value was within normal limits.

  Mild focal scarring was seen at the sites of injection in both treated and control dogs.

- **Five-Week IV/IM – Dogs:** In a five-week toxicity study, midazolam base (5.0 mg/mL) was administered intravenously once daily for five weeks to dogs (three/sex/group) at doses of 1.0 or 6.0 mg/kg. Two additional groups of dogs (two/sex/group) received 2.5 mg/kg/day intravenously or intramuscularly. The control group received 1.2 mL/kg/day intravenous saline.

  All animals survived the five-week treatment period. In the first week, dose-related sedation and ataxia were noted for up to three to five hours after intravenous or intramuscular injection. These effects became considerably less pronounced after one week. Alkaline phosphatase values were slightly increased in treated animals, although no clear dose-relationship was evident. Increased $alpha_1$-globulins and decreased $alpha_2$-globulins were noted in treated animals. Slight and nonsignificant dose-related increases in absolute pituitary and liver weights were observed, however, relative organ weights did not show similar trends. Postmortem evaluation showed that the frequency and severity of the inflammatory changes at the intravenous injection sites were similar in all groups except at the high dose where both parameters were somewhat greater than in the controls.

- **Two-Week IV – Rabbits:** In a two-week toxicity study, a saline solution of midazolam maleate (0.5%) or diazepam injectable formulation (0.5%) was administered intravenously into the marginal ear veins of rabbits (four/group) at doses of 1.5 or 5.0 mg/kg/day. A fifth group received a 0.25% solution of midazolam maleate, 1.5 mg/kg/day.

  At the 5.0 mg/kg/day dose, two rabbits received midazolam for 14 days and the other two for ten consecutive days.

  The diazepam injections could not be continued beyond seven days due to the necrotic condition of the ears. The other irritation parameters, swelling, erythema and hemorrhage, were severe after the injection of diazepam and moderate after midazolam.

  At the 1.5 mg/kg/day dose, midazolam was injected for 14 days while diazepam could be administered for 11 to 13 consecutive days. Necrosis was slight in the midazolam-treated rabbits and severe in the diazepam-treated animals. Swelling, erythema and hemorrhage were slight to moderate after midazolam, and moderate to severe after diazepam. Rabbits receiving 1.5

mg/kg/day of midazolam in the 0.25% solution showed less irritation than rabbits receiving the same dose of midazolam in the 0.5% solution.

Decreased motor activity, muscle relaxation and hypnosis (in some animals) were noted in the midazolam-treated animals while the diazepam-treated rabbits showed ataxia, decreased motor activity and muscle relaxation.

Serum alkaline phosphatase levels were elevated in a few midazolam-treated rabbits, although this was not a dose-related phenomenon. One high-dose midazolam-treated rabbit exhibited an elevated white blood cell count.

Chronic Toxicity

- **One-Year Oral – Dogs:** A one-year toxicity study was conducted in beagle dogs (nine/sex/group) with midazolam maleate. The compound was administered orally in gelatin capsules at doses of 0 (control), 1.0, 7.0 or 45 mg/kg/day, seven days per week. The 53-week treatment period was followed by a 14-week recovery period.

  Two dogs from the mid-dose group and one dog from the high-dose group died during the study after having received 280, 60, and 212 doses of midazolam, respectively. However, the gross and microscopic findings indicated that the deaths were not treatment-related.

  Female dogs receiving the high dose and male dogs receiving the mid and high doses of midazolam gained significantly less weight than the controls.

  Treatment-related clinical effects included CNS depression and some behavioural changes, both of which declined after a few weeks of treatment. Abnormal stools and salivation, licking and emesis were observed in both treated and control groups, but the incidences were greater in the treated dogs and showed dose-dependency.

  Serum alkaline phosphatase levels increased substantially in both male and female dogs in the 45 mg/kg/day groups; the increase was on the average eight-fold over pretreatment levels. The values were somewhat higher in female dogs. The abnormality was reversible and at the end of the 14-week recovery period, serum alkaline phosphatase levels were greatly decreased, although they did not reach pretreatment levels. Serum alkaline phosphatase levels were also increased in the mid-dose midazolam groups, although to a lesser extent and returned to normal during the recovery period.

  Gamma glutamyl transpeptidase (GGTP) levels were significantly and dose-dependently elevated in male dogs and significantly elevated at the highest dose in female dogs at week 52. The values were within normal limits. Serum alanine amino-transferase (SGPT) levels were significantly elevated in male dogs in the high-dose group at week 52.

  Liver weights were significantly increased; this change was both dose- and time-related. At week 26, the increase was statistically significant in the high-dose group, while at week 52, it occurred in both the mid- and high-dose groups. At the end of the 14-week recovery period, the mean liver weights of treated and control dogs were statistically not different.

  Microscopic evaluation of the liver revealed the following pathology: parenchymal cell hypertrophy, altered cytoplasmic staining, yellow-brown granules in parenchymal cells and whorls of eosinophilic material. These changes reverted to normal in 3 of 4 dogs by the end of the 14-week recovery period.

Mutagenicity

In the Ames test, with and without metabolic activation, using five *Salmonella typhimurium* strains: TA 1535, TA 1537, TA 1538, TA 100 and TA 98, results were negative at concentrations of 50, 100 and 500 mcg of midazolam per plate. A concentration of 750 mcg/plate was too toxic to the bacteria and could not be evaluated.

The fluctuation test (without metabolic activation) also revealed no mutagenicity of midazolam for *Salmonella typhimurium* strains TA 1535, TA 1537, and TA 1538 at concentrations up to 25 mcg/mL. Higher concentrations could not be evaluated because of toxicity of the bacteria.

Carcinogenicity

- **Mice (2-year):** A twenty-four month oral (dietary admix) carcinogenicity study with midazolam was conducted in mice (80 males and 80 females/group) at doses of 0 (control 1), 0 (control 2), 1, 9 or 80 mg/kg/day.

  In male mice in the high-dose group, survival was decreased when compared to controls. Mean body weights were significantly increased in male and female mice in the high-dose group and in female mice in the mid-dose group.

  The 24-month administration of midazolam, at the 80 mg/kg/day dose level, in male mice led to decreased white blood cell counts, ulceration/abrasion of the prepuce, inflammatory changes of the urinary tract and distention of the urinary bladder.

  Mean absolute and relative liver weights were significantly increased in male and female mice in the high-dose group and in male mice in the mid-dose group.

  Hepatocellular hypertrophy was a prominent histological finding in both male and female mice at the 80/mg/kg/day dose and in male mice at the 9 mg/kg/day dose. In female mice, the 80 mg/kg/day dose of midazolam markedly increased the incidence of hepatic neoplasms. The hepatic masses or nodules, seen at necropsy, were found to be primary adenomas and carcinomas upon histologic examination. Hepatic neoplasms were also seen in female mice in the mid and low-dose groups, at a frequency higher than in controls, however, the difference was not statistically significant.

  In female mice in the high-dose group, there was an increase in the incidence of follicular hyperplasia, adenoma/carcinoma of the thyroid, and a significant increase in the incidence of adrenal cortical hypertrophy and adrenomedullary hyperplasia.

- **Rats (2-year):** A twenty-four month oral (dietary admix) carcinogenicity study with midazolam was conducted in rats (90 males and 90 females/group) at doses of 0 (control 1), 0 (control 2), 1, 9 or 80 mg/kg/day.

  In female rats, midazolam administration was associated with a decrease of body weight at the high dose and an increase of body weight at the mid dose. In male animals, the 80 mg/kg/day dose caused an increase in body weight during the earlier part of the study.

  The 80 mg/kg/day dose was associated with the following changes in clinical chemical parameters: a decrease of serum glucose in both male and female rats at 26 weeks, an increase of serum urea nitrogen in female rats at 26 weeks and albuminuria in male rats after 26 weeks persisting to 78 weeks. At later times, all parameters were similar to control.

Absolute and relative liver weights were increased in both male and female animals, treated with 80 and 9 mg/kg/day of midazolam. Absolute liver weights were also increased in low-dose treated female rats.

In addition, the following organ weight changes were observed in animals treated with the 80 mg/kg/day dose of midazolam and were considered treatment related: increase in absolute and relative kidney weights in both sexes, increase in absolute and relative thyroid weights in both sexes, increase in absolute and relative adrenal gland weights in male rats, decrease in absolute and relative pituitary gland weights in female rats and decreased weights of the testes.

Dose-related centrilobular hepatocytic hypertrophy and centrilobular fatty changes were observed in the livers of both sexes. In addition, there was a statistically non-significant increase in the incidence of hepatocellular adenomas/carcinomas in female rats at all three doses.

In male rats, treated with 80 mg/kg/day of midazolam, the incidence of thyroidal tumors (adenomas/carcinomas) was significantly increased. The increase was limited to follicular adenomas; there was no increase observed in the incidence of follicular carcinomas.

Reproduction and Developmental Toxicology

- **Fertility and General Reproductive Performance:** In a reproduction study, rats were administered midazolam maleate injection at doses of 1.0, 4.0, or 16.0 mg/kg/day by oral intubation. The highest dose produced pronounced pharmacological effects, namely sedation and ataxia, which lasted up to 2 hours. Twenty-four male rats were treated for 62 days prior to mating and through the mating period and 24 female rats for 14 days prior to mating and through day 13 of gestation (Group A) or day 21 of lactation (Group B). Control rats received daily intubation of the vehicle. Approximately one-half of the rats were sacrificed on gestation day 13. The remaining dams were allowed to deliver for subsequent perinatal and postnatal evaluations and were sacrificed on lactation day 21.

  Gonadal function, mating behaviour, conception rate, early and late stages of gestation, parturition, lactation, neonatal viability, and growth of the pups were not adversely affected when midazolam was administered orally at doses up to 16 mg/kg/day.

- **Teratology-Rats (IV):** A teratology study was performed with groups of 30 rats given midazolam maleate intravenously at doses of 0.2, 1.0 or 4.0 mg/kg/day from day 7 through 15 of gestation. One group of females was not injected and served as a non- treated control. A second control group was injected with the vehicle. Fetuses from 20 rats per group were delivered by Cæsarean section. An additional ten rats per group were allowed to deliver for subsequent postnatal evaluation of the pups.

  In the Cæsarean section group, the average maternal body weight decreased significantly during gestation in dams receiving the 4.0 mg/kg/day dose.

  There were no significant differences between control and treated animals in the average litter size, average fetal body weight, distribution of fetuses by sex, the number of fetuses born dead, resorption rate or percent litters showing resorptions. No increase in external soft tissue or skeletal abnormalities was noted and the incidence of skeletal variations was comparable in all groups.

  In the 1.0 and 4.0 mg/kg/day group of rats, that were allowed to deliver, a small increase in post-implantation loss was noted. This is considered to be the result of resorbed fetuses and/or pup

cannibalism. In the 4.0 mg/kg/day treatment group, two of 133 pups exhibited partial paralysis of fore and hind limbs and poor motor coordination.

- **Teratology-Rabbits (IV):** A teratology study was conducted in groups of 15 female white rabbits given midazolam maleate intravenously at doses of 0.2, 0.6, or 2.0 mg/kg/day from days 7 through 18 of gestation. A control group of 30 rabbits received injections of the vehicle. A second group of 15 rabbits served as a non-treated control.

  Sedation was present in all midazolam-treated rabbits, its severity and duration being dose dependent. Pretreatment parameters (percentage of animals pregnant, average number of corpora lutea and implantation sites) were similar in treated and control groups. Furthermore, there were no significant differences between control and treated animals in the average litter size, the average fetal body weight, average crown-rump length, distribution of fetuses by sex and 24-hr viability index of the kits. The resorption rate and percentage of litters showing resorptions were slightly higher in those receiving the 2.0 mg/kg/day dose of midazolam. The frequency of external, visceral and skeletal abnormalities was similar in control animals and those treated with the mid and high dose of midazolam. However, in one dose receiving 0.2 mg/kg/day of midazolam, 9/10 and 6/10 fetuses had external (open eyelids) and skeletal (cleft palate) abnormalities, respectively.

- **Perinatal and Postnatal-Rats (IV):** A perinatal and postnatal study was performed in groups of 20 female rats given midazolam maleate intravenously at doses of 0.2, 1.0 or 4.0 mg/kg/day from day 15 of gestation through day 21 of lactation. A control group of 20 rats received injections of the vehicle. A second control group served as a non-treated control.

  Intravenous midazolam induced ataxia in the dams, the severity and duration of which was dose-dependent.

  Maternal weight gains were significantly reduced in the 4.0 mg/kg/day dose group on the day of delivery and in the 1.0 and 4.0 mg/kg/day dose groups on lactation day 7. The following slight but significant effects were observed in the 4.0 mg/kg/day dose group: prolonged gestation period, smaller average litter size and increased post-implantation loss.

  Late fetal development, lactation, neonatal viability and growth of the pups were not affected by midazolam treatment. External, visceral and skeletal abnormalities were not seen in any of the treatment groups.

Dependence Liability

To date only animal data are available.

- **Physical Dependence:** Physical dependence was studied in several species. In phenobarbital-dependent cynomolgus monkeys, midazolam, in oral doses up to 10 mg/kg, did not suppress the abstinence symptoms which appeared when phenobarbital was withdrawn. A 20 mg/kg dose of midazolam suppressed some of the minor signs (apprehension, hyperirritability, piloerection), but the effect was probably due to general sedation.

  Midazolam, when administered at a maximal oral dose of 135 mg/kg/day, for 28 consecutive days, produced only mild symptoms of withdrawal in cynomolgus monkeys. An additional 28 days of drug administration did not intensify the withdrawal symptoms. In contrast, phenobarbital produced withdrawal of intermediate severity, and several benzodiazepines caused intensified withdrawal after the second, as compared to the first, 28-day period.

Signs indicative of withdrawal were not seen in either rats or dogs at the end of the 18 or 12 months toxicity study, respectively.

The intravenous administration of the benzodiazepine antagonist, flumazenil (Ro 15- 1788), did not precipitate withdrawal symptoms in monkeys chronically treated with midazolam.

- **Self-Administration:** In baboons trained to intravenously self-inject cocaine, both the barbiturates and the benzodiazepines were self-administered, but with different intensities. The barbiturates maintained high levels of self-injection in all the animals and over a wide dose range. Midazolam also produced high rates of self-injection, although not in all of the animals and only in a narrow dose range. Benzodiazepines, with a slow rate of elimination, maintained modest levels of self-administration. The rapid elimination of midazolam might contribute to the effect observed.
- **Drug Discrimination:** In rats trained to discriminate between saline and diazepam, midazolam, like other benzodiazepines, produced a dose-dependent, diazepam- appropriate response**.**

Irritation Studies

- **Venous Irritation-Rabbits:** Midazolam base (2.0 and 5.0 mg/mL), administered intravenously into the ear veins of rabbits at a single dose of 0.7 mg/kg produced minimal irritation to the ears.
- **Muscle Irritation-Rabbits:** The intramuscular irritation potential of midazolam base (5.0 mg/mL) and its vehicle was tested in rabbits in volumes of 1.0 and 0.1 mL. Single dose administration of 1.0 mL of midazolam produced moderate hemorrhage and necrosis while the vehicle produced slight hemorrhage and minimal necrosis. At 0.1 mL, midazolam produced very slight hemorrhage and well-defined necrosis; the vehicle also produced very slight hemorrhage but no necrosis. The study indicated that midazolam can cause slight muscle irritation following intramuscular administration.
- **Hemolysis Testing-Dogs:** Intravenous administration of midazolam base (1.0 mg/mL) to dogs did not produce hemolysis after a dose of 0.7 mg/kg (0.7 mL/kg) administered over approximately 30 seconds.

  However, intravenous injection of a dose of 0.7 mg/kg (0.14 mL/kg) of the 5.0 mg/mL injectable midazolam base formulation produced a slight hemolysis in one post-treatment undiluted plasma sample.

  No hemolysis occurred in the animals treated with normal saline at a volume of 0.7 or 0.14 mL/kg.

17 SUPPORTING PRODUCT MONOGRAPHS

1. T/CVERSED INJECTION® (solution, 1 mg/mL and 5 mg/mL), submission control number 041163, Product Monograph, Hoffman-La Roche Limited. (JUN 16, 1997)
2. T/C MIDAZOLAM INJECTION (solution, 1 mg/mL and 5 mg/mL), submission control number 250748, Product Monograph, Sandoz Canada Inc. (NOV 12, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

$^{C/T}$MIDAZOLAM INJECTION, USP

Midazolam injection

Read this carefully before you start taking **Midazolam Injection, USP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Midazolam Injection, USP**.

Serious Warnings and Precautions

Serious Heart and Breathing Problems: Serious, and sometimes fatal, heart and breathing problems have occurred in people taking Midazolam Injection, USP. Midazolam Injection, USP should only be used in a healthcare setting where you can be closely monitored and where there is access to oxygen and the appropriate medication and equipment required for resuscitation.

Addiction, Abuse and Misuse: Even if you are given Midazolam Injection, USP exactly as prescribed, you are at risk for abuse, misuse, addiction, physical dependence and withdrawal. Abuse and misuse can result in an overdose or death, especially if you take Midazolam Injection, USP with:

- **opioids**
- **alcohol or**
- **illicit drugs**

Your healthcare professional should:

- **talk to you about the risks of treatment with Midazolam Injection, USP as well as other treatment (including non-drug) options**
- **assess your risk for these behaviours before prescribing Midazolam Injection, USP**
- **monitor you while you are taking Midazolam Injection, USP for the signs and symptoms of misuse and abuse. If you feel like you are craving Midazolam Injection, USP, or not using it as directed, talk to your healthcare professional right away.**

Store Midazolam Injection, USP in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking Midazolam Injection, USP, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Other warnings you should know about)

- **Always talk to your healthcare professional before stopping or lowering your dose of Midazolam Injection, USP or changing your medicine.**

Midazolam Injection, USP with Opioids: Taking Midazolam Injection, USP with opioid medicines can cause:

- **severe drowsiness**
- **decreased awareness**
- **breathing problems**

- **coma**
- **death**

What is Midazolam Injection, USP used for?

Midazolam Injection, USP is used before surgery and other medical procedures. It helps to cause drowsiness, decrease anxiety, and to decrease your memory of the procedure. It is also used in patients in the ICU (Intensive Care Unit) who are sedated and on breathing machines.

If you are 65 years or older, talk to your healthcare professional before starting Midazolam Injection, USP. Midazolam Injection, USP may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does Midazolam Injection, USP work?

Midazolam Injection, USP belongs to a group of drugs called benzodiazepines. It works by calming the brain and nerves.

What are the ingredients in Midazolam Injection, USP?

Medicinal ingredients: midazolam

Non-medicinal ingredients: benzyl alcohol, disodium edetate, hydrochloric acid, sodium chloride, sodium hydroxide, water for injection

Midazolam Injection, USP comes in the following dosage forms:

Solution; 1 mg / mL or 5 mg / mL

Do not use Midazolam Injection, USP if:

- you are allergic (hypersensitive) to midazolam, benzodiazepines or any of the other ingredients in Midazolam Injection, USP (See **What are the ingredients in Midazolam Injection, USP?**)
- you have severe lung problems, such as chronic obstructive pulmonary disease (COPD)
- you have increased pressure in your eye (acute narrow angle glaucoma)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Midazolam Injection, USP. Talk about any health conditions or problems you may have, including if you:

- have heart or lung problems
- have liver or kidney problems
- have myasthenia gravis, a disease that causes muscle weakness
- have ever had problem with
    - substance abuse, including prescribed or illegal drugs, or
    - alcohol
- have ever a seizure or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)
- have ever had hallucinations (seeing or hearing things that are not there) or other severe mental health problems

- have ever had skin problems
- have ever had stomach or gut problems
- have ever had severe allergic reactions
- have vision problems such as blurred vision
- are pregnant or planning to become pregnant
- are breastfeeding. Midazolam Injection, USP passes into breastmilk.

Other warnings you should know about:

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop Midazolam Injection, USP.

Your risk of going through withdrawal is higher if you are taking Midazolam Injection, USP for a long time or at high doses. However, symptoms can still occur if you are taking Midazolam Injection, USP as directed for a short period of time or slowly reducing the dose.

The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).

Tell your healthcare professional **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:

- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)
- seeing or hearing things that are not there (hallucinations)
- overactive behavior and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide

For other symptoms of withdrawal, see the **Serious side effects and what to do about them** table (below).

To reduce your chances of going through withdrawal:

- always talk to your healthcare professional before stopping or reducing your dose of Midazolam Injection, USP or changing medications
- always follow your healthcare professional's instructions on how to reduce your dose carefully and safely

- tell your healthcare professional right away if you experience any unusual symptoms after changing or stopping your treatment

Midazolam Injection, USP with Opioids: Taking Midazolam Injection, USP with opioid medicines can cause severe drowsiness and breathing problems.

Tell your healthcare professional if you:

- are taking opioid medicines
- are prescribed an opioid medicine after you start taking Midazolam Injection, USP

Driving and Using Machines: Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and Midazolam Injection, USP affects you. Even if you are not taking Midazolam Injection, USP with an opioid you should not drive or do other tasks that require attention for at least 24 hours after taking Midazolam Injection, USP, or until all of the effects, such as drowsiness, have worn off.

Falls and Fractures: Benzodiazepines like Midazolam Injection, USP can cause you to feel sleepy, dizzy, and affect your balance. This increases your risks of falling, which can cause fractures or other fall related-injuries especially if you:

- take other sedatives
- consume alcohol
- are elderly or
- have a condition that causes weakness or frailty.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Taking Midazolam Injection, USP and opioids may cause:

- severe drowsiness
- trouble breathing
- coma
- death

The following may interact with Midazolam Injection, USP:

- barbiturates and other medicines that cause drowsiness or decrease anxiety
- medicines used to treat fungal infections, such as itraconazole and fluconazole
- erythromycin, an antibiotic used to treat bacterial infections
- saquinavir, a medicine used to treat HIV/AIDS
- sodium valproate, a medicine used to prevent seizures
- alcohol

How to take Midazolam Injection, USP:

- Midazolam Injection, USP will be given to you either as an injection into your muscle or an injection directly into your vein
- Your healthcare professional will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your healthcare professional's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Usual dose:

Your healthcare professional will decide on the dose that is right for you based on your age, your weight and the type of medical procedure you are having.

Overdose:

If you think you, or a person you are caring for, have taken too much Midazolam Injection, USP, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

Midazolam Injection, USP will be given to you in a healthcare setting. Your healthcare professional will make sure you do not miss a dose.

What are possible side effects from using Midazolam Injection, USP?

These are not all the possible side effects you may have when taking Midazolam Injection, USP. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- falls and fractures
- headache
- dizziness
- drowsiness
- feeling agitated
- confusion
- nausea, vomiting
- hiccups
- cough
- skin, rash especially in children

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			✓
Respiratory Depression: slow, shallow or weak breathing.			✓
Withdrawal: **Severe symptoms include: Catatonia:** feeling like you cannotmove or respond **Delirium Tremens:** severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed** **Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollableshaking **Thoughts or actions of suicide** **Other symptoms include:** stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a		✓	

burning or prickling feelingin the hands, arms, legs or feet; sweating.			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat,difficulty swallowing or breathing.			✓
Injection Site Reaction: pain, burning, redness, warmth or swelling at the injection site.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of reach and sight of children.
- Store between 15 °C and 30 °C. Protect from light. Discard unused portion 28 days after initial puncture.

If you want more information about Midazolam Injection, USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website https://www.fresenius-kabi.com/en-ca/, or by calling 1-877-821-7724.

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