MIDAZOLAM (Systemic)

Category

Sedative-hypnotic; anesthetic, general, adjunct; anesthetic, local, adjunct.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.
WARNING: Midazolam should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, that provide for continuous monitoring of respiratory and cardiac function; also, flumazenil, resuscitative drugs and age- and size-appropriate resuscitative equipment, and personnel trained in their use, should be immediately available 1 . Midazolam has been associated with respiratory depression and respiratory arrest, especially when used concomitantly with opioid analgesics for conscious sedation or when rapidly administered intravenously 1, 6, 38, 74 , and when used orally for sedation in noncritical care settings 96 ; in some cases, death or hypoxic encephalopathy has occurred 1, 96.

Accepted

Sedation and amnesia¾Midazolam is indicated for preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of perioperative events 1, 28.

Sedation, conscious¾Midazolam, used either alone or in conjunction with a narcotic, is indicated to produce sedation, anxiolysis, and amnesia prior to short diagnostic procedures or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, and cardiac catheterization 1.

Midazolam also is indicated for sedation, anxiolysis, and amnesia prior to certain dental and minor surgical * procedures 85.

This medication may be preferable to diazepam for intravenous sedation because of its faster onset of action, more consistent anterograde amnesia, and virtual lack of venous complications 7, 28, 57, 75, 76, 81, 82, 83.

Sedation¾Midazolam is indicated for the sedation of patients in intensive care settings, including intubated patients receiving mechanical ventilation 1.

Anesthesia, general, adjunct¾Midazolam is indicated for induction of general anesthesia prior to administration of other anesthetic agents. It may be used in conjunction with narcotic premedication, thereby achieving induction of anesthesia within a relatively narrow dose range and in a short period of time. It may also be used for intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures; however, the recovery time may be prolonged compared to that of thiopental 17.

The use of midazolam in longer surgical procedures has not been studied 1.

[Anesthesia, local, adjunct] *¾Midazolam is indicated as an adjunct to local or regional anesthesia for some diagnostic and therapeutic procedures 3.

It may be used for sedation of healthy patients receiving subarachnoid or epidural anesthesia 3, 45, 46.

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

Midazolam is a relatively short-acting benzodiazepine central nervous system (CNS) depressant 1.

Its effects on the CNS are dependent on the dose administered, the route of administration, and whether it is used concomitantly with other medications 1.

Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and anterograde amnestic effects, which are characteristic of benzodiazepines 2, 3, 12, 15, 28.

Although the exact mechanisms of the actions of benzodiazepines have not been completely established, it has been postulated that the actions of benzodiazepines are mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which is one of the major inhibitory neurotransmitters in the brain. Benzodiazepines are believed to increase the activity of GABA, thereby calming the patient, relaxing skeletal muscles, and, in high doses, producing sleep.
Benzodiazepines act as agonists at the benzodiazepine receptors, which have been shown to form a component of the benzodiazepine-GABA receptor-chloride ionophore complex. Most anxiolytics appear to act through at least one component of this complex to enhance the inhibitory action of GABA. Other actions of benzodiazepines, such as sedative, anticonvulsant, and muscle relaxant effects, may be mediated through a similar mechanism, although different receptor subtypes may be involved 20.

The hypnotic effect of midazolam appears to be related to GABA accumulation and occupation of the benzodiazepine receptor. Midazolam has a relatively high affinity (about twice that of diazepam) for the benzodiazepine receptor. It is believed that there are separate benzodiazepine and GABA receptors coupled to a common ionophore (chloride) channel, and that occupation of both receptors produces membrane hyperpolarization and neuronal inhibition. Midazolam interferes with reuptake of GABA, thereby causing accumulation of GABA. Also, it is postulated that the action of midazolam in induction of anesthesia involves excess GABA at neuronal synapses 26.

The site and mechanism of the amnestic action of midazolam are not known; however, the degree of amnesia usually, but not always, parallels the degree of drowsiness produced by midazolam 28, 29.

Other actions/effects:

Midazolam causes a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that produced by thiopental, when it is used for induction of anesthesia in patients without intracranial lesions 1.

In intracranial surgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements), midazolam attenuates the increase in intracranial pressure due to intubation to a degree comparable to that of thiopental 1.

Studies have shown that intraocular pressure is lowered moderately when midazolam is used for induction of anesthesia in patients without eye disease; studies have not been done in patients with glaucoma 1.

Respiratory depression is produced 3, 6, 12, 30, 33, 38, 72, 79, 80 ; however, the respiratory depressant effect of midazolam is dose-related 1, 2, 35.

The cardiovascular effects of midazolam appear to be minimal. Cardiac hemodynamic studies have shown midazolam to cause a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume, and systemic vascular resistance when used for induction of anesthesia 47.

In a study comparing the systemic vascular effects of midazolam and lorazepam in patients on cardiopulmonary bypass, midazolam was more effective than lorazepam in attenuating the increase in systemic vascular resistance accompanying cardiopulmonary bypass 48.

Midazolam may cause slow heart rates (less than 65 per minute) to rise slightly, especially in patients taking propranolol for angina; it may cause faster heart rates (e.g., 85 per minute) to slow slightly 1.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to other benzodiazepines may be sensitive to this medication also.

Carcinogenicity/Tumorigenicity

In 2-year studies in mice, midazolam was administered with the diet in doses of 1, 9, and 80 mg per kg of body weight (mg/kg) per day. At doses of 80 mg/kg per day, midazolam greatly increased the incidence of hepatic tumors in female mice and caused a small but significant increase in benign thyroid follicular cell tumors in male mice. These tumors occurred after chronic administration of midazolam, whereas only a single dose or several doses are usually used in humans. When midazolam was administered at doses of 9 mg/kg per day (25 times a human dose of 0.35 mg/kg per day), there was no increase in the incidence of tumors 1.

Mutagenicity

Midazolam was shown to have no mutagenic activity in Salmonella typhimurium (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice 1.

Pregnancy/Reproduction

Fertility¾A reproduction study in male and female rats did not show midazolam to cause any impairment of fertility when given at doses up to 10 times the human intravenous dose of 0.35 mg/kg 1.

Pregnancy¾Midazolam crosses the placenta. Since chlordiazepoxide and diazepam have been reported to increase the risk of congenital malformations when used during the first trimester of pregnancy, midazolam may be associated with this increased risk also 1.

Segment II teratology studies in rabbits and rats did not show midazolam to cause teratogenic effects when the medication was administered in doses 5 to 10 times the human dose of 0.35 mg/kg 1.

In addition, studies in rats did not show midazolam to cause any adverse effects during gestation and lactation when administered at doses approximately 10 times the human dose of 0.35 mg/kg 1.

FDA Pregnancy Category D 1.

Labor and delivery¾In humans, measurable concentrations of midazolam have been found in maternal venous serum, umbilical venous and arterial serum, and amniotic fluid, indicating placental transfer of the medication 1.

Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and umbilical arterial serum concentrations were lower than maternal concentrations 1.

Midazolam was compared with thiopental for rapid-sequence intubation in women delivering babies by cesarean section 89.

The neonates whose mothers received midazolam were more likely than the neonates whose mothers received thiopental to require tracheal intubation 89.

In a second similar study, neonates whose mothers received midazolam were more likely to experience hypothermia and reduced body tone as compared with neonates whose mothers received thiopental 64.

Additionally, midazolam is usually not recommended for induction of anesthesia prior to cesarean section because of the secondary CNS depressant effects on the neonate 1.

Administration of other benzodiazepines during the last weeks of pregnancy has caused neonatal CNS depression 1.

Also, use of benzodiazepines just prior to or during labor may cause neonatal flaccidity.

Breast-feeding

Midazolam is distributed into breast milk 1.

Midazolam received in the breast milk by neonates may be eliminated slowly because of their immature organ function. Neonates may be more susceptible to respiratory depression than older pediatric patients are 1.

Pediatrics

The weight-adjusted clearance of midazolam in pediatric patients older than 1 year of age is the same as or higher than in adult patients. Clearance is slower and the terminal elimination half-life is longer in critically ill neonates than in other pediatric patients or adult patients.
Neonates are more likely than other pediatric patients or adult patients to experience respiratory depression following administration of midazolam.
Midazolam injection contains benzyl alcohol. Administration of excessive amounts of benzyl alcohol to neonates has been associated with toxicity, including death 1.

Although midazolam administered to neonates in the recommended doses does not contain amounts of benzyl alcohol associated with toxicity, the total load of benzyl alcohol from all sources must be considered 1.

The 1-mg-per-mL and the 5-mg-per-mL vials of midazolam contain equal amounts of benzyl alcohol 1.

The amount of benzyl alcohol the neonates receive may be decreased by diluting the 5-mg-per-mL vials to prepare neonatal dosages.

Geriatrics

The clearance of midazolam is reduced in geriatric patients as compared with that in younger adults 1, 6, 11.

When midazolam is used intravenously to produce sedation, anxiolysis, and amnesia in patients 60 years of age and older, debilitated, and/or chronically ill, dosage increments should be smaller and the rate of injection slower than in younger adults because the risk of underventilation or apnea is greater and the time to peak effect may be longer in older patients 1, 8.

Also, if concomitant CNS depressant premedication is used, the dose of midazolam should be reduced by at least 50%.
When midazolam is used for induction of anesthesia, patients older than 55 years of age, whether premedicated or not, usually require lower doses 1, 8.

Also, time to complete recovery after midazolam administration for the induction of anesthesia may be prolonged in the elderly 1.

In addition, elderly patients are more likely to have age-related chronic renal failure, which may require reduction of dosage in patients receiving midazolam.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Alcohol or

>> CNS depression-producing medications, other, including those commonly used for preanesthetic medication or induction or supplementation of anesthesia (see Appendix II)

(concurrent use may increase the CNS depressant, respiratory depressant, and hypotensive effects of either these medications or midazolam; decrease dosage requirements of either these medications or midazolam; and prolong recovery from anesthesia 1, 6, 74, 87, 88 ; midazolam dosage may be reduced by at least 50% in elderly or debilitated patients receiving other CNS depression-producing medications 1)
(when midazolam is used as an intramuscular premedication prior to use of thiopental as an induction agent, a reduction in thiopental dosage of about 15% may be required 1)
(severe hypotension may occur in neonates receiving a continuous infusion of midazolam followed by a rapid injection of fentanyl 1, 38)

Cimetidine or

Diltiazem or

Erythromycin or

Fluconazole or

Indinavir or

Itraconazole or

Ketoconazole or

Ranitidine or

Ritonavir or

Roxithromycin or

Verapamil or

Cytochrome P450 3A inhibitors, other

(inhibition of the cytochrome P450 3A enzyme system may cause a decrease in the metabolism of midazolam, which may result in delayed elimination and increased blood concentration 1, 13, 16, 23, 24, 43, 50, 62, 84, 90, 96 ; interaction with cytochrome P450 3A inhibitors is more likely when midazolam is administered orally than when it is administered parenterally 94)

Grapefruit or

Grapefruit juice

(decreased metabolism of midazolam, with resulting increased blood concentrations of midazolam, may occur; there may be an increased risk of toxicity; because this interaction occurs in large part in the gut

wall, it is more likely when midazolam is administered orally than when it is administered parenterally 94, 96)

Hypotension-producing medications, other (see Appendix II)

(hypotensive effects may be potentiated when these medications are used concurrently with midazolam; patients should be monitored for excessive fall in blood pressure during and following concurrent use 1)

Rifampin or

Cytochrome P450 3A inducers, other

(induction of the cytochrome P450 3A enzyme system may cause an increase in the metabolism of midazolam, which may result in its accelerated elimination and decreased blood concentration 95 ; the interaction is more likely when midazolam is administered orally than when it is administered parenterally 94)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Allergy to midazolam, history of

Risk-benefit should be considered when the following medical problems exist

Alcohol intoxication, acute, with depressed vital signs

(potential additive CNS depression 1)

Coma or

Shock

(hypnotic or hypotensive effects may be intensified or prolonged 1)

Congestive heart failure

(possible twofold to threefold increase in elimination half-life and a 40% increase in the volume of distribution 1)

Hepatic function impairment

(midazolam is metabolized by the liver; in one study, patients with cirrhosis of the liver had reduced clearance and a longer elimination half-life of midazolam than healthy control subjects 93)

>> Myasthenia gravis 5 or

Neuromuscular disorders, other, such as muscular dystrophies and myotonias 5

(condition may be exacerbated 2)

Obesity

(midazolam's elimination half-life may be prolonged and volume of distribution may be increased)

>> Pulmonary disease, obstructive, chronic, severe or

>> Pulmonary insufficiency, acute

(midazolam has respiratory depressant effects; sedation and respiratory depression may be prolonged 1 ; patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effects of midazolam 1)

Renal failure, chronic

(peak concentration of midazolam may be higher 57 in these patients than in healthy patients; induction of anesthesia may occur more rapidly, and recovery may be prolonged 1)

Sensitivity to other benzodiazepines

Caution is recommended in geriatric or debilitated patients and in higher-risk surgical patients, whether premedicated or not, because they may require lower doses for induction of anesthesia 1 ; caution should be used when intravenous midazolam is administered to patients with uncompensated acute illnesses, such as electrolyte disturbances 1

Also, caution should be used in ophthalmology patients during surgery because some patients may be confused or disoriented if they awaken during the procedure. This is especially important in patients with an open globe for cataract surgery or in patients for whom movement might be critical 67

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
>> Blood oxygenation (pulse oximetry) 1 and

>> Blood pressure 1 and

>> Respiratory status 1 and

>> Vital signs, other 1

(it is recommended that patients be monitored continuously; when midazolam is used by non-anesthesiologists to produce deep sedation for surgical or diagnostic procedures, it is recommended that the patient be monitored continuously by someone not involved in conducting the surgical or diagnostic procedure; patients should be monitored for early signs of hypoventilation or apnea 1)

Note: Various organizations, including the American Society of Anesthesiologists (ASA) and the American Academy of Pediatrics (AAP), have established guidelines for pre-, intra-, and post-procedural care, evaluation, and monitoring of patients receiving sedation for diagnostic and therapeutic procedures 31, 32, 34.

The level of monitoring should be appropriate to the level of sedation and the procedure being performed. When midazolam is used for light sedation (i.e., the patient is able to tolerate unpleasant procedures without cardiorespiratory compromise and is able to respond purposefully to verbal commands) by non-anesthesiologists, the American Society of Anesthesiologists recommends that a designated individual, other than the person performing the procedure, be present to monitor the patient 34.

That designated person would be permitted to assist with other minor, interruptible tasks 34.

However, when midazolam is used to produce deep sedation, the patient should be monitored continuously by someone not involved in conducting the surgical or diagnostic procedure 34.

For deeply sedated patients, the person monitoring the patient should not assist with other tasks, even if the tasks are minor and interruptible 34.

Side/Adverse Effects

Note: The most frequent side/adverse effects of midazolam during anesthesia and surgery include decreased tidal volume and/or respiratory rate (in 23.3% of patients following intravenous administration and in 10.8% of patients following intramuscular administration) and apnea (in 15.4% of patients following intravenous administration). In addition, variations in blood pressure and pulse rate may occur.
Serious cardiorespiratory side/adverse effects have occurred primarily in older, chronically ill patients, with concomitant administration of other cardiorespiratory depressants (such as opioid [narcotic] analgesics) and with rapid administration of midazolam; these side/adverse effects have included respiratory depression, apnea, respiratory arrest, and/or cardiac arrest, sometimes resulting in death 1, 6.

Patients undergoing procedures involving the upper airway (e.g., upper endoscopy or dental procedures) are more likely than patients undergoing other types of procedures to experience respiratory depression, apnea, and respiratory arrest 1.

Midazolam administered intravenously has been associated with respiratory depression and respiratory arrest, especially when used concomitantly with opioid analgesics for conscious sedation or when rapidly administered 6 ; in some cases, death or hypoxic encephalopathy has occurred 71 .

Midazolam administered orally has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings 96.

Impairment of psychomotor skills may occur following midazolam sedation or anesthesia and may persist for varying lengths of time, depending upon the combination of medications and total dosages administered. Possible adverse effects on the patient's ability to drive or perform other tasks requiring alertness and coordination should be kept in mind when midazolam is administered for an outpatient procedure. It is recommended that patients not operate hazardous machinery or a motor vehicle until the effects of midazolam, such as drowsiness and amnesia, have subsided or until the day after anesthesia and surgery, whichever period of time is longer 1, 51.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Apnea; hypotension¾especially in patients premedicated with narcotic 1, 2; respiratory depression
Incidence rare¾ < 1%, primarily following intravenous administrationEmergence delirium 1, 2, 69; hyperventilation 1; irregular or fast heartbeat 1, 2; muscle tremor; phlebitis 1; skin rash, hives, or itching 1; uncontrolled or jerky movements of body; unusual excitement, irritability, or restlessness 69; wheezing or difficulty in breathing 1, 66

Note: Muscle tremor, uncontrolled or jerky movements of body, unusual excitement, irritability, or restlessness possibly are due to inadequate or excessive dosing or improper administration of medication; also, the possibility of cerebral hypoxia or paradoxical reaction should be considered 69.

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Hiccups 1; pain at intramuscular injection site 1; pain during intravenous injection 1; tenderness at intravenous injection site 1
Incidence less frequent or rare

Blurred vision or other changes in vision 1, 2; coughing 1; dizziness, lightheadedness, or feeling faint 1; drowsiness, prolonged 1, 2; headache 1, 2; lumps or hardness at injection site 1; muscle stiffness at intramuscular injection site 1; nausea 1, 2; numbness, tingling, pain, or weakness in hands or feet 1; redness at injection site 1; vomiting 1, 2

Overdose

For specific information on the agents used in the management of midazolam overdose, see:
- Flumazenil (Systemic) monograph; and/or
- Sympathomimetic Agents¾Cardiovascular Use (Parenteral-Systemic) monograph.

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Acute

Cardiovascular depression; respiratory depression 6
Treatment of overdose

To enhance elimination¾
It is not known if peritoneal dialysis, forced diuresis, or hemodialysis is useful in the treatment of midazolam overdose 1.

Specific treatment¾
Administering flumazenil. See the package insert or the Flumazenil (Systemic) monograph for specific dosing guidelines for the use of this product.
For hypotension: Treatment may include intravenous fluid therapy, repositioning, vasopressors (if indicated), and other appropriate countermeasures 1.

Monitoring¾
Monitoring of respiration, pulse rate, and blood pressure 1.

Supportive care¾
General supportive measures 1.

Maintenance of a patent airway and support of ventilation 1.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Midazolam (Systemic) .

Note: The capacity of midazolam to cause anterograde amnesia should be considered when providing consultation to patients. Patients counseled after receiving midazolam may not remember being counseled.
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before receiving this medication

>> Conditions affecting use, especially:

Sensitivity to midazolam or other benzodiazepines
Carcinogenicity/Tumorigenicity

In 2-year studies in mice, chronic administration of midazolam at doses of 80 mg per kg of body weight (mg/kg) per day greatly increased incidence of hepatic tumors in female mice and caused a small but significant increase in benign thyroid follicular cell tumors in male mice
Pregnancy¾Risk of congenital malformations may be increased when midazolam is used during first trimester

Labor and delivery¾Midazolam usually is not recommended for induction of anesthesia prior to cesarean section because of secondary CNS depressant effects on neonate; use of benzodiazepines just prior to or during labor may cause neonatal flaccidity
Breast-feeding¾Midazolam is distributed into breast milk; neonates may have difficulty eliminating the midazolam received in breast milk; neonates may experience respiratory depression after receiving midazolam in breast milk
Use in children¾Critically ill neonates have reduced clearance of midazolam, and they are more likely than older pediatric patients or adult patients to experience respiratory depression after receiving midazolam; midazolam contains benzyl alcohol; excessive amounts of benzyl alcohol can cause toxicity in neonates
Pediatric patients may require a higher dose of midazolam on a weight-adjusted basis than required for adult patients
Use in the elderly¾When midazolam is used intravenously to produce sedation, anxiolysis, and amnesia in patients 60 years of age and older, dosage increments should be smaller and the rate of injection slower than in younger adults because risk of underventilation or apnea is greater and the time to peak effect may be longer in older patients; if concomitant CNS depressant premedication is used, dosage of midazolam should be reduced by at least 50%; time to complete recovery after midazolam administration for induction of anesthesia may be prolonged in the elderly
Other medications, especially alcohol or other CNS depression-producing medications
Other medical problems, especially myasthenia gravis, severe chronic obstructive pulmonary disease, or acute pulmonary insufficiency
Precautions after receiving this medication

>> Possibility of psychomotor impairment following use of midazolam; using caution in driving or performing other tasks requiring alertness and coordination until the effects of midazolam have subsided or until the day after receiving midazolam, whichever period of time is longer 1

>> Avoiding use of alcohol or other CNS depressants within 24 hours after receiving midazolam, except as directed by doctor

General Dosing Information

Midazolam has been shown to be three to four times as potent per mg as diazepam 1.

The dosage of midazolam must be individualized for each patient. Lower doses are usually required for elderly, debilitated, or high-risk surgical patients and for neonates. The dosage of midazolam should be adjusted according to the type and amount of premedication used 1.

Additionally, the dose requirement of midazolam of each patient may vary. The dose always should be individualized and titrated slowly. The doses given in Usual adult and adolescent dose and Usual pediatric dose should be regarded as general guidelines only.
Midazolam should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, that provide for continuous monitoring of respiratory and cardiac function.
Prior to administration of midazolam, flumazenil, age- and size-appropriate resuscitative equipment, oxygen, and skilled personnel for the maintenance of a patent airway and support of ventilation must be immediately available. When midazolam is used to produce deep sedation for surgical or diagnostic procedures, it is recommended that the patient be monitored continuously by someone not involved in conducting the surgical or diagnostic procedure 1 .

Midazolam should be administered intravenously as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only when a person skilled in maintaining a patent airway and supporting ventilation is present, because of possible respiratory depression 1.

When midazolam is administered intravenously for conscious sedation, it should be injected slowly in multiple small injections to attain the desired effect; it should not be administered by rapid or single bolus intravenous injection, because of the risk of respiratory depression and/or arrest, especially in elderly or debilitated patients 1.

Three to five minutes should elapse between each small injection, so the full effect of the injection can be assessed before another injection is administered 1.

To facilitate slower intravenous injection of midazolam, the 1-mg-per-mL solution or dilution of the 1-mg-per-mL or 5-mg-per-mL solution is recommended.
During intravenous administration of midazolam, patients should be monitored continuously for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are immediately taken. Also, monitoring of vital signs should be continued during the recovery period. In one case series, respiratory arrest occurred in patients 30 to 120 minutes after administration of midazolam 22.

Patients should be monitored for several hours following use of midazolam 22.

Adult and pediatric patients undergoing procedures involving the upper airway (e.g., upper endoscopy or dental procedures) are more likely than patients undergoing other types of procedures to experience respiratory depression, apnea, and respiratory arrest when midazolam is used 1.

Caution should be taken to avoid intra-arterial injection because adverse effects of intra-arterial administration of intravenous midazolam in humans are not known. Extravasation should also be avoided 1.

Midazolam contains benzyl alcohol and so may not be administered by the intrathecal or epidural routes 1.

Administration of excessive amounts of benzyl alcohol to neonates has been associated with toxicity, including death 1.

Although midazolam administered to neonates in the recommended doses does not contain amounts of benzyl alcohol associated with toxicity, the total load of benzyl alcohol from all sources must be considered 1.

The 1-mg-per-mL and the 5-mg-per-mL vials of midazolam contain equal amounts of benzyl alcohol 1.

The amount of benzyl alcohol may be decreased for neonatal patients by diluting the 5-mg-per-mL vials to prepare neonatal dosages.
When midazolam is administered intramuscularly, it is recommended that the medication be injected deep into a large muscle mass 1.

When midazolam is used for peroral endoscopic procedures, a topical anesthetic agent and the availability of necessary countermeasures are recommended because an increase in cough reflex and laryngospasm may occur 1.

When midazolam is used for bronchoscopic procedures, a narcotic premedication is recommended 1.

Midazolam may produce partial or complete impairment of recall for up to several hours, depending on the dose 1.

Although midazolam is approved by the Food and Drug Administration (FDA) for administration by the intramuscular, intravenous, and oral routes only, the intranasal, rectal, and sublingual routes are sometimes used in pediatric patients 19, 21, 40, 41, 42, 49, 52, 53, 54, 55, 59, 60, 64, 68.

The 5-mg-per-mL midazolam injection has been used intranasally and sublingually for preoperative sedation and amnesia and sedation, anxiolysis, and amnesia prior to diagnostic or short therapeutic procedures by placing midazolam into a small syringe (with the needle removed) and administering it intranasally or sublingually 19, 61, 92.

In one study, pediatric patients receiving intranasal midazolam were more likely to cry and cried longer than pediatric patients receiving the drug sublingually 61.

Oral midazolam should not be mixed in any other liquid prior to ingestion 96.

Patients receiving midazolam for sedation in the intensive care unit also may require appropriate analgesia. Administration of an opioid analgesic in addition to midazolam will reduce the dose requirement for midazolam 1.

Abrupt discontinuation of long-term midazolam therapy may result in precipitation of symptoms of withdrawal 70, 73.

Midazolam should be tapered gradually if it has been administered for more than a few days 70.

Diet/Nutrition

Bioavailability of orally administered midazolam may be increased by ingestion of grapefruit or grapefruit juice, resulting in higher blood concentrations of midazolam 94.

Oral Dosage Forms

Note: The dosing and dosage forms available are expressed in terms of midazolam base.

MIDAZOLAM HYDROCHLORIDE ORAL SOLUTION

Usual pediatric dose

Sedation, preoperative, and amnesia or
Sedation, conscious (sedation, anxiolysis, and amnesia)¾

Infants and children 6 months of age and older: Oral, 0.25 to 0.5 mg (base) per kg of body weight thirty to forty-five minutes prior to induction of anesthesia or to the diagnostic or therapeutic procedure 1, 19, 21, 40, 49, 52, 54, 96.

Younger (6 months to 6 years of age) and less cooperative children may need higher doses (i.e., up to 1 mg per kg of body weight). Lower doses (i.e., 0.25 mg per kg of body weight) may be sufficient for older and more cooperative patients 96.

Usual pediatric prescribing limits

15 to 20 mg 96.

Note: When midazolam is administered concomitantly with narcotic analgesics or other CNS depressants, the dosage of midazolam should be reduced 96.

Strength(s) usually available
U.S.¾2 mg (base) per mL (Rx)[Versed 96 (sorbital) (glycerin) (citric acid anhydrous) (sodium citrate) (sodium benzoate) (sodium saccharin) (edetate disodium) (FD&C Red #33)]

Canada¾Dosage form not commercially available.

Packaging and storage:

Store in a tight, light-resistant container 96.

Store between 15 and 30 °C (59 and 86 °F), preferably at 25 °C (77 °F) 96.

Auxiliary labeling:

· Protect from light.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.
The dosing and dosage forms available are expressed in terms of midazolam base.

MIDAZOLAM HYDROCHLORIDE INJECTION

Usual adult dose

Sedation, preoperative, and amnesia¾
Patients younger than 60 years of age¾
American Society of Anesthesiologists (ASA) I or II (good-risk surgical patients):
Intramuscular, 70 to 80 mcg (0.07 to 0.08 mg) (base) per kg of body weight, approximately thirty to sixty minutes before surgery 1.

ASA III or IV (patients with severe systemic disease or debilitation):

Intramuscular, 20 to 50 mcg (0.02 to 0.05 mg) (base) per kg of body weight, approximately thirty to sixty minutes before surgery 1.

Patients 60 years of age and older¾

Intramuscular, 20 to 50 mcg (0.02 to 0.05 mg) (base) per kg of body weight, approximately thirty to sixty minutes before surgery 1

Note: Lower doses may be sufficient in elderly or debilitated patients 83.

Midazolam may be administered concurrently with atropine or scopolamine hydrochloride and reduced doses of narcotics 1.

Sedation, conscious (sedation, anxiolysis, and amnesia)¾

Unpremedicated patients younger than 60 years of age¾

Intravenous, initially no more than 2.5 mg (base) 83 , administered slowly over a period of at least two minutes, immediately prior to the procedure; after an additional two or more minutes to allow for clinical effect, dosage may be further titrated in small increments of the initial dose (with intervals of two or more minutes being allowed after each increment) to the desired effect. A total dose of more than 5 mg is not usually necessary. Additional maintenance doses may be administered, if necessary, in increments of 25% of initial dose to maintain desired level of sedation 1 .

Note:

When midazolam is administered concomitantly with narcotic analgesics or other CNS depressants, the dosage of midazolam should be reduced by approximately 30%.

The desired endpoint for conscious sedation can usually be attained within three to six minutes, depending on the total dose administered and whether or not narcotic premedication is used concomitantly.

The therapeutic dosage range between sedation and unconsciousness or disorientation appears to be narrower than for other benzodiazepines (e.g., diazepam, lorazepam) 51.

Unpremedicated patients 60 years of age and older, and debilitated or chronically ill patients¾

Intravenous, initially no more than 1.5 mg (base), administered slowly over a period of at least two minutes, immediately prior to procedure; after an additional two or more minutes to allow for clinical effect, dosage may be further titrated, if necessary, but the rate of administration should not exceed 1 mg over a two-minute period (intervals of two or more minutes should be allowed each time). A total dose of more than 3.5 mg is not usually necessary. Additional maintenance doses may be administered, if necessary, in increments of 25% of initial dose to maintain desired level of sedation.

Note:

When midazolam is administered concomitantly with narcotic analgesics or other CNS depressants, the dosage of midazolam should be reduced by 50%.

Also, dosage increments should be smaller and the rate of injection slower because the danger of underventilation or apnea is greater in elderly patients and patients with chronic disease states or decreased pulmonary reserve; also, it may take longer to achieve the peak effect in these patients.

The desired endpoint for conscious sedation can usually be attained within three to six minutes, depending on the total dose administered and whether or not narcotic premedication is used concomitantly.

The therapeutic dosage range between sedation and unconsciousness or disorientation appears to be narrower than for other benzodiazepines (e.g., diazepam, lorazepam) 51.

Anesthesia, general, adjunct (prior to administration of other general anesthetics)¾
Unpremedicated patients¾

Up to 55 years of age¾Intravenous, initially 200 to 350 mcg (0.2 to 0.35 mg) (base) per kg of body weight, administered over a period of five to thirty seconds and allowing two minutes for effect 1 .
Note:

If necessary to complete induction, additional doses may be given in increments of about 25% of initial dose, or inhalation general anesthetics may be used 1.

Up to 600 mcg (0.6 mg) (base) per kg of body weight as a total dose may be used for induction, if necessary; however, larger doses may prolong recovery 1.

55 years of age and older¾ASA I or II (good-risk surgical patients): Intravenous, initially 150 to 300 mcg (0.15 to 0.3 mg) (base) per kg of body weight, administered over a period of twenty to thirty seconds 1.

ASA III or IV (patients with severe systemic disease or debilitation): Intravenous, initially 150 to 250 mcg (0.15 to 0.25 mg) (base) per kg of body weight, administered over a period of twenty to thirty seconds.

Premedicated (sedative or narcotic) patients¾

Up to 55 years of age¾Intravenous, 150 to 350 mcg (0.15 to 0.35 mg) (base) per kg of body weight, administered over a period of twenty to thirty seconds and allowing two minutes for effect. A dose of 250 mcg (0.25 mg) per kg of body weight is usually sufficient 1, 83.

55 years of age and older¾ASA I or II: Intravenous, initially 200 mcg (0.2 mg) (base) per kg of body weight 1.

ASA III or IV: Intravenous, 150 mcg (0.15 mg) (base) per kg of body weight may be sufficient 1 .
Note:

When sedative or, especially, narcotic premedication has been administered, the recommended dose range of midazolam is 150 to 250 mcg (0.15 to 0.25 mg) (base) per kg of body weight 1.

Additional doses may be given in increments of about 25% of induction dose in response to signs of lightening anesthesia, repeated as necessary 1.

Narcotic premedications frequently used include: fentanyl (1.5 to 2 mcg [0.0015 to 0.002 mg] per kg of body weight intravenously five minutes before induction); morphine (up to 150 mcg [0.15 mg] per kg of body weight intramuscularly, the dosage being individualized); meperidine (up to 1 mg per kg of body weight intramuscularly, the dosage being individualized); and fentanyl citrate and droperidol combination (0.02 mL per kg of body weight intramuscularly) 1.

Sedative premedications frequently used include: hydroxyzine pamoate (100 mg orally) and secobarbital sodium (200 mg orally) 1.

Premedications should be administered at least thirty to sixty minutes 51 prior to midazolam induction, with the exception of narcotic analgesics (e.g., fentanyl 89), which should be administered two to 89 five minutes before induction 1.

Sedation in critical care settings¾

Intravenous infusion, 20 to 100 mcg (0.02 to 0.1 mg) (base) per kg of body weight per hour, initially, then titrated to the desired level of sedation. If a loading dose is needed, 10 to 50 mcg (0.01 to 0.05 mg) per kg of body weight may be administered over several minutes prior to initiation of the continuous infusion 1.

[Anesthetic, local, adjunct (epidural or axillary block)] *¾
Intravenous, 30 to 60 mcg (0.03 to 0.06 mg) (base) per kg of body weight, the dosage being slowly titrated 51.

Usual pediatric dose

Sedation, preoperative, and amnesia or
Sedation, conscious (sedation, anxiolysis, and amnesia)¾
Infants up to 6 months of age¾
The dose is not clearly established because there is variability in when pediatric patients progress from neonatal to infant physiology in terms of their abilities to tolerate, metabolize, and eliminate midazolam. Pediatric patients up to 6 months of age are especially vulnerable to airway obstruction and hypoventilation. Titration with small increments and careful monitoring are especially important when midazolam is used in pediatric patients up to 6 months of age 1.

Infants and children 6 months to 5 years of age¾
Intravenously by intermittent injection, 50 to 100 mcg (0.05 to 0.1 mg) (base) per kg of body weight; sometimes up to 600 mcg (0.6 mg) per kg of body weight may be necessary, but usually no more than a total of 6 mg is needed to reach the desired endpoint 1.

Intramuscular, 100 to 150 mcg (0.1 to 0.15 mg) (base) per kg of body weight 1.

Doses of up to 500 mcg (0.5 mg) per kg of body weight have been used for deep sedation 1.

Children 6 to 12 years of age¾
Intravenously by intermittent injection, 25 to 50 mcg (0.025 to 0.05 mg) (base) per kg of body weight; sometimes up to 400 mcg (0.4 mg) per kg of body weight may be necessary, but usually no more than a total of 10 mg is needed to reach the desired endpoint.
Intramuscular, 100 to 150 mcg (0.1 to 0.15 mg) (base) per kg of body weight 1.

Doses of up to 500 mcg (0.5 mg) per kg of body weight have been used for deep sedation 1.

Adolescents 12 to 16 years of age¾
See Usual adult dose.

Some adolescents may require higher doses than adults, but usually no more than a total of 10 mg is needed to reach the desired endpoint 1.

Note: In obese pediatric patients, the dose should be calculated based on ideal body weight 1.

Anesthesia, general, adjunct (prior to administration of other general anesthetics)¾
Infants up to 6 months of age¾

The dose is not clearly established because there is variability in when pediatric patients progress from neonatal to infant physiology in terms of their abilities to tolerate, metabolize, and eliminate midazolam 1.

Pediatric patients up to 6 months of age are especially vulnerable to airway obstruction and hypoventilation. Titration with small increments and careful monitoring are especially important when midazolam is used in pediatric patients up to 6 months of age 1.

Infants and children 6 months to 5 years of age¾
Intravenously by intermittent injection, 50 to 100 mcg (0.05 to 0.1 mg) (base) per kg of body weight; sometimes up to 600 mcg (0.6 mg) per kg of body weight may be necessary, but usually no more than a total of 6 mg is needed to reach the desired endpoint 1.

Children 6 to 12 years of age¾
Intravenously by intermittent injection, 25 to 50 mcg (0.025 to 0.05 mg) (base) per kg of body weight; sometimes up to 400 mcg (0.4 mg) per kg of body weight may be necessary, but usually no more than a total of 10 mg is needed to reach the desired endpoint 1.

Adolescents 12 to 16 years of age¾
See Usual adult dose.

Some adolescents may require higher doses than adults, but usually no more than a total of 10 mg is needed to reach the desired endpoint 1.

Sedation in critical care settings¾
Neonates up to 32 weeks gestation¾
Intravenous infusion in patients whose trachea is intubated, 30 mcg (0.03 mg) (base) per kg of body weight per hour 1 .
Note:
Intravenous loading doses should not be administered to neonatal patients.

Neonates 32 weeks gestation and older¾
Intravenous infusion in patients whose trachea is intubated, 60 mcg (0.06 mg) (base) per kg of body weight per hour 1 .
Note:
Intravenous loading doses should not be administered to neonatal patients 1.

Infants and children¾
Intravenous infusion in patients whose trachea is intubated, initially, 60 to 120 mcg (0.06 to 0.12 mg) (base) per kg of body weight per hour, then titrated to desired effect 1.

An intravenous loading dose of 50 to 200 mcg (0.05 to 0.2 mg) per kg of body weight administered over at least two to three minutes can be used prior to initiation of the continuous infusion 1.

Strength(s) usually available

U.S.¾1 mg (base) per mL (Rx)[Versed 1 (benzyl alcohol 1%) (disodium edetate 0.01%) (sodium chloride 0.8%)]

5 mg (base) per mL (Rx)[Versed 1 (benzyl alcohol 1%) (disodium edetate 0.01%) (sodium chloride 0.8%)]

Canada¾5 mg (base) per mL (Rx)[Versed 5 (benzyl alcohol 10.45 mg) (disodium edetate 0.1 mg) (sodium chloride 8 mg)]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Preparation of dosage form:

Midazolam injection is compatible with 5% dextrose in water, 0.9% sodium chloride, and lactated Ringer's solution 1.

Midazolam injection may be mixed in same syringe with frequently used premedicants, such as morphine sulfate, meperidine hydrochloride, atropine sulfate, or scopolamine hydrobromide 1, 3.

Stability:

Midazolam injection should not be used if it contains a precipitate or is discolored 1.

When midazolam injection is mixed in the same syringe with frequently used premedicants, such as morphine sulfate, meperidine hydrochloride, atropine sulfate, or scopolamine hydrobromide, the solution is stable for 30 minutes 89.

When midazolam injection is diluted in 5% dextrose in water or 0.9% sodium chloride, the solution is stable for 24 hours; if mixed with lactated Ringer's solution (Hartmann's solution), the solution should be used within 4 hours.

Note: Controlled substance in the U.S.

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