**Doctor leaflet**

**MIDOLAM 1 MG/ML, 5MG/ML**  
Solution for INJECTION  
Ampoules for IM, IV administration

**Composition:**  
Midazolam 1mg/ml in ampoules of 5 ml.  
Midazolam 5mg/ml in ampoules of 1, 3, 10 ml.  
(Preservative-free).

**List of excipients:** Sodium chloride, water for Injection, sodium hydroxide, HCl.

**Action**  
Midazolam is a benzodiazepine, and as such, has anxiolytic, sedative, amnestic, anti-convulsant and muscle-relaxant effects. Although the precise mechanism of action of benzodiazepines has not been established, it is likely that they enhance the activity of GABA, a major inhibitory neurotransmitter in the brain. It is believed that benzodiazepines bind at specific receptors that are linked to the GABA receptor and chloride ionophore complex.

The drug differs from other benzodiazepines by the presence of an imidazole ring, which enables it to readily form salts when combined with acids. These water-soluble salts have increased aqueous solubility and stability to hydrolysis, producing a stable injectable benzodiazepine. At physiological pH (7.4) the drug is completely ring-closed, resulting in increased lipophilicity. This characteristic makes it a useful agent for premedication/anesthesia. Compared with other anesthetic agents, Midolam has low toxicity due to the fact that its respiratory depressant effect is relatively mild and dose-related, and it has minimal cardiovascular effects. Midazolam is 2-3 times more potent than diazepam on a mg per mg basis and has a stronger amnestic action.

**Pharmacokinetics:**  
The mean absolute bioavailability of midazolam following IM administration is >90%. It has a large volume of distribution and is 97% plasma protein bound. Midazolam undergoes hepatic metabolism to hydroxylated metabolites (primarily 1-hydroxy-midazolam) that are conjugated and excreted in the urine. The elimination half-life is approximately 2.5 hours (range 1-5), but can be extended in patients with renal or liver impairment, congestive heart failure, obesity, and in the elderly.

When midazolam is used as a premedicant or for conscious sedation, onset of sedation occurs within 15 min after IM injection reaching a peak at 30-60 min, and within 1.5-5 min after IV injection. When used IV to induce anesthesia, onset of action occurs in 1.5-3 min and more rapidly (0.75-1.5 min) with concomitant administration of opioid analgesics. After IM or IV administration, anterograde amnesia of short duration occurs (The patient does not recall events that occurred during the peak of activity of the compound). Time to recovery is usually within 2 hr, but may take up to 6 hr.

Thus, Midolam Injection is short-acting with a rapid onset of action due to high lipophilicity and rapid metabolic clearance.
Indications
Premedication before induction of anesthesia (IM).
Basal sedation before diagnostic or surgical interventions carried out under local anesthesia (IV administration).
Induction and maintenance of anesthesia.
As an induction agent in inhalation anesthesia or a sleep-inducing component in combined anesthesia, including total intravenous anesthesia (IV injection, IV infusion).
Ataralgesia in combination with ketamine in children (IM administration).
Status epilepticus.

Contraindications
Midolam Injection should not be given to patients who are hypersensitive to benzodiazepines.
Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma.
(Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy.)

Warnings
Midolam injection has been associated with severe cardiorespiratory adverse events including respiratory depression, apnea, airway obstruction, oxygen desaturation, respiratory arrest, and cardiac arrest, especially when used for conscious sedation and in concomitant use with opioid agonists or other sedatives, or when rapidly administered. In some cases, where this was not recognized promptly and treated effectively, death, permanent neurologic injury or hypoxic encephalopathy has resulted.
Midolam should be used only in hospital or ambulatory care settings, including physicians’ offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of oxygen, resuscitative drugs and equipment and personnel trained in their use should be assured. Midolam 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.
During intravenous administration of midazolam, patients should be monitored continuously for early signs of underventilation airway obstruction or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are immediately taken. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Also, monitoring of vital signs should be continued during the recovery period.
After receiving Midolam, patients should not be discharged from hospital or consulting room for at least three hours and then only if accompanied by an attendant.

When used for conscious sedation, Midolam Injection should be injected slowly and should not be administered by rapid or single bolus intravenous administration.

Concomitant use of opioids or other CNS depressants (including alcohol) may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effects (see Drug Interactions).
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 Midolam and all other drugs, including local anesthetics, should be evaluated before proceeding.

There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received midazolam. Hypotension may occur more frequently in conscious sedation patients premedicated with a narcotic.

Special care is required when administering Midolam to neonates, who may be more susceptible to the respiratory depressant and hypotensive effects of midazolam. Seizures have been reported in several neonates following rapid IV administration, particularly with concomitant use of fentanyl.

Midolam should not be administered to patients in shock or coma, or in acute alcohol intoxication with depression of vital signs.

Midolam should be used with extreme care in the presence of acute neurological injuries since it produces a severe risk of raised intracranial pressure, and the risk of airway obstruction compounds the problem.

There have been limited reports of intra-arterial injection of midazolam. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

Use in Pregnancy

Pregnancy Category D.

An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. Midazolam, which crosses the placenta, may be associated with this increased risk also. Risk/benefit should be carefully considered, and the patient should be apprised of the potential hazard to the fetus if used during pregnancy.

Midazolam is usually not recommended for obstetric procedures (e.g. prior to Cesarean section), or during labour and delivery since benzodiazepines used during the last few weeks of pregnancy and during labor have caused CNS depressant effects and flaccidity in the neonate. Moreover, high single doses may produce irregularities in the fetal heart rate, hypotonia, poor sucking, and hypothermia in the neonate.

Use in Breastfeeding

Midazolam may pass into breast milk, and caution should be exercised when administering to nursing mothers.

Use in Pediatrics

Appropriate studies on the relationship of age to the effects of midazolam have not been performed in children. However, as a group, pediatric patients (<12 years of age, not including neonates) generally require higher dosages of midazolam (mg/kg) than do adults. Younger (<6 years old) pediatric patients may require higher dosages (mg/kg) than older pediatric patients and may require closer monitoring. In obese pediatric patients, calculate the dose based on ideal body weight. The neonate has reduced or immature organ function and is also vulnerable to profound or prolonged respiratory effects of midazolam.

Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should also be avoided in this population.
Use in the Elderly
Elderly patients usually require lower doses and a slower injection rate than younger adults. If concomitant CNS depressant medication is used, the midazolam dosage should be reduced by 50%. Midazolam may cause a more profound or prolonged effect in the elderly, increasing time to complete recovery.

Administration of IM and IV midazolam to elderly and/or high risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics.

Adverse Reactions

Midazolam injection is usually well tolerated. The most frequent 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, slight variations in blood pressure and pulse rate may occur. As a rule, the systolic blood pressure falls by a maximum of 15%, while the pulse rate simultaneously shows a corresponding rise. Significant hypotension is more likely to occur in patients premedicated with a narcotic. The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam is administered with other medications capable of depressing the central nervous system. The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube (e.g., upper endoscopy and dental procedures).

Other less serious adverse experiences include headache, hiccups, nausea, vomiting, coughing, "oversedation", drowsiness. Local effects at the IM injection site: pain, induration, redness, muscle stiffness. Local effects at the IV site: pain during injection, tenderness or redness, induration, phlebitis.

Other adverse experiences, observed mainly following IV injection as a single sedative/anxiolytic/amnesia agent and occurring at an incidence of <1.0% in adult and pediatric patients, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea.

Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching.

CNS/Neuromuscular:
Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, gogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. Partial or complete impairment of recall for up to several hours (anterograde amnesia) may occur, particularly after IV administration.

Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness.

Integumentary: Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site.

Hypersensitivity: Allergic reactions including anaphylactoid reactions, hives, rash, pruritus.

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Administration of IM midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics.

Pediatric Patients: The following adverse events related to the use of IV midazolam in pediatric patients were reported in the medical literature: desaturation, apnea, hypotension, paradoxical reactions, hiccough, seizure-like activity and nystagmus. The majority of airway-related events occurred in patients receiving other CNS depressing medications and in patients where midazolam was not used as a single sedating agent.

Precautions

Particular care is needed when administering Midolam Injection to a patient with myasthenia gravis or other neuromuscular disorders since pre-existing muscle weakness may be exacerbated. In addition, extreme caution should be used in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Caution should be exercised when administering Midolam Injection to higher risk surgical patients including elderly and debilitated patients, who may require lower doses for induction of anesthesia. Patients with obstructive pulmonary disease or acute pulmonary insufficiency may be more sensitive to the respiratory depressant effect of midazolam. Patients with chronic renal failure and congestive heart failure eliminate midazolam more slowly, which may result in slower recovery. The elimination half-life of midazolam may be extended in patients with renal or hepatic impairment, obese patients, or neonates.

Patients undergoing procedures involving the upper airway such as upper endoscopy or dental care are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction.
Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam injection; patients with glaucoma have not been studied.

Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

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 is longer.

**Drug Interactions**

**Midazolam/CNS Depressants or Alcohol**

Concurrent use of Midolam with neuroleptics, tranquilizers, opioids, benzodiazepines, barbiturates, hypnotics, antidepressants, analgesics, anesthetics, droperidol or alcohol, may increase the CNS depressant, respiratory depressant, apnea, hypoventilation, airway obstruction, desaturation and hypotensive effects of either midazolam or these medications, and may prolong recovery from anesthesia. Special attention must be paid to the possibility of potentiation in high-risk patients. The dosage of midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response.

When midazolam is used as premedication prior to the use of thiopental, a 15% reduction in the thiopental dosage may be required. The IV administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. Patients should be advised not to drink alcoholic beverages for at least 12 hours after Midolam. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

**Midazolam/Hypotension Producing Agents**

Concurrent use of Midolam with these medications may potentiate the hypotensive effects. Severe hypotension has been reported when midazolam is used concurrently with fentanyl.

**Midazolam/Inhibitors of Cytochrome P450-3A4 Enzyme System**

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450-3A4 enzyme system such as cimetidine, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation caused by a decrease in plasma clearance of midazolam.

In a placebo-controlled study, saquinavir administered as a 1200 mg dose, tid, for 5 days (n=12), a 56% reduction in the clearance of midazolam following a single 0.05 mg/kg IV dose was observed. The half-life was approximately doubled.

**Benzodiazepines/Neuromuscular Blockers**

Benzodiazepines, including midazolam, may sometimes unpredictably alter the depth and duration of neuromuscular blockade.

Although the possibility of minor interactive effects has not been fully studied, midazolam and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of
succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

Benzodiazepines/Theophyllines
Theophyllines, such as aminophylline, may antagonize the sedative effects of benzodiazepines, including midazolam.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

Dosage and Administration
General Dosing Information
Because serious and life-threatening cardiorespiratory adverse events have been reported, provision for monitoring, detection and correction of these reactions must be made for every patient to whom Midolam Injection is administered, regardless of age or health status. Excessive doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest (see Warnings).

In addition, reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. Should such reactions occur, caution should be exercised before continuing administration of Midolam Injection (see Warnings).
Midolam Injection should only be administered IM or IV. For IM injections, it is recommended that the medication be injected deep into a large muscle mass. Care should be taken to avoid intra-arterial injection or extravasation.
When administered IV, the initial dose and all subsequent doses should never be given as a bolus: administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. Lower doses, smaller increments and slower injection rates are necessary for elderly (over 60 years), debilitated or high-risk surgical patients, and in patients receiving concomitant narcotics or other CNS depressants.
When Midolam Injection is given with potent analgesics, the latter should be administered first so that the sedative effects of Midolam Injection can be safely titrated on top of any sedation caused by the analgesic.

Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients.
The following dosing instructions are only intended to serve as general guidelines since the dosage of Midolam must always be individualized, depending on the patient’s age, medical condition and concurrent medication. Continuous monitoring of respiratory and cardiac function is required (i.e., pulse oximetry).

Adults and Pediatrics: Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to sedation/analgesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

Titration to effect with multiple small doses is essential for safe administration. It should be noted that adequate time to achieve peak central nervous system effect (3 to 5 minutes) for midazolam should be allowed between doses to minimize the potential for oversedation. Sufficient time must elapse between doses of concomitant sedative medications to allow the effect of each dose to be assessed before subsequent drug administration. This is an important consideration for all patients who receive intravenous midazolam.

Immediate availability of resuscitative drugs and age- and size-appropriate equipment and personnel trained in their use and skilled in airway management should be assured.

Pediatrics: For deeply sedated pediatric patients a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure. Intravenous access is not thought to be necessary for all pediatric patients sedated for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose of sedating the child; rather, emphasis should be placed upon having the intravenous equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

**Usual Adult Dose**

**Sedation, preoperative and amnesia – IM administration**

Midazolam should be injected deep in a large muscle mass. The recommended premedication dose of midazolam for good risk (ASA Physical Status I & II) adult patients below the age of 60 years is 0.07 to 0.08 mg/kg (approximately 5 mg IM), approximately 30-60 min before surgery. Lower doses (0.02-0.05 mg/kg) may be sufficient in elderly or debilitated patients. The dose of 1 mg IM midazolam may suffice for some older patients if the anticipated intensity and duration of sedation is less critical.

Onset is within 15 minutes, peaking at 30 to 60 minutes.

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

**Sedation, conscious (endoscopic or cardiovascular procedures) – IV administration**

**UNPREMEDICATED – Healthy Adults Below the Age of 60:** Initially no more than 2.5 mg (1.5 mg in elderly/debilitated/Chronically Ill Patients), some patients may respond to as little as 1 mg, administered slowly over a period of at least 2 min, immediately prior to procedure; after an additional 2 or more min to allow for clinical effect, dosage may be further titrated in small increments (≤ 1 mg) of the initial dose (with intervals of 2 or more min being allowed after each increment) to the desired effect. A total dose of more than 5 mg (3.5 mg in elderly/debilitated) is not usually necessary. Additional maintenance doses may be administered, if necessary, in increments of 25% of the initial dose, but only by slow titration, to maintain the desired level of sedation.
PREMEDICATED -- When midazolam is administered concomitantly with narcotic analgesics or other CNS depressants, the dosage of midazolam should be reduced by approximately 30% (50% in elderly/debilitated).

**Note:** The desired endpoint for conscious sedation can usually be attained within 3 to 6 min. The therapeutic dosage range between sedation and unconsciousness or disorientation appears to be narrower than for other benzodiazepines (e.g. diazepam).

When midazolam is used for peroral endoscopic procedures, a topical anesthetic agent is recommended; when used for bronchoscopic procedures, a narcotic premedication is recommended.

**Anesthesia, general, adjunct (prior to administration of other general anesthetics) – IV administration**

UNPREMEDICATED -- In adults under the age of 55 years, the usual initial dose is 0.2-0.35 mg/kg. In patients 55 years of age and over who are ASA I or II (good surgical risk), the usual initial dose is 0.15-0.3 mg/kg. In ASA III or IV patients (severe systemic disease or debilitation), the usual initial dose is 0.15-0.25 mg/kg.

The dose should be administered over a period of 20-30 seconds, allowing 2 min for clinical effect.

**Note:** If necessary to complete induction, additional doses may be given in increments of about 25% of the initial dose, or inhalation general anesthetics may be used. In resistant cases, up to 0.6 mg/kg as a total dose may be used for induction, if necessary; however, larger doses may prolong recovery.

PREMEDICATED (sedative or narcotic) – When sedative or, especially, narcotic premedication has been administered, the recommended dose range of midazolam is 0.15-0.35 mg/kg. In adults below the age of 55 years, a dose of 0.25 mg/kg is usually sufficient. In patients 55 years of age and over who are ASA I or II, the initial recommended dose is 0.2 mg/kg. In patients who are ASA III or IV, a dose of 0.15 mg/kg may be sufficient. The dose should always be administered over a period of 20-30 seconds and allowing 2 min for effect.

**Anesthesia, maintenance (short surgical procedures) – IV administration**

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

When used for the maintenance of anesthesia, as a component of balanced anesthesia, narcotic premedication is especially recommended. Long surgical procedures have not been studied.

**Note:** The endpoint for induction of anesthesia does not appear to be as clearly defined with midazolam as it is with thiopental.

Narcotic premedications frequently used include: fentanyl (1.5-2 mcg/kg IV), morphine (up to 0.15 mg/kg IM), meperidine (up to 1 mg/kg IM), and fentanyl citrate and droperidol combination (0.02 ml/kg IM).

Sedative premedications frequently used include: hydroxyzine HCl (100 mg orally).

Premedications should be administered at least 30-60 min prior to midazolam induction, with the exception of fentanyl, which should be administered 2-5 min before induction.

**Status Epilepticus**

The usual dose is 0.15-0.2 mg/kg intramuscularly or intravenously.
Usual Pediatric Dose
Unlike adult patients, pediatric patients generally receive increments of midazolam on mg/kg basis.

Sedation, preoperative, and amnesia - IM administration
0.08-0.2 mg/kg.
Sedation after 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 have been used. Although not systematically studied, the total dose usually does not exceed 10 mg. If midazolam is given with an opioid, the initial dose of each must be reduced.

Sedation, conscious (endoscopic or cardiovascular procedures) - IV administration
Pediatric patients less than 6 months of age: limited information is available in non-intubated pediatric patients less than 6 months of age. It is uncertain when the patient transfers from neonatal physiology to pediatric physiology, therefore the dosing recommendations are unclear. Pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful monitoring are essential.

Dosage must be individualized by physician. Some authorities have recommended an initial dose of 0.05-0.1 mg/kg in children aged 6 months to 5 years (total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but usually does not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.)
and 0.025-0.05 mg/kg in children aged 6-12 years (total dose up to 0.4 mg/kg may be needed to reach the desired endpoint but usually does not exceed 10 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses).

Pediatric patients 12 to 16 years of age: should be dosed as adults. Prolonged sedation may be associated with higher doses; some patients in this age range will require higher than recommended adult doses but the total dose usually does not exceed 10 mg.

Anesthesia, general, adjunct (prior to administration of other general anesthetics) – IV administration
0.05-0.2 mg/kg.

Drug Abuse and Dependence
Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, hallucinations, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuation of benzodiazepines, including midazolam. Abdominal distention, nausea, vomiting, and tachycardia are prominent symptoms of withdrawal in infants. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. There is no consensus in the medical literature regarding tapering schedules; therefore, practitioners are advised to individualize therapy to meet patient’s needs. In some case reports, patients who have had severe withdrawal reactions due to abrupt discontinuation of high-dose long-term midazolam, have been successfully weaned off of midazolam over a period of several days.

Overdosage
Manifestations
The symptoms of midazolam injection overdosage are mainly an intensification of the therapeutic effects (sedation, muscle weakness, profound sleep). In addition, confusion, impaired coordination, paradoxical excitation, or adverse effects on vital signs may be observed. In most cases only observation of vital functions is required. Extreme overdosage may lead to impaired reflexes, respiratory depression and apnea, cardiovascular depression, or coma.

Treatment
Respiration, pulse rate and blood pressure should be monitored and supportive measures employed. A patent airway should be maintained and ventilation supported, including administration of oxygen and an IV infusion started. Hypotension should be treated with IV fluid therapy, repositioning, judicious use of vaspressors and other appropriate measures. The value of peritoneal dialysis, forced diuresis or hemodialysis is unknown.

Flumazenil (Anexate), a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases of overdose. (See the flumazenil monograph for specific dosing guidelines.) Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose.

Pharmaceutical Precautions
Both concentrations of Midolam Injection can be diluted with sodium chloride 0.9% or dextrose 5%.

Midolam Injection may be mixed in the same syringe with the following frequently used premedications: morphine sulphate, meperidine, atropine sulphate or scopolamine.

Midazolam precipitates in sodium bicarbonate.

Midolam Injection should not be used if it contains a precipitate or is discolored. It should be stored below 25°C and protected from freezing. Protect from light.

Presentation
Midolam 1 mg/ml - Drug registration number: 108 42 29066
5 ampoules of 5mg/5ml
Midolam 5 mg/ml - Drug registration number: 108 43 29067
5 ampoules of 5mg/ml
5 ampoules of 15mg/3ml
5 ampoules of 50mg/10ml

Manufacturer and Registration holder:
Rafa Laboratories Ltd, P.O.Box. 405, Jerusalem 9100301.
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