

MIDAZOLAM INJECTION
Midazolam 1mg/ml and 5mg/mL

Qualitative and Quantitative Composition

Composition of Midazolam Injection

Ingredient ^{*1}	Quantity		Function	Reference to Standards
	1mg/mL	5mg/mL		
Midazolam <i>Midazolamum</i>	1mg	5mg	active	<i>Ph. Eur.</i>
Sodium Chloride <i>Natrii Chloridum</i>	8.0mg	8.0mg	to adjust tonicity	<i>Ph. Eur.</i>
Hydrochloric Acid <i>Acidum Hydrochloridum Concentratum</i>	0.3µL	1.6µL	to produce the 'hydrochloride' of midazolam and to adjust pH	<i>Ph. Eur.</i>
Sodium Hydroxide ^{*2} <i>Natrii Hydroxidum</i>	qs ^{*2}	qs ^{*2}	to adjust pH	<i>Ph. Eur.</i>
Water for Injections <i>Aqua ad Inyectabilia</i>	qs to 1mL	qs to 1mL	diluent	<i>Ph. Eur.</i>

*1 All ingredients used in the formulation are of non-animal origin.

*2 Sodium Hydroxide is only needed if the pH is over adjusted with hydrochloride acid.

Pharmaceutical Form

Product Description: Midazolam Injection is a sterile, isotonic, clear, colourless to pale yellow solution in a ready-to-use, single dose presentation. Midazolam Injection contains midazolam, sodium chloride, hydrochloric acid and Water for Injections. Sodium hydroxide may be present if used for the adjustment of pH. It does not contain preservatives.

Strength: 1mg/mL and 5mg/mL

Dosage Form: Solution for Injection

Routes of Administration: Intravenous and intramuscular

Indications

Midazolam Injection is indicated as a short acting central nervous system depressant which induces sedation, hypnosis, amnesia and anaesthesia. It is used intravenously for conscious sedation prior to short surgical procedures, for sedation in intensive care units, and for the induction of anaesthesia before the administration of other anaesthetic agents and intramuscularly for preoperative sedation. With the use of an opioid premedicant, induction of anaesthesia can be obtained with a narrower dose range and in a shorter period of time.

Dosage and Method of Administration

This product is for single patient use only. Use once and discard any residue.

Dosage should be individualised and drug should be administered slowly.

Lower doses may be required in elderly or debilitated patients or in patients with hepatic or renal insufficiency. 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 midazolam is administered, regardless of age or health status. The dosage of midazolam administered should be adjusted according to the type and amount of premedication used.

Paediatric use:

Safety and effectiveness of midazolam in children below the age of 8 have not been established. Pharmacokinetics in children have not been established and may differ from adults.

Intravenous administration:

Endoscopic or cardiovascular procedures: For conscious sedation, midazolam can be used either alone or together 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 anaesthetic is recommended. For bronchoscopic procedures, the use of an opioid premedicant is recommended. Individual response will vary with age, physical status and concomitant medications, but may also vary independent of these factors.

Titrate dosage to desired sedative end point, such as slurring of speech, with slow administration immediately prior to the procedure. The initial dose should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. When titrating the dose 2 or more minutes should be allowed after each increment.

In healthy adults the initial dose is approximately 2.5 mg. Some patients may respond to as little as 1 mg. Further doses of 1 mg may be given if necessary. A total dose greater than 5 mg is not usually necessary to reach the desired end point.

In cases of severe illness and in elderly patients the initial dose must be reduced to 1 to 1.5 mg. Total doses greater than 3.5 mg are not usually necessary.

If an opioid premedicant or other CNS depressant is used the dose of midazolam should be lowered by 25% to 30%.

Induction of anaesthesia: The dosage of midazolam should be determined by the response of the individual patient. Administration should be by slow intravenous injection until consciousness is lost using approximately 0.15-0.2 mg/kg (10-15 mg) administered at a rate of approximately 2.5 mg per 10 seconds. Maximum sedation is usually reached after 2-3 minutes but if required a further dose up to a total of 0.35 mg/kg may be administered. The onset of sedation has not been found to be dose-dependent but the time to recovery is related to the amount of drug administered.

Midazolam should be used with opioid analgesics as it does not have analgesic properties and opioid analgesics

enhance its anaesthetic-inducing properties.

Intravenous sedation in ICU: For sedation in ICU, the recommended infusion rate is 0.03-0.2 mg/kg/hour. The dosage should be individualised and midazolam titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication. It may be possible to reduce the dose (infusion rate) once the therapeutic effect has been obtained.

The dosage should be reduced in hypovolemic, vasoconstricted and hypothermic patients.

After prolonged IV administration of midazolam, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of midazolam is recommended. Midazolam can be used in neurosurgical patients with increased intracranial pressure.

Intramuscular administration:

For preoperative sedation: (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of preoperative events.

For intramuscular use, midazolam should be injected deep in a large muscle mass.

The recommended premedication dose of midazolam for good risk adult patients below the age of 60 years is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM) administered approximately one hour before surgery.

The dose must be individualised and reduced when IM midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant opioids or other CNS depressants. In a study of patients 60 years or older who did not receive concomitant administration of opioids, 2 to 3 mg (0.02 to 0.05 mg/kg) of midazolam produced adequate sedation during the preoperative period. In approximately 25% of patients, 1 mg provided satisfactory sedation. As with any potential respiratory depressant, these patients require special observation for signs of cardio-respiratory depression after receiving IM midazolam.

Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concomitantly with atropine sulfate or hyoscine hydrobromide and reduced doses of opioids.

Dilution and Admixture

Midazolam may be mixed in the same syringe with frequently used premedicants: morphine sulfate, pethidine, atropine sulfate or hyoscine. Midazolam is compatible with normal saline, glucose 5% and 10% in water, fructose intravenous infusion (levulose 5%), potassium chloride, sodium chloride and calcium chloride intravenous infusion (Ringer's solution) and compound sodium lactate intravenous infusion (Hartmann's solution).

The 15 mg/3 mL, 5 mg/mL and 5 mg/5 mL formulations may be diluted to facilitate slow injection.

The 50 mg/10 mL ampoules may be added to the infusion solutions in a mixing ratio of 15 mg midazolam per 100-1000 mL infusion solution.

The product and its admixtures contain no antimicrobial agent. In order to reduce microbiological hazards it is recommended that further dilution be effected immediately prior to use and infusion commenced as soon as practicable after preparation of the admixture. Infusion should be completed within 24 hours of preparation and the residue discarded, however infusion with calcium chloride intravenous infusion (Ringer's solution) and

compound sodium lactate intravenous infusion (Hartmann's solution) should be completed within 4 hours as the potency of midazolam is known to decrease. Any storage of diluted solution should be at 2°C to 8°C.

Contraindications

Patients with a hypersensitivity to benzodiazepines,

Myasthenia gravis,

Patients in shock, coma or in acute alcoholic intoxication with depression of vital signs,

Patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy. Measurements of intra-ocular pressure in patients without eye disease show a moderate lowering following induction with midazolam. Patients with glaucoma have not been studied.

Special Warnings and Special Precautions for Use:

Intravenous midazolam should only be used where appropriate equipment and personnel are available for continuous monitoring of cardiorespiratory function and for resuscitation procedures.

Midazolam must never be used without individualisation of dosage. Midazolam should not be administered by rapid or single bolus intravenous administration. Extravasation should also be avoided. The hazards of intra-arterial injection of midazolam into humans are unknown. Precautions against unintended intra-arterial injection should be taken.

Patients should be continuously monitored for early signs of underventilation or apnoea. Vital signs should continue to be monitored during the recovery period. During intravenous application of midazolam respiratory depression, apnoea, respiratory and/or cardiac arrest have occurred. In some cases where this was not recognised promptly and treated, hypoxic encephalopathy or death has resulted. These life-threatening incidents may occur especially in elderly patients or patients with pre-existing respiratory insufficiency, especially if the injection is given too rapidly or with excessive doses. Particular care must be taken when administering the drug by IV route, in the elderly, to very ill patients, high-risk surgical patients and to those with significant hepatic impairment, chronic renal insufficiency, or with limited pulmonary reserve because of the possibility of apnoea or respiratory depression. These patients require lower doses whether premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam.

Elderly patients frequently have inefficient function of one or more organ systems and dosage requirements have been shown to be reduced with age. Patients with chronic renal failure or congestive heart failure eliminate midazolam more slowly.

In some intensive care patients and in some elderly patients given midazolam by IV infusion for prolonged sedation, the elimination half-life was found to increase by up to six times.

An increase risks for falls and fractures have been recorded in elderly benzodiazepine users.

Particular care should be exercised in the use of intravenous midazolam in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received midazolam. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with an opioid.

A gradual dose reduction is recommended in patients on a prolonged IV dose of midazolam. Abrupt cessation of therapy may lead to withdrawal symptoms.

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 anaesthetics should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other central nervous system depressants increases the risk of underventilation or apnoea and may contribute to a profound and/or prolonged drug effect. When midazolam is used with an opioid analgesic, the dosage of both agents should be reduced. Opioid premedication also reduces the ventilatory response to carbon dioxide stimulation.

After administration of midazolam, patients should not be discharged from hospital for at least three hours and then, if possible, only if accompanied by a responsible person. The decision as to when patients may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualised. Gross tests of recovery from the effects of midazolam cannot be relied upon to predict reaction time under stress. When midazolam is used with other drugs during anaesthesia, the contribution of these can vary and should be considered accordingly.

Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate machinery until effects such as drowsiness, have subsided or until the day after anaesthesia and surgery, whichever is longer. The physician should decide when activities such as driving a vehicle or operating a machine may be resumed. The patient's attendants should be made aware that anterograde amnesia may persist longer than the sedation and therefore patients may not carry out instructions even though they appear to acknowledge them.

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 anaesthesia.

Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anaesthetic agent and the availability of necessary counter measures are recommended. The use of an opioid premedicant is recommended for bronchoscopies.

Administration of a muscle relaxant may sometimes be necessary to overcome midazolam-associated hiccoughs.

As with other benzodiazepines midazolam may have the potential to cause dependence.

Carcinogenicity:

Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 80mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumours. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumours. Dosages of 9 mg/kg/day of midazolam maleate do not increase the incidence of tumours. The pathogenesis of induction of these tumours is not known. These tumours were found after chronic administration, whereas human use will ordinarily be of single dose or of short duration. Midazolam did not

have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

Impairment of Fertility:

A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human IV dose of 0.35mg/kg.

Interactions With Other Medicaments and Other Forms of Interactions

Midazolam can enhance the central sedative effect of neuroleptics, tranquillisers, antidepressants, sleep-inducing drugs, analgesics, anaesthetics, antipsychotics, anxiolytics, antiepileptic drugs and sedative antihistamines. This potentiation of effect can in certain cases be of advantage therapeutically.

There is potentially relevant interaction between midazolam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 IIIA). Data clearly indicates that these compounds influence the pharmacokinetics of midazolam and may lead to prolonged sedation. At present this reaction is known to occur with cimetidine, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole.

Therefore patients receiving the above compounds or others which inhibit P450 IIIA together with midazolam should be monitored carefully for the first few hours after administration of midazolam. (Studies have shown that ranitidine has no influence on the pharmacokinetics of parenterally given midazolam).

In some patients the mutual potentiation of alcohol and midazolam can produce unforeseeable reactions (no alcoholic beverages for at least 12 hours after parenteral administration).

The sedative effect of intravenous midazolam is accentuated by premedication. Consequently, the dosage of midazolam should be adjusted according to the type and amount of premedication administered.

The plasma concentration of midazolam, following oral administration, has been shown to increase when used in combination with erythromycin and this results in a potentiation of midazolam's sedative effect. A much smaller change in plasma concentration with no observed potentiation of the sedative effects was observed following IV administration of midazolam, however, caution is advised.

A moderate reduction in induction dosage requirements of thiopentone (about 15%) has been noted following use of intramuscular midazolam for premedication.

Simultaneous administration of cimetidine (but not ranitidine) has been reported to reduce clearance of midazolam.

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia. This decrease correlates with the dose of midazolam administered.

The effects of midazolam can be reversed by the benzodiazepine antagonist flumazenil.

Effects on Laboratory Tests:

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

Pregnancy and Lactation

Use in pregnancy:

Midazolam crosses the placenta and other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression. Midazolam is therefore not recommended for obstetric use. Teratological studies with midazolam in a number of animal species have not shown association between administration of the drug and disturbances of fetal development, nor has clinical experience so far yielded any evidence of such an association. However, like any other drug, midazolam should not be used in the first three months of pregnancy unless considered absolutely necessary by the physician.

Use in lactation:

There is evidence that midazolam is excreted in breast milk and its effects on the new born are not known. Therefore midazolam is not recommended for use in nursing mothers.

Effects on Ability to Drive and Use Machinery

Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate machinery until effects such as drowsiness, have subsided or until the day after anaesthesia and surgery, whichever is longer.

Undesirable Effects

Local: The following additional adverse reactions were reported after intramuscular administration:

- local effects at intramuscular injection site: pain (3.7%)
- headache (1.3%)
- induration (0.5%)
- redness (0.5%)
- muscle stiffness (0.3%)

The following additional adverse reactions were reported subsequent to intravenous administration:

- local effects at the IV site: tenderness (7%)
- pain during injection (6.2%)
- hiccough (5.5%)
- redness (3.8%)
- nausea (3%)
- vomiting (2.9%)
- coughing (1.9%)
- induration (1.9%)
- drowsiness (1.3%)
- oversedation (1%)
- phlebitis (0.5%)

Systemic: Fluctuations in vital signs that have been noted following parenteral administration of midazolam include:

- respiratory depression (22.9% following IV administration and 10.8% of patients following IM administration)
- apnoea (19% following IV administration)
- variations in blood pressure and pulse rate

These common occurrences during anaesthesia and surgery are affected by the lightening or deepening of anaesthesia, instrumentation, intubation and use of concomitant drugs.

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 opioid analgesics.

Overdose

Symptoms of overdosage: The manifestations of midazolam overdosage are similar to those observed with other benzodiazepines and include: sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs, cerebrovascular perfusion. Hepatic function should be monitored.

Treatment of overdosage: Treatment of midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Flumazenil can be used to reverse the effects of midazolam (refer to Flumazenil Product Information leaflet). Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the judicious use of other accepted antihypotensive measures. There is no information as to whether peritoneal dialysis, forced diuresis or haemodialysis are of any value in the treatment of overdosage.

Pharmacological Properties

Pharmacodynamic Properties

Pharmacotherapeutic Group: Central nervous system depressant

Mechanism of Action: Midazolam is a short-acting central nervous system depressant which induces sedation, hypnosis, amnesia and anaesthesia. As with all benzodiazepines, Midazolam will also induce muscle relaxation. Pharmacokinetic and pharmacodynamic data in chronic intravenous usage are not available beyond 15 days. The mechanism of action of the benzodiazepines is under continuous investigation. Benzodiazepines appear to intensify the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the brain.

Pharmacokinetic Properties

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration and the presence or absence of other premedications. Onset time of sedative effects after IM administration is 15 minutes. Peak sedation occurs 30 to 60 minutes following injection.

When used intravenously (as a sedative for endoscopic or other short therapeutic or diagnostic procedures) the end point of slurred speech can be attained within 2.8 to 4.8 minutes, depending on the total dose administered and whether or not preceded by opioid premedication. The time to induction of anaesthesia for surgical procedures is variable occurring in approximately 1.5 minutes (0.3-8 minutes) when an opioid premedicant has been administered and in 2 to 2.5 minutes without premedication or with a sedative premedication.

Approximately two hours are required for full recovery from midazolam-induced anaesthesia. Duration of effect is dependent on the dose and other drugs used. Induction of anaesthesia is unsuccessful in approximately 14% of patients with midazolam alone but in only about 1% when given with an opioid.

At doses sufficient to induce sedation, intravenous midazolam decreases the sensitivity of the ventilatory response to elevated CO₂ tension in normal subjects and in those with chronic obstructive lung disease, who are at special risk of hypoxia. Sedation with midazolam has no adverse effects on pulmonary compliance and does not cause bronchoconstriction or significantly affect functional residual capacity or residual volume. Midazolam may cause a modest decrease in mean arterial pressure. Baroreceptor response is not affected and decreases in arterial pressure are accompanied by increases in heart rate. Intravenous midazolam at doses of 0.15 to 0.2 mg/kg did not have a deleterious effect on cardiac haemodynamics. Intravenous administration of midazolam does not alter intracranial pressure unless the patient is intubated. As with thiopentone, the intracranial pressure rises during intubation. Cerebral blood flow may be reduced by up to 35%, which is of the same order as caused by equivalent doses of diazepam. The effect on cerebral metabolism is not clearly established.

Midazolam reduces the intraocular pressure to the same degree as thiopentone and diazepam. However, the increase in intraocular pressure after succinylcholine administration or endotracheal intubation is not prevented by midazolam, thiopentone or diazepam.

The pharmacokinetic profile of midazolam in man is linear over the 0.05 to 0.4 mg/kg dose range. In normal subjects the drug exhibited a short elimination half-life (1 to 2.8 hours) with a large volume of distribution (0.8 to 1.86 L/kg) and a rapid plasma clearance (0.24 to 0.73 L/hr/kg).

Pharmacokinetics in special clinical situations: In some intensive care and elderly patients given midazolam by IV infusion for prolonged sedation, the elimination half-life was found to increase by up to six times. Particular risk factors in the elderly include abdominal pathology, sepsis and poor renal function. In these patients infusion at an unchanged rate resulted in higher plasma levels at steady state. Consequently, the infusion rate should be reduced once a satisfactory clinical response has been obtained.

Bioavailability: The mean absolute bioavailability of midazolam following IM administration is greater than 90%. The mean time of maximum midazolam plasma concentrations following IM dosing occurs within 45 minutes post-administration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after IM administration are about one-half of those achieved after equivalent IV doses.

Metabolism: Less than 0.03% is excreted in the urine unchanged. The drug is rapidly metabolised to 1-hydroxymethyl midazolam which is conjugated with subsequent excretion in the urine. The elimination half-life of the active metabolite is similar to that of parent drug. The concentration of midazolam is 10 to 30 times greater than that of 1-hydroxymethyl midazolam.

Protein binding: 97% of midazolam becomes bound to plasma proteins. The extent of protein binding does not vary in renal failure.

Pharmaceutical Particulars

List of Excipients

Sodium Chloride
Water for Injections
Hydrochloric Acid
Sodium Hydroxide (may be present if required for pH adjustment)

Incompatibilities

A white precipitate was found to be formed with dimenhydrinate, pentobarbitone sodium, perphenazine, prochlorperazine edisylate and ranitidine hydrochlorate.

Shelf Life

5mg in 5mL, 5mg in 1mL, 15mg in 3mL and 50mg in 10mL: 36 months from date of manufacture.

Midazolam Injection does not contain a preservative or bacteriostatic agent, hence, vials are for single use only and any unused portion should be discarded.

Special Precautions for Storage

Store below 25°C. Protect from light. Use once only and discard any remaining portion.

Nature & Contents of Container

Midazolam Injection is presented in ampoules manufactured from medical grade, low density polyethylene which conforms to the specification of the European Pharmacopoeia 3.1.4 "Polyethylene - Low Density for Containers for Preparations for Parenteral Use and Ophthalmic Preparations" (1997).

Instructions for Use/Handling

Spill Procedures: Where possible, dam the spill. Cover with absorbent towels or pads or other absorbent material. Place in closed containers for disposal. Wash affected area with copious quantities of water. Dispose of in an approved facility for controlled incineration.

Medicine Classification

Controlled Drug C5.

Package Quantities

5mg in 1mL and 5mg in 5mL - 10s
15mg in 3mL and 50mg in 10mL - 5s

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