



For Healthcare Professionals only

# idazol 5mg/5mL Injection

(Midazolam)

آئڈازول انجکشن ۵ ملی گرام / ۵ ملی لیٹر  
(میڈازولام)

## WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; AND DEPENDENCE AND WITHDRAWAL REACTIONS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Monitor patients for respiratory depression and sedation.
- The use of benzodiazepines, including midazolam, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing Midazolam Injection and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.
- Although Midazolam Injection is indicated only for intermittent use, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of Midazolam Injection may precipitate acute withdrawal reactions, which can be life-threatening. For patients using Midazolam Injection more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue Midazolam Injection.

## QUALITATIVE AND QUANTITATIVE COMPOSITION

### Idazol 5mg/5mL Injection

Each ampoule contains:  
Midazolam HCl eq. to Midazolam USP .... 5mg  
(Product Specs.: USP)

## PHARMACEUTICAL FORM

Solution for Injection

## CLINICAL PARTICULARS

### Therapeutic indications

Idazol is a short-acting hypnotic with the following indications for use:

#### Adults

- Conscious sedation with or without local anesthesia before or during diagnostic or therapeutic procedures
- Anesthesia
  - Premedication before the induction of anesthesia and induction of anesthesia
  - As a sedative component in the maintenance of anesthesia
- Sedation in the Intensive Care Unit
- Indicated for the treatment of status epilepticus in adults

#### Children

- Conscious sedation with or without local anesthesia before or during diagnostic or therapeutic procedures
- Anesthesia and Premedication before the induction of anesthesia
- Sedation in the Intensive Care Unit

## Posology and Method of Administration

### Posology:

#### Standard Dosages

Idazol is a potent sedative agent that requires slow administration and titration. For patients over 60 years of age, debilitated patients, or chronically ill patients and children, the medicine should be administered with care, and the risk factors related to each patient should be evaluated on an individual basis.

Standard dosages are provided in the table below.

Indication	Adults <60 years	Adults ≥60 years / debilitated or chronically ill patients	Children
Conscious sedation	<b>IV</b> Initial dose: 2 - 2.5mg Titration doses: 1mg Total dose: 3.5 - 7.5mg	<b>IV</b> Initial dose: 0.5 - 1mg Titration doses: 0.5 - 1mg Total dose: <3.5mg	<b>IV</b> in patients 6 months - 6 years Initial dose: 0.05 - 0.1mg/kg Total dose: <0.9mg <b>IV</b> in patients 6 - 12 years Initial dose: 0.025 - 0.05mg/kg Total dose: <1.0mg <b>rectal</b> ≥6 months 0.3 - 0.5mg/kg <b>IM</b> 1 - 15 years 0.05 - 0.15mg/kg
Anesthesia premedication	<b>IV</b> 1 - 2mg repeated <b>IM</b> 0.07 - 0.1mg/kg	<b>IV</b> Initial dose: 0.5mg Slow up titration as needed <b>IM</b> 0.025-0.05mg/kg	<b>rectal</b> ≥6 months 0.3 - 0.5mg/kg <b>IM</b> 1 - 15 years of age 0.05 - 0.2mg/kg
Anesthesia induction	<b>IV</b> 0.15 - 0.2mg/kg (0.3-0.35 mg/kg without premedication)	<b>IV</b> 0.05 - 0.15mg/kg (0.15 - 0.2mg/kg without premedication)	
Sedative component in combined anesthesia	<b>IV</b> intermittent doses of 0.03 - 0.1mg/kg or continuous infusion of 0.03 - 0.1mg/h	<b>IV</b> lower doses than recommended for adults <60 years	
Sedation in the Intensive Care Unit (ICU)	<b>IV</b> Loading dose: 0.03 - 0.3mg/kg in increments of 1-2.5mg Maintenance dose: 0.03 - 0.2mg/kg/h		<b>IV</b> in neonates <32 weeks gestational age 0.03mg/kg/h <b>IV</b> in neonates ≥32 weeks and children up to 6 months 0.06mg/kg/h <b>IV</b> in patients ≥6 months of age Loading dose: 0.05 - 0.2mg/kg Maintenance dose: 0.06 - 0.12mg/kg

## Conscious Sedation

**Dosage:** For sedation required for diagnostic and surgical procedures, Idazol is administered intravenously. The suitable dose is determined on an individual basis. The medicine should not be administered rapidly or as a bolus injection but by titrating the dose. The onset of the sedation vary individually, depending on the physical status of the patient and the dosage method used (e.g. rate of administration, dose level). If necessary, additional doses may be administered. The onset of action is approximately 2 minutes after the injection. The maximum effect is obtained in approximately 5 to 10 minutes.

**Adults:** Idazol should be administered slowly as an intravenous injection at a rate of approximately 1mg/30sec. In adults under 60 years of age, 2 to 2.5mg is administered 5 to 10 minutes before the beginning of the procedure as an initial dose.

The initial dose may be followed by additional 1mg doses as necessary. The average total dosage is 3.5 to 7.5mg. Administration of a total dosage higher than 5mg is usually not necessary.

The initial dose for patients over 60 years of age, debilitated patients or chronically ill patients is 0.5 to 1mg, administered 5 to 10 minutes before the beginning of the procedure. Additional doses of 0.5 to 1mg of Idazol may be administered as necessary. In these patients, it may take more time to reach the peak effect; therefore, additional doses of Idazol should be titrated very slowly and carefully. Administration of a total dosage higher than 3.5mg is usually not necessary.

## Pediatric population

Doses of IV Idazol are titrated slowly until the desired clinical effect is reached. The initial dose is administered in 2 to 3 minutes.

To fully evaluate the sedative effect, one should wait another 2 to 5 minutes before beginning with the procedure or repeating the dose. If it is necessary to increase the sedative effect, continue to administer additional low doses until the appropriate sedation level is reached.

For infants and children under 6 years of age, significantly higher doses may be required (mg/kg) compared to older children and adolescents.

- Children under 6 months of age: Conscious sedation is not recommended in children under 6 months of age.
- Patients 6 months to 5 years of age: The initial dose is 0.05 to 0.1mg/kg. To reach the desired effect, it may be necessary to administer a dose up to 0.6mg/kg. However, the total dosage should not exceed 6mg. Higher doses may cause prolonged sedation and risk of hypoventilation.
- Children 6 to 12 years of age: The initial dose is 0.025 to 0.05mg/kg. It may be necessary to administer a total dosage of 0.4mg/kg (10mg as the maximum dosage). Higher doses may cause prolonged sedation and risk of hypoventilation.
- Children 12 to 16 years of age: Use the recommended dosages for adults
- Rectal administration: The total dosage of midazolam is usually 0.3 to 0.5mg/kg. The whole dose should be administered at once. Avoid repeated rectal administration. Not recommended in children under 6 months

**Intramuscular administration:** Doses range from 0.05 to 0.15mg/kg. Usually, the total dose greater than 10mg is not required. The intramuscular route should only be used in exceptional cases. Rectal administration should be preferred, as intramuscular injection is painful. In children weighing less than 15kg, midazolam solutions with a concentration higher than 1mg/mL are not recommended. Higher concentrations should be diluted to 1mg/mL.

#### **Anesthesia Dose (premedication)**

Administration of midazolam immediately before the procedure causes sedation and preoperative impairment of memory. Midazolam can also be administered in combination with anticholinergics. In such case midazolam is administered intravenously or intramuscularly (deep into the muscle mass, 20 to 60 minutes before the induction of anesthesia), and in children rectal administration should be preferred. Patient should be carefully and constantly monitored

**Adults:** The recommended intramuscular initial dose is 0.025 to 0.05mg/kg. In the case of concomitant administration of narcotics, midazolam dosage should be reduced. The usual dosage is 2 to 3mg.

#### **Pediatric population**

**Neonates and children up to 6 months of age:** This medicine is not recommended in children under 6 months of age, due to limited data.

#### **Children over 6 months of age**

**Rectal administration:** The total dosage of midazolam (usually in the range of 0.3 to 0.5mg/kg) should be administered 15 to 30 minutes before the induction of anaesthesia. Intramuscular is painful. The proven and safe dosage for intramuscular administration is 0.08 to 0.2mg/kg. Rectal administration is preferred.

Children between 1 to 15 years of age require proportionally higher dosages per body weight than adults. In children 15 to 16 years of age, midazolam solutions with a concentration higher than 1mg/mL are not recommended. Higher concentrations should be diluted to 1mg/mL.

#### **Induction (Adults)**

If midazolam is used before or in combination with other intravenous or inhalational medicines used for induction of anesthesia, the initial doses of all these medicines should be significantly reduced to as low as 25% of the usual initial dose. The desired level of anesthesia is reached by gradually increasing the dose.

For intravenous induction of anesthesia, midazolam is administered at a slow rate in increments. Each increment of not more than 5mg should be injected over 20 to 30 seconds, with 2-minute intervals between the doses.

- For pre-medicated adults under 60 years of age, usually a 0.15 to 0.2mg/kg dose administered intravenously is sufficient.
- For non-premedicated adults under 60 years of age, higher doses (0.3 to 0.35mg/kg IV) may be used. If full induction is sought, the additional doses may comprise approximately 25% of the patient's initial dose. Induction may also be conducted with inhalational anesthetics. In refractory cases, a total dosage of up to 0.6mg/kg may be used for induction, but such higher doses may cause prolonged recovery from anesthesia.
- For pre-medicated adults over 60 years of age, debilitated patients, or chronically ill patients, the dosage should be significantly reduced, e.g., up to 0.05 to 0.15mg/kg administered intravenously over 20 to 30 seconds, with 2 minute waiting time for the drug to take effect.
- For non-premedicated adults over 60 years of age usually higher midazolam doses are required for induction; the recommended initial dose is 0.15 to 0.3mg/kg. For non-premedicated debilitated patients or patients with severe systemic disease, less midazolam should usually be administered for induction. An initial dose of 0.15 to 0.25mg/kg is generally sufficient.

#### **Sedative Component in Combined Anesthesia (Adults)**

Midazolam can be given as a sedative component in combined anesthesia by either further intermittent small IV doses (range between 0.03 and 0.1mg/kg) or continuous infusion of IV

Idazol (range between 0.03 and 0.1mg/kg/h) typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction.

In adults over 60 years of age, debilitated patients, or chronically ill patients, lower doses are required for maintenance.

#### **Sedation in the Intensive Care Unit (ICU)**

The desired level of sedation is reached by stepwise titration of midazolam followed by either continuous infusion or intermittent bolus. Idazol is administered according to clinical need and the patient's condition, age, and concomitant medications

#### **Adults:**

**Intravenous loading dose:** 0.03 to 0.3mg/kg administered with 15-minute increments. Every 1 to 2.5mg dose should be administered over 20 to 30 seconds, with 2 minute intervals between the doses. For patients with hypovolemia, vasoconstriction, or hyperthermia, the loading dose should be reduced or omitted.

If Idazol is administered together with strong analgesics, the analgesics should be administered first.

**Intravenous maintenance dose:** Ranging from 0.03 to 0.2mg/kg/h. For patients with hypovolemia, vasoconstriction, or hyperthermia, the maintenance dose should be reduced. The sedation level should be assessed on a regular basis. Long term sedation may lead to tolerance, which may require increasing the dose.

#### **Pediatric population**

**Neonates and children up to 6 months of age:** Idazol is administered as an intravenous continuous infusion. The initial dose for neonates born before 32 weeks of gestation is 0.03mg/kg/h (0.5µg/kg/min) and in neonates born after 32 weeks of gestation as well as children up to 6 months of age, 0.06 mg/kg/h (1µg/kg/min).

Intravenous loading doses are not recommended in preterm infants, neonates, and children up to 6 months of age; rather, the infusion rate should be higher during the first hours to reach the therapeutic concentration. The infusion rate should be frequently and carefully re-evaluated especially over the first 24 hours. Careful monitoring of breathing rate and oxygen saturation is required.

**Children over 6 months of age,** Intubated and ventilated children should be administered a loading dose of 0.05 to 0.2mg/kg IV, slowly over 2 to 3 minutes, to achieve the desired clinical effect.

Idazol should not be administered as a rapid intravenous injection. Following the loading dose, administered as continuous infusion at a rate of 0.06 to 0.12mg/kg/h (1 to 2µg/kg/min). As necessary, the infusion rate can be increased or reduced (generally, 25% of the initial or following infusion rate)

If the Idazol infusion is initiated in hemodynamically unstable patients, the usual loading dose should be titrated with low doses and the patient should be monitored for hemodynamic alterations (e.g. hypotension). Careful monitoring of respiratory rate and oxygen saturation is required.

In premature infants, neonates, and children with body weight below 15kg, it is not recommended to use Idazol solutions with a concentration above 1mg/mL. Higher concentrations should be diluted to 1mg/mL.

#### **Special populations**

**Renal impairment:** In patients with severe renal impairment (creatinine clearance below 30mL/min), Idazol may be accompanied by more pronounced and prolonged sedation, it should, therefore, be dosed carefully and titrated for the desired effect.

**Hepatic impairment:** Reduces the clearance of intravenously administered Idazol with a subsequent increase in terminal half-life. The required dose of midazolam may be reduced, and vital signs should be properly monitored.

**Method of administration:** For intravenous, intramuscular and rectal use.

#### **Contraindications**

- Hypersensitivity to midazolam or benzodiazepines.
- Use of this drug for conscious sedation in patients with severe respiratory failure or acute respiratory depression.

#### **Special Warnings and Precautions for use**

Midazolam should be administered only by experienced physicians in hospital settings. Benzodiazepines are not recommended for the primary treatment of psychotic illness. Special caution is required for conscious sedation in patients with impaired respiratory function. Pediatric patients under 6 months of age are especially predisposed to develop airway obstruction and hypoventilation, to titrate the dosage with small increments and carefully monitor respiratory rate and oxygen saturation.

Special caution is required when administering midazolam to high-risk patients:

- Adult patients over 60 years of age
- Chronically ill or debilitated patients, e.g. patients with chronic respiratory insufficiency, patients with chronic renal failure, patients with impaired hepatic function patients with

- impaired cardiac function, pediatric patients, especially those with cardiovascular instability.
- Special caution is required when administering midazolam to patients with myasthenia gravis.

**Tolerance:** Some loss of efficacy has been reported when using midazolam as long term sedation in Intensive Care Unit.

**Dependence:** When midazolam is used in long-term sedation the possible development of physical dependence should be taken into account.

**Withdrawal Symptoms:** Abrupt termination of treatment leads to withdrawal symptoms. It is recommended to decrease doses gradually.

**Amnesia:** Anterograde amnesia may occur with therapeutic doses, with the risk increasing at higher dosages.

**Paradoxical reactions:** In the event of these reactions, discontinuation of the drug should be considered.

**Altered elimination of midazolam:** Midazolam elimination time may also be extended in patients with liver dysfunction and low cardiac output and in neonates.

**Sleep apnea:** Extreme caution required in patients with sleep apnea syndrome and patients should be regularly monitored.

**Preterm infants and neonates:** Due to an increased risk of apnea, extreme caution is required when sedating preterm and former preterm non-intubated children.

**Rapid injection should be avoided in neonates:** Adverse hemodynamic reactions have been reported in children with cardiovascular instability; rapid intravenous administration should be avoided in these patients.

**Concomitant use of alcohol / CNS depressants:** Concomitant use may increase the clinical effect of midazolam, causing profound sedation that could result in coma or death, or clinically relevant respiratory depression.

**Risk from concomitant use of opioids:** Concomitant use of Midazolam and opioids may result in sedation, respiratory depression, coma and death. If a decision is made to prescribe Midazolam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

**Medical history of alcohol or drug abuse:** Use of midazolam as well as other benzodiazepines should be avoided for patients with history of alcohol or drug abuse.

**Discharging criteria:** Patients may be discharged from hospital accompanied by an attendant.

**Sodium content:** This medicinal product contains 3.158mg sodium per mL of solution, equivalent to 0.16% of the WHO recommended maximum daily intake of 2g sodium for an adult.

#### **Interaction with Other Medicinal Products and other forms of Interaction**

**Pharmacokinetic interactions:** Midazolam is metabolized by CYP3A4 and CYP3A5. The effect of midazolam may be weaker and last shorter when co-administered with a CYP3A inducer and a higher dose may be required.

**Drugs that inhibit CYP3A:** Azole antifungals: If parenteral midazolam is co-administered with ketoconazole, it should be done in an intensive care unit

Voriconazole increased the plasma concentrations of intravenously administered midazolam 3.4-fold while the elimination half-life also increased approximately 3-fold. Both fluconazole and itraconazole increased the plasma concentrations of intravenously administered midazolam 2.3-fold, associated with terminal half-life extension 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.

**Midazolam ampoules are not indicated for oral administration**

**Macrolide antibiotics:** Erythromycin & clarithromycin increased the plasma concentrations of intravenously administered midazolam approximately 1.5-2.0, associated with terminal half-life extension of midazolam 1.5-2.0-fold

Intravenous midazolam was also changed by intravenous propofol (AUC and half-life increased by 1.6- fold).

**HIV protease inhibitors:** Saquinavir and other HIV (human immunodeficiency virus) including ritonavir, lopinavir may cause a significant increase in the concentration of midazolam. If parenteral midazolam is co-administered, the treatment setting should follow in the above setting for azole antifungals. Bicopovir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of IV administration and prolonged its elimination half-life 4-fold. Roxithromycin: Although there is no data available. The effect of roxithromycin on intravenously administered midazolam may be minor.

**Calcium-channel blockers:** Administration of a single dose of diltiazem given to patients undergoing coronary artery bypass grafting increased the plasma concentration of IV administered midazolam by approximately 25% and the terminal half-life was extended by 43%.

**Various medicines/herbal substances:** Co-administration of atorvastatin increased the plasma concentrations of intravenously administered midazolam.

Intravenous fentanyl is a weak inhibitor of midazolam elimination: AUC and half-life of IV midazolam were increased by 1.5-fold in the presence of fentanyl.  
For a number of drugs or herbal medicines (everolimus, cyclosporine, simvastatin, propiverine) a weak interaction with midazolam's elimination was observed with concomitant changes.

**Drugs that induce CYP3A:** Rifampicin decreased the plasma concentrations of intravenously administered midazolam by 60% after administration of rifampicin 600mg/day for 7 days.

Ticagrelor has only small effects on intravenously administered Midatone or enzalutamide resulted in a profound and long-lasting decrease of midazolam levels in cancer patients. Clozaban and efavirenz are weak inducers of midazolam metabolism and reduce the AUC of the parent compound by approximately 30%.

**Herbal substances and food:** St John's Wort decreased plasma concentrations of midazolam by about 20-40 % associated with a decrease in terminal half-life of about 15 - 17%.

**Acute protein displacement:** Clinical relevance of such an interaction is not known.

**Pharmacodynamic interactions:** Co-administration of midazolam with other sedative / hypnotic agents and CNS depressants is likely to result in enhanced sedation and cardiorespiratory depression, coma and death (because of additive CNS depressant effect). These include opiates derivatives, analgesics, antitussives or substitutive treatments, antipsychotics. Other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate, sedative antidepressants, H1-antihistamines, and centrally acting antihypertensive drugs.

#### **Fertility, Pregnancy And Lactation**

**Pregnancy:** Midazolam should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean section. The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

**Breast-feeding:** Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of midazolam.

**Fertility:** No data on fertility are available.

#### **Effects on the ability to drive and use machines**

Midazolam has a major influence on the ability to drive and use machines. Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines. The physician should decide when these activities may be resumed.

#### **Undesirable effects**

Frequency categories according to the MedDRA convention are as follows:  
very common:  $\geq 1/10$ ; common:  $\geq 1/100$  to  $<1/10$ ; uncommon:  $\geq 1/1,000$  to  $<1/100$ ; rare:  $\geq 1/10,000$  to  $<1/1,000$ ; very rare:  $<1/10,000$ ; not known: cannot be estimated from the available data. The following undesirable effects have been reported.

**Immune system disorder:** Hypersensitivity, angioedema, anaphylactic shock  
**Psychiatric disorder:** Confusional state, disorientation, emotional and mood disturbances, changes in libido, paradoxical reactions including restlessness, agitation, irritability, nervousness, hostility, anger, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement, physical drug dependence and withdrawal syndrome, abuse  
**Nervous system disorder:** Drug withdrawal Convulsions, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, sedation (prolonged and post-operative), alertness decreased, somnolence, headache, dizziness, ataxia, anterograde amnesia, the duration of which is directly related to the administered dose, convulsions have been reported in premature infants and neonates.

**Cardiac & vascular disorder:** Cardiac arrest, bradycardia, kounis syndrome, hypotension, vasodilatation, thrombophlebitis, thrombosis.

**Respiratory disorders:** Respiratory depression, apnoea, respiratory arrest, dyspnea, laryngospasm.

**GI disorders:** Hiccups, nausea, vomiting, constipation, dry mouth.

**Skin and subcutaneous disorders:** Skin rash, urticaria, pruritus.

**General disorders and administration site reactions:** Fatigue, injection site erythema, injection site injury, poisoning and procedural complications: Pain, falls, fractures

**Social circumstances:** Assault  
The frequency of above undesirable effects is not known.

#### **Overdose**

A patient's vital signs should be monitored and supportive treatment started according to the patient's clinical status. In particular, patients may require symptomatic treatment for cardiorespiratory or central nervous system effects. If activated charcoal is used away protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be

considered, however not as a routine measure.

If central nervous system depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants).

#### PHARMACOLOGICAL PROPERTIES

**Pharmacotherapeutic group:** Hypnotics and sedatives, benzodiazepine derivatives, ATC code: N05C08.

Midazolam is a derivative of the imidazobenzodiazepine group.

**Mechanism of action:** The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

#### Pharmacodynamic properties

The pharmacological effect of midazolam is characterised by rapid onset and short duration of action of a rapid metabolic transformation given or by intravenous administration, anterograde amnesia of short duration occurs.

#### Pharmacokinetic properties

**Absorption after intramuscular & rectal administration:** Midazolam is rapidly and fully absorbed from the muscle tissue. The peak plasma concentration is reached within 30 minutes. The absolute bioavailability after intramuscular administration is over 90%. Midazolam is rapidly absorbed after rectal administration. The peak plasma concentration is reached within approximately 30 minutes. The absolute bioavailability is approximately 50%.

**Distribution:** After intravenous administration of midazolam one or two distinct distribution phases form on the plasma concentration time curve. The steady-state distribution volume is 0.7 to 1.2L/kg. 96 - 98% of midazolam binds to plasma proteins, mostly albumin. Midazolam passes slowly and in small quantities into the cerebrospinal fluid. It has been shown in humans that midazolam crosses the placental barrier slowly and enters foetal circulation. Midazolam has been found in human breast milk in small quantities. Midazolam is not a substrate for drug transporter.

**Biotransformation:** Midazolam is almost entirely eliminated by biotransformation. It has been estimated that the fraction of the dose metabolised through the liver is 30 - 60%. The main metabolite in plasma and urine is 1'-hydroxymidazolam. 1'-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

**Elimination:** Midazolam is mostly eliminated through the kidneys (60 - 80% of the dose injected) and is recovered as glucuronide-conjugated 1'-hydroxymidazolam. Less than 1% of the dose is recovered as an unmodified substance in the urine. The elimination half-life of 1'-hydroxy-midazolam is under one hour. The elimination kinetics of midazolam when given by intravenous infusion are similar to that of bolus injection. Repeated administration of midazolam does not induce drug-metabolising enzymes.

#### Pharmacokinetics in special populations

**Elderly:** In adults over 60 years of age, the elimination half-life may be prolonged up to four times. **Paediatric population:** While the absorption rate of rectally administered midazolam is similar in children and adults, the bioavailability is lower in children (5 - 18%).

**Neonates:** In neonates the elimination half-life is on average 6-12 hours. Neonates with apnoea-related hepatic and renal impairment are at risk of generating unexpectedly high serum midazolam concentration due to a significantly decreased and variable clearance.

**Obese:** The mean half-life is greater in obese than in non-obese patients (5.9 vs 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight.

**Patients with hepatic impairment:** The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared to those in healthy volunteers.

**Patients with renal impairment:** The pharmacologically mildly active major midazolam metabolite, 1'-hydroxymidazolam glucuronide accumulates in patients with severe renal impairment. This accumulation produces a prolonged sedation. It should therefore be administered carefully and titrated to the desired effect.

**Critically ill patients:** The elimination half-life of midazolam is prolonged up to six times in the critically ill patients.

#### PHARMACEUTICAL PROPERTIES

##### Incompatibilities

Midazolam solution for injection/infusion must not be diluted with Dextran 60 solution in glucose.

Midazolam solution for injection/infusion must not be mixed with alkaline solutions for injection.

Midazolam precipitates in solutions containing hydrogen carbonate.

**Shelf life:** 2 years

##### Special precautions for storage

Protect from heat & sunlight, store between 15°C - 30°C. Avoid freezing.

The expiration date refers to the product correctly stored at the required condition. Keep out of the reach of children.

Do not use if injection is leaking, solution is cloudy or contains undissolved particles.

**To be sold on the prescription of a registered medical practitioner only.**

##### Nature and content of container / Presentation

5 Ampoules

##### REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER

###### Head office:

Bosch Pharmaceuticals (Pvt.) Ltd.,  
8, Modern Society, Tipu Sultan Road, Karachi-Pakistan.

###### Manufacturer:

Bosch Pharmaceuticals (Pvt.) Ltd.  
221-223, Sector 23, Korangi Industrial Area, Karachi-Pakistan.

##### REGISTRATION / MARKETING AUTHORIZATION NUMBER: 053441

##### DATE FROM WHICH MARKETING IS AUTHORIZED/RENEWAL OF AUTHORIZATION:

23-12-2008 / 22-12-2023

##### DATE OF REVISION OR PREPARATION OF THE TEXT:

24-04-2024

ہدایات:

دستوب اور گری سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ورنہ حرارت کے درمیان رکھیں۔

نہند ہونے سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

احتیاط: انجکشن لیک ہونے، دھندلا ہونے یا اس میں کوئی فیبریل پزیر ہے

نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔

صرف مستعد اکثر کے لئے پروفونٹ کے لئے۔



Manufactured by:

**Bosch PHARMACEUTICALS (PVT.) LTD.**

221-223, Sector 23, Korangi Industrial Area,  
Karachi - Pakistan



LAB 168  
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