# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

MIDOLAM 5 INJECTION (MIDAZOLAM INJECTION BP 5 MG/5ML)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:
Midazolam BP ..... 1mg

Excipient with Known Effect:

Benzyl Alcohol BP ..... % v/v

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for Injection.

Clear, colorless sterile solution.

## 4. CLINICAL PARTICULARS

### 3.1 Therapeutic indications

Midazolam is a short-acting sleep-inducing drug that is indicated:

In adults
• Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia.
• Anaesthesia − Premedication before induction of anaesthesia. − Induction of anaesthesia. − As an induction agent or as a sedative component in combined anaesthesia. • Sedation in intensive care units

In children
• Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia.
• Anaesthesia − Premedication before induction of anaesthesia
• Sedation in intensive care units

### 3.2 Posology and method of administration

**Posology**
**Standard Dosage**
Midazolam is a potent sedative agent that requires titration and slow administration. Titration is strongly recommended to safely obtain the desired level of sedation according to the clinical need, physical status, age and concomitant medication.
In adults over 60 years, debilitated or chronically ill patients and paediatric patients, dose should be determined with caution and risk factors related to each patient should be taken into account. Standard dosages are provided in in Table 1 and additional details are provided in the text following the table.

Table 1: Standard dosages of midazolam

| Indication | Adults < 60 y | Adults 60 y / debilitated or chronically ill | Children |
|---|---|---|---|
| Conscious sedation | ***i.v.***<br>Initial dose: 2 - 2.5mg<br>Titration doses: 1mg<br>Total dose: 3.5 - 7.5mg | ***i.v***<br>Initial dose: 0.5 - 1mg<br>Titration doses: 0.5 - 1mg<br>Total dose: < 3.5mg | ***i.v. in patients 6 months - 5 years***<br>Initial dose: 0.05 - 0.1mg/kg<br>Total dose: < 6mg<br>***i.v. in patients 6-12 years***<br>Initial dose: 0.025 - 0.05mg/kg<br>Total dose: < 10mg<br>***rectal > 6 months***<br>0.3 - 0.5mg/kg<br>***i.m. 1 - 15 years***<br>0.05 - 0.15mg/kg |
| Anaesthesia premedication | ***i.v.***<br>1-2mg repeated<br>***i.m.***<br>0.07 - 0.1mg/kg | ***i.v.***<br>Initial dosage: 0.5mg<br>Slow uptitration as needed<br>***i.m.***<br>0.025 - 0.05mg/kg | ***rectal > 6 months***<br>0.3 - 0.5mg/kg<br>***i.m. 1 - 15 years***<br>0.08 - 0.2mg/kg |
| Anaesthesia induction | ***i.v.***<br>0.15 - 0.2mg/kg (0.3 - 0.35 without premedication) | ***i.v.***<br>0.05 - 0.15mg/kg (0.15 -0.3 without premedication) | |
| Sedative component in combined anaesthesia | ***i.v.***<br>intermittent doses of 0.03 - 0.1mg/kg or continuous infusion of 0.03 -0.1mg/kg/h | ***i.v.***<br>lower doses than recommended for adults < 60 years | |

| | | |
|---|---|---|
| Sedation in ICU | ***i.v.***<br><br>Loading dose: 0.03 - 0.3mg/kg in increments of 1 - 2.5mg<br><br>Maintenance dose: 0.03 - 0.2mg/kg/h | ***i.v. in neonates ≤ 32 weeks gestational age***<br><br>0.03mg/kg/h<br><br>***i.v in neonates > 32 weeks and children up to 6 months***<br><br>0.06mg/kg/h<br><br>***i.v. in patients > 6 months of age***<br><br>Loading dose: 0.05 - 0.2mg/kg<br><br>Maintenance dose: 0.06 - 0.12mg/kg/h |

Conscious sedation dosage For conscious sedation prior to diagnostic or surgical intervention, midazolam is administered i.v. The dose must be individualised and titrated and should not be administered by rapid or single bolus injection. The onset of sedation may vary individually depending on the physical status of the patient and the detailed circumstances of dosing (e.g. speed of administration, amount of dose). If necessary, subsequent doses may be administered according to the individual need. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes.

Adults
The i.v. injection of midazolam should be given slowly at a rate of approximately 1mg in 30 seconds.
In adults below the age of 60 the initial dose is 2 to 2.5mg given 5 to 10 minutes before the beginning of the procedure. Further doses of 1mg may be given as necessary. Mean total doses have been found to range from 3.5 to 7.5mg. A total dose greater than 5mg is usually not necessary.
In adults over 60 years of age, debilitated or chronically ill patients, the initial dose must be reduced to 0.5-1.0 mg and given 5-10 minutes before the beginning of the procedure. Further doses of 0.5 to 1mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional midazolam should be titrated very slowly and carefully. A total dose greater than 3.5mg is usually not necessary.

Children
I.V. administration: midazolam should be titrated slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. One must wait an additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. Infants and young children less than 5 years of age may require substantially higher doses (mg/kg) than older children and adolescents.
• Paediatric patients less than 6 months of age: paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation. For this reason, the use in conscious sedation in children less than 6 months of age is not recommended.

• Paediatric patients 6 months to 5 years of age: initial dose 0.05 to 0.1mg/kg. A

total dose up to 0.6mg/kg may be necessary to reach the desired endpoint, but the total dose should not exceed 6mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
• Paediatric patients 6 to 12 years of age: initial dose 0.025 to 0.05mg/kg. A total dose of up to 0.4mg/kg to a maximum of 10mg may be necessary. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
• Paediatric patients 12 to 16 years of age: should be dosed as adults.

Rectal administration:
the total dose of midazolam usually ranges from 0.3 to 0.5mg/kg.

Rectal administration of the solution is performed by means of a plastic applicator fixed on the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10ml. Total dose should be administered at once and repeated rectal administration avoided. The use in children less than 6 months of age is not recommended, as available data in this population are limited.

I.M. administration:
the doses used range between 0.05 and 0.15mg/kg. A total dose greater than 10.0mg is usually not necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as i.m. injection is painful.
In children less than 15kg of body weight, midazolam solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

Anaesthesia Dosage

Premedication
Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and pre-operative impairment of memory. Midazolam can also be administered in combination with anticholinergics. For this indication midazolam should be administered i.v. or i.m., deep into a large muscle mass 20 to 60 minutes before induction of anaesthesia, or preferably via the rectal route in children (see below). Close and continuous monitoring of the patient after administration of premedication is mandatory as inter-individual sensitivity varies and symptoms of overdose may occur.

Adults
For pre-operative sedation and to impair memory of pre-operative events, the recommended dose for adults of ASA Physical Status I & II and below 60 years is 1-2 mg i.v. repeated as needed, 0.07 to 0.1mg/kg administered i.m. The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, debilitated, or chronically ill patients. A dose of 0.025 to 0.05mg/kg administered i.m. is recommended. In case of concomitant administration of narcotics the midazolam dose should be reduced. The usual dose is 2 to 3mg. Paediatric population Neonates and children up to 6 months The use in children less than 6 months of age is not recommended as available data are limited.

Children over 6 months of age
Rectal administration:
The total dose of midazolam, usually ranging from 0.3 to 0.5mg/kg should be administered 15 to 30 minutes before induction of anaesthesia. Rectal administration of the solution is performed by means of a plastic applicator fixed on

the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10ml.

I.M. administration:
As i.m. injection is painful, this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08 to 0.2mg/kg of midazolam administered i.m. has been shown to be effective and safe. In children between ages 1 and 15 years, proportionally higher doses are required than in adults in relation to body-weight. The use in children less than 6 months of age is not recommended as available data are limited. In children less than 15kg of body weight, midazolam solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

Induction
Adults
If midazolam is used for induction of anaesthesia before other anaesthetic agents have been administered, the individual response is variable. The dose should be titrated to the desired effect according to the patient's age and clinical status. When midazolam is used before or in combination with other i.v. or inhalation agents for induction of anaesthesia, the initial dose of each agent should be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents. The desired level of anaesthesia is reached by stepwise titration. The i.v. induction dose of midazolam should be given slowly in increments. Each increment of not more than 5mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.

• In premedicated adults below the age of 60 years, an i.v. dose of 0.15 to 0.2mg/kg will usually suffice.
• In non-premedicated adults below the age of 60 the dose may be higher (0.3 to 0.35mg/kg i.v.). If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with inhalational anaesthetics. In resistant cases, a total dose of up to 0.6mg/kg may be used for induction, but such larger doses may prolong recovery.
• In premedicated adults over 60 years of age, debilitated or chronically ill patients, the dose should significantly be reduced, e.g., down to 0.05 to 0.15mg/kg administered i.v. over 20 -30 seconds and allowing 2 minutes for effect.
• Non-premedicated adults over 60 years of age usually require more midazolam for induction; an initial dose of 0.15 to 0.3mg/kg is recommended. Non-premedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.15 to 0.25mg/kg will usually suffice. Sedative component in combined anaesthesia Adults Midazolam can be given as a sedative component in combined anaesthesia by either further intermittent small i.v. doses (range between 0.03 and 0.1mg/kg) or continuous infusion of i.v. midazolam (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 or chronically ill patients, lower maintenance doses will be required.

Sedation in intensive care units
The desired level of sedation is reached by stepwise titration of midazolam followed by either continuous infusion or intermittent bolus, according to the clinical need, physical status, age and concomitant medication (see section 4.5).

Adults
I.V. loading dose: 0.03 to 0.3mg/kg should be given slowly in increments. Each increment of 1 to 2.5mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments. In hypovolaemic, vasoconstricted, or hypothermic patients the loading dose should be reduced or omitted. When midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of midazolam can be safely titrated on top of any sedation caused by the analgesic.

I.V. maintenance dose: doses can range from 0.03 to 0.2mg/kg/h. In hypovolaemic, vasoconstricted, or hypothermic patients the maintenance dose should be reduced. The level of sedation should be assessed regularly. With long-term sedation, tolerance may develop and the dose may have to be increased.

Neonates and children up to 6 months of age Midazolam should be given as a continuous i.v. infusion, starting at 0.03mg/kg/h (0.5µg/kg/min) in neonates with a gestational age ≤ 32 weeks or 0.06mg/kg/h (1µg/kg/min) in neonates with a gestational age > 32 weeks and children up to 6 months. Intravenous loading doses is not recommended in premature infants, neonates and children up to 6 months, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. Careful monitoring of respiratory rate and oxygen saturation is required.

Children over 6 months of age
In intubated and ventilated paediatric patients, a loading dose of 0.05 to 0.2mg/kg i.v. should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. Midazolam should not be administered as a rapid intravenous dose. The loading dose is followed by a continuous i.v. infusion at 0.06 to 0.12mg/kg/h (1 to 2µg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental i.v. doses of midazolam can be administered to increase or maintain the desired effect. When initiating an infusion with midazolam in haemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for haemodynamic instability, e.g., hypotension. These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation. In premature infants, neonates and children less than 15 kg of body weight, midazolam solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

Use in Special Populations
Renal Impairment
In patients with severe renal impairment (creatinine clearance below 30 ml/min) midazolam may be accompanied by more pronounced and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression. Midazolam should therefore be dosed carefully in this patient population and titrated for the desired effect (see section 4.4). In patients with renal failure (creatinine clearance < 10 ml/min) the pharmacokinetics of unbound midazolam following a single i.v. dose is similar to that reported in healthy volunteers. However, after prolonged infusion in intensive care unit (ICU) patients, the mean

duration of the sedative effect in the renal failure population was considerably increased most likely due to accumulation of α-hydroxymidazolam glucuronide (see sections 4.4 and 5.2).

Hepatic Impairment
Hepatic impairment reduces the clearance of i.v. midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects in patients with hepatic impairment may be stronger and prolonged. The required dose of midazolam may have to be reduced and proper monitoring of vital signs should be established (See section 4.4).

Paediatric population See above and section 4.4.

Method of administration
For i.v., i.m. and rectal administration.

## 4.3 Contraindications

• Hypersensitivity to the active substance, benzodiazepines or to any excipient.
• Use of this drug for conscious sedation in patients with severe respiratory failure, or acute respiratory depression
•

## 4.4 Special warnings and precautions for use

Midazolam should be administered only by experienced physicians in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.
Severe cardiorespiratory adverse events have been reported. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered.
Special caution is required for the indication of conscious sedation in patients with impaired respiratory function.

**Paediatric population**
In this population, midazolam is indicated for sedation in ICU only. Paediatric 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 respiratory rate and oxygen saturation monitoring are essential.
When midazolam is used for premedication, adequate observation of the patient after administration is mandatory as inter-individual sensitivity varies and symptoms of overdose may occur.
Special caution should be exercised when administering midazolam to high-risk patients:
− adults over 60 years of age
− chronically ill or debilitated patients, e.g.
− patients with chronic respiratory insufficiency
− patients with chronic renal failure, impaired hepatic function or with impaired cardiac function
− pediatric patients specially those with cardiovascular instability.

These high-risk patients require lower dosages and should be continuously monitored for early signs of alterations of vital functions.
As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering midazolam to a patient with myasthenia gravis.

Tolerance
Some loss of efficacy has been reported when midazolam was used as long-term sedation in intensive care units (ICU).

Dependence
When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on midazolam may develop. The risk of dependence increases with dose and duration of treatment it is also greater in patients with a medical history of alcohol and/or drug abuse.

Withdrawal symptoms
During prolonged treatment with midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

Amnesia
Midazolam causes anterograde amnesia (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant.

Paradoxical reactions
Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported to occur with midazolam. These reactions may occur with high doses and/or when the injection is given rapidly. The highest incidence to such reactions has been reported among children and the elderly.

Altered elimination of midazolam
Midazolam elimination may be altered in patients receiving compounds that inhibit or induce CYP3A4 and the dose of midazolam may need to be adjusted accordingly. Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates.

Preterm infants and neonates
Due to an increased risk of apnoea, extreme caution is advised when sedating preterm and former preterm non intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required.
Rapid injection should be avoided in the neonatal population.
Neonates have reduced and/or immature organ function and are also

vulnerable to profound and/or prolonged respiratory effects of midazolam.
Adverse haemodynamic events have been reported in paediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.

Concomitant use of alcohol / CNS depressants
The concomitant use of midazolam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam possibly including severe sedation 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. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as midazolam with opioids should be reserved for patients for whom alternative treatment options are not possible. 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.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms.

Medical history of alcohol or drug abuse
Midazolam as other benzodiazepines should be avoided in patients with a medical history of alcohol or drug abuse.

Discharging criteria
After receiving midazolam, patients should be discharged from hospital or consulting room only when recommended by treating physician and if accompanied by an attendant. It is recommended that the patient is accompanied when returning home after discharge.
This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium- free'

## 4.5 Interaction with other medicinal products and other forms of interaction Pharmacokinetic Interactions

Midazolam is metabolised by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly.
Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to i.v midazolam, in particular since CYP3A4 also exists in the upper gastro-intestinal tract. This is because for the oral route both systemic clearance and availability will be altered while for the parenteral route only the change in the systemic clearance becomes effective. After a single dose of i.v midazolam the maximal clinical effect of CYP3A4 inhibition will be minor, but the duration of effect may be prolonged. However after prolonged dosing midazolam, both the magnitude and duration of effect will be increased in the presence of CYP3A4 inhibition.
There are no available studies on CYP3A4 modulation on the pharmacokinetics of midazolam after rectal and intramuscular

administration. It is expected that these interactions will be less pronounced for the rectal than for the oral route because the gastro-intestinal tract is by-passed whereas after i.m administration the effects of CYP3A4 modulation should not substantially differ from those seen with i.v midazolam.
It is therefore recommended to carefully monitor the clinical effects and vital signs during the use of midazolam, taking into account that they may be stronger and longer after co-administration of a CYP3A4 inhibitor, be it given only once. Notably, administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors,
e.g. during intensive care, may result in long-lasting hypnotic effects, delayed recovery and respiratory depression, thus requiring dose adjustments.
With respect to induction, it should be considered that the inducing process needs several days to reach its maximum effect and also several days to dissipate. Contrary to a treatment of several days with an inducer, a short-term treatment is expected to result in less apparent DDI with midazolam. However, for strong inducers a relevant induction even after short-term treatment cannot be excluded.
Midazolam is not known to change the pharmacokinetics of other drugs.

**Drugs that inhibit CYP3A4**
**Azole antifungals**
Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold. If parenteral midazolam is coadministered with the strong CYP3A4 inhibitor ketoconazole, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single i.v. dose of midazolam is administered.
4.5.A Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.
4.5.B Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 – 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.
4.5.C Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.
4.5.D It should be kept in mind that if midazolam is given orally, its exposure will drastically be higher than the above-mentioned ones, notably with ketoconazole, itraconazole, voriconazole.
Midazolam ampoules are not indicated for oral administration.

**Macrolide antibiotics**
4.6.E Erythromycin increases the plasma concentrations of intravenous midazolam by about 1.6 – 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 – 1.8-fold.
4.5.E Clarithromycin increased the plasma concentrations of midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 – 2-fold.

**Additional information from oral midazolam**
4.5.F Roxithromycin: There is no information on roxithromycin with i.v midazolam but the mild effect on the terminal half-life of oral midazolam increase of 30%, indicates that the effects on i.v midazolam may be minor.
4.5.G Quinupristin/ dalfopristin and telithomycin may increase plasma

concentration of midazolam

**HIV Protease inhibitors**

4.5.H Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon coadministration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral midazolam is co-administered with HIV protease inhibitors, treatment setting should follow the description in the above section for azole antifungals, ketoconazole.

**Additional information from oral midazolam**

Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore protease inhibitors should not be co-administered with orally administered midazolam

**Calcium-channel blockers**

4.5.I Diltiazem: A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

**Additional information from oral midazolam**

4.5.J Verapamil/diltiazem increased the plasma concentrations of oral midazolam by 3- and 4-fold, respectively. The terminal half-life of midazolam was increased by 41% and 49% respectively

**Various drugs/Herbs**

4.5.K Atorvastatin showed a 1.4-fold increase in plasma concentrations of IV midazolam compared to control group.

**Additional information from oral midazolam**

4.5.L Nefazodone increased the plasma concentrations of oral midazolam by 4.6-fold with an increase of its terminal half-life by 1.6-fold.

4.5.M Aprepitant dose dependently increased the plasma concentrations of oral midazolam by 3.3-fold after 80 mg/day associated with an increase in terminal half-life by ca. 2-fold. therefore increasing the risk of prolonged sedation.

**Drugs that induce CYP3A4**

4.5.N Rifampicin decreased the plasma concentrations of intravenous midazolam by about 60% after 7 days of rifampicin 600mg o.d. The terminal half-life decreased by about 50-60%.

**Additional information from oral midazolam**

4.5.O Rifampicin decreased the plasma concentrations of oral midazolam by 96% in healthy subjects and its psychomotor effects were almost totally lost.

4.5.P Carbamazepine / phenytoin: Repeat dosages of carbamezepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 90% and a shortening of the terminal half-life by 60%.

4.5.Q Efavirenz: The 5-fold increase in the ratio of the CYP3A4 generated metabolite α-hydroxymidazolam to midazolam confirms its CYP3A4-inducing effect.

**Herbs and food**
4.5.R 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%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

**Pharmacodynamic Drug-Drug Interactions (DDI) Sedative and hypnotics**
The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.
Examples include opiate derivatives (be they used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non-recent H1-antihistamines, sodiumoxybate, and centrally acting antihypertensive drugs.

**Opioids**
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as midazolam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited.

**Alcohol**
Alcohol may markedly enhance the sedative effect of midazolam, so concurrent intake should be strongly avoided.

**Muscle relaxants**
Increased sedative effect with baclofen and tizanidine.

**Inhalation anaesthetics**
Midazolam decreasesthe minimumalveolar concentration (MAC) of inhalational anaesthetics.

**Antihypertensives, vasodilators & diuretics:**
Enhanced hypotensive effect with ACE-inhibitors, alpha-blockers, angiotensin-II receptor antagonists, calcium channel blockers, adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics.

**Anti-epileptics**
Carbamazepine reduces the plasma concentrations of midazolam. Benzodiazepines may alter ie. Either increase or decrease the plasma concentrations of phenytoin.

**Others**
Nilotinib and Nabilone may increase plasma concentration of midazolam.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**
Midazolam should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean.
Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but

foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.
The administration of high doses of midazolam in the last trimester of pregnancy, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or foetal adverse effects (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).
Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the post-natal period.
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.

## 4.7 Effects on ability to drive and use machines
Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines.
Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.

Where midazolam is used concurrently with other central nervous system depressants (e.g. potent analgesics) recovery may be prolonged. Patients should therefore be assessed carefully before being allowed to go home or resume normal activities.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

4.7.A The medicine is likely to affect your ability to drive

| SOC | **Frequency** | **Adverse event** |
|---|---|---|
| Immune system disorders | Not known | Hypersensitivity, anaphylactic shock, angioedema |
| Psychiatric disorders | Not known | Confusional state, euphoric mood, hallucination<br>Agitation*, hostility*, rage*, hyperactivity, aggressiveness*, excitement*, Assault*<br>Physical drug dependence and withdrawal syndrome, Abuse |
| Nervous system disorders | Not known | Sedation (prolonged and postoperative), alertness decreased, somnolence, headache, dizziness, ataxia, anterograde amnesia**, the duration of which is directly related to the administered dose Convulsions local have been reported in premature infants and neonates<br>Involuntary movements (including tonic/clonic movements and muscle tremor)*, psychomotor hyperactivity*<br>Drug withdrawal convulsions |
| Cardiac disorders | Not known | Cardiac arrest, bradycardia, cardiovascular disorder, Hypotension, vasodilation |
| Respiratory, thoracic and mediastinal disorders | Not known | Respiratory depression, apnoea, respiratory arrest, dyspnea, laryngospasm, hiccups, bronchospasm |
| Gastrointestinal disorders | Not known | Nausea, vomiting, constipation, dry mouth |
| Skin and subcutaneous tissue disorders | Not known | Rash, urticaria, pruritus, skin reactions, |
| General disorders and administration site conditions | Not known | Fatigue, injection site erythema, injection site pain, thrombophlebitis, thrombosis |
| Injury, poisoning and procedural complications | Not known | Falls, fractures*** |

4.7.B Do not drive until you know how the medicine affects you

4.7.C It is an offence to drive while under the influence of this medicine

4.7.D However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and

in the information provided with the medicine and
o It was not affecting your ability to drive safely

**4.8 Undesirable effects**

The following undesirable effects have been reported to occur when midazolam is injected:

Frequency categories are as follows:
Very common: ≥1/10;
Common ≥1/100 to <1/10;
Uncommon ≥1/1,000 to <1/100 Rare (≥1/10,000 to <1/1,000) Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

* Such paradoxical drug reactions have been reported particularly among children and the elderly.

** Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

*** The risk of falls and fractures is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Dependence: Use of midazolam even in therapeutic doses may lead to the development of physical dependence. After prolonged i.v administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions. Cases of abuse have been reported.

Severe cardio-respiratory adverse events have occurred. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered.

*Reporting of adverse Effects*

Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org

**4.9 Overdose Symptoms**

Like other benzodiazepines, midazolam commonly causes drowsiness, ataxia, dysarthria and nystagmus. Overdose of midazolam is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and in rare cases to coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

**Management** Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If taken orally further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated

charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.
If CNS 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). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug.
The correct information for using Flumazenil can also be obtained from the UK National Poison Information Service by calling on the following telephone number.
Tel: 0844-892-0111 (directs caller to relevant local centre.)

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Hypnotics and sedatives (benzodiazepine derivatives), ATC code: N05CD08.
Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water.
The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of midazolam to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.
Mechanism of action
The pharmacological action of midazolam is characterised by short duration because of rapid metabolic transformation. Midazolam has a sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect.
After i.m. or i.v. administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).

### 5.2 Pharmacokinetic properties Absorption after i.m. injection
Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after i.m. injection is over 90%.

**Distribution**
When midazolam is injected i.v., the plasma concentration-time curve shows one or two distinct phases of distribution. The volume of distribution at steady state is 0.7 - 1.2 l/kg. 96 - 98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

**Biotransformation**
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30 - 60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxymidazolam. Plasma concentrations of

alpha-hydroxymidazolam are 12% of those of the parent compound. Alpha-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

**Elimination**
In healthy volunteers, the elimination half-life of midazolam is between 1.5 - 2.5 hours. Plasma clearance is in the range of 300 - 500ml/min. Midazolam is excreted mainly by renal route (60 - 80% of the injected dose) and recovered as glucuroconjugated alpha-hydroxymidazolam. Less than 1% of the dose is recovered in urine as unchanged drug. The elimination half-life of alpha-hydroxy-midazolam is shorter than 1 hour. When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection.

**Pharmacokinetics in special populations**
**Elderly**
In adults over 60 years of age, the elimination half-life may be prolonged up to four times.

**Children**
The elimination half-life after i.v. administration is shorter in children 3 - 10 years old (1 - 1.5 hours) as compared with that in adults. The difference is consistent with an increased metabolic clearance in children.

**Neonates**
In neonates the elimination half-life is on average 6 - 12 hours, probably due to liver immaturity and the clearance is reduced.

**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. The clearance is not significantly different in obese and non-obese patients.

**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 elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.
**Critically ill patients**
The elimination half-life of midazolam is prolonged up to six times in the critically ill.
**Patients with cardiac insufficiency**
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects.
**5.3 Preclinical safety data**
There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
Hydrochloric acid
Sodium hydroxide
Water for injections

### 6.2 Incompatibilities

Midazolam Injection is stable, both physically and chemically, for up to 1 hour at room temperature when mixed in the same syringe with Atropine Sulphate Injection BP or HyoscineHydrobromide Injection 0.4mg/ml. There is no evidence of the adsorption of midazolam onto the plastic of infusion apparatus or syringes.
Midazolam Injection when mixed with 500ml infusion fluids containing dextrose 4% with sodium chloride 0.18%, dextrose 5% or sodium chloride 0.9% is chemically and physically stable for up to 24 hours at 25°C and up to 72 hours at 2 to 8°C. However, for pharmaceutical microbiological reasons, the product should be used immediately after dilution. When aseptically prepared, the diluted solution may be kept for not more than 24 hours if stored under refrigeration at a temperature between 2-8°C.
Admixture with Hartmann's solution is not recommended, as the potency of midazolam decreases.

### 6.3 Shelf life

Unopened: 2 years.

After reconstitution: not applicable

After first opening: not applicable

### 6.4 Special precautions for storage

Protect from light.

Store below 30°C.

### 6.5 Nature and contents of container

5 ml glass amber vial

### 6.6 Special precautions for disposal and other handling

If only part used, discard the remaining solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESS

Krishna Chemists Limited,
Industrial Area, Lusaka Road,3 Rd Floor,
Metrix Hardware, Nairobi
Kenya

**Manufactured By:**
Armein Pharmaceuticals Private Ltd,
Survey # 494, Dharmaj - Khambhat Road,
At Bamanva Ta. Khambhat , Gujarat-388580
India

## 8. MARKETING AUTHORIZATION NUMBER

H2025/CTD11429/23999

## 9. DATE OF FIRST REGISTRATION/ RENEWAL OF THE REGISTRATION

27/08/2025

## 10. DATE OF REVISION 0F THE TEXT

27/08/2025