PACKAGE LEAFLET

Please read carefully!

Midazolam-hameln Injection

Preparations:

Midazolam-hameln 1 mg/ml Injection; 5 ml

Midazolam-hameln 5 mg/ml Injection; 1 ml

Midazolam-hameln 5 mg/ml Injection; 3 ml

Active ingredient: midazolam hydrochloride

Midazolam is a sedative drug belonging to the group called "benzodiazepines".

Midazolam-hameln 5 mg/ml Injection; 1 & 3 ml
Composition:

Active ingredient:

1 ml contains midazolam hydrochloride	5.56 mg
equivalent to midazolam	5.00 mg

Each 1 ml and 3 ml ampoule contains 5 mg and 15 mg midazolam, respectively.

Midazolam 1 mg/ml Injection; 5 ml
Composition:

Active ingredient

5 ml contains midazolam hydrochloride	5.56 mg
equivalent to midazolam	5.00 mg

Each 5 ml ampoule contains 5 mg midazolam.

Other Ingredients:

Water for injections

Sodium chloride

Hydrochloric acid

Pharmaceutical form and content:

The medicinal product is a clear and colourless solution available in packs of 5 and 10 ampoules for all 3 types of preparation.

Manufacturer:

Mefar İlaç Sanayii A.Ş., Razamanoğlu Mah. Enser Cad. No:20 Kurtköy/Pendik, 34906, İstanbul, Türkiye

Therapeutic indications

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

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 a sedative component in combined anaesthesia.
- SEDATION IN INTENSIVE CARE UNITS

In Paediatrics

- 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

Recommended Dosage

STANDARD DOSAGE

Midazolam is a potent sedative agent that requires slow titration and individualisation of dosage.

The dose should be individualised and titration is strongly recommended to safely obtain the desired state 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.

The drug takes effect in about 2 minutes after intravenous injection. Maximum effect is obtained in about 5 to 10 minutes.

Standard dosages are provided in the table below. Additional details are provided in the text following the table.

Indication	Adults <60 years old	Adults ≥60 years/ critically ill, high-risk patients	Paediatrics
Conscious sedation	IV: Initial dose: 2-2.5 mg Titration doses: 1 mg Total dose: 3.5-7.5 mg	IV: Initial dose: 0.5-1 mg Titration doses: 0.5-1 mg Total dose: <3.5 mg	IV in 6 months-5 years: Initial dose: 0.05-0.1 mg/kg Total dose: <6 mg IV in patients 6-12 years: Initial dose: 0.025-0.05 mg/kg Total dose: <10 mg 13-16 years: As adults rectal >6 months 0.3-0.5 mg/kg IM: 1-15 years 0.05-0.15 mg/kg
Anaesthesia premedication	IV: 1-2 mg repeated IM: 0.07-0.1 mg/kg	IV: Initial dose: 0.5 mg Slow uptitration as needed IM: 0.025-0.05 mg/kg	rectal >6 months: 0.3-0.5 mg/kg IM: 1-15 years 0.08-0.2 mg/kg
Anaesthesia induction	IV: 0.2 mg/kg (0.2-0.35 mg/kg without premedication)	IV: 0.05-0.15 mg/kg (0.15-0.2 mg/kg without premedication)	Not indicated in paediatrics
Sedative component in combined anaesthesia	IV: intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	IV: lower doses than recommended for adults <60 years	Not indicated in paediatrics
Sedation in ICU	IV: Loading dose: 0.03 -0.3 mg/kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		IV in neonates <32 weeks gestational age 0.03 mg/kg/h IV in neonates >32 weeks and children up to 6 months 0.06 mg/kg/h IV in patients >6 months of age Loading dose: 0.05-0.2 mg/kg Maintenance dose: 0.06-0.12 mg/kg/h

METHOD OF ADMINISTRATION

CONSCIOUS SEDATION

For basal (conscious) sedation prior to diagnostic or surgical intervention, Midazolam is administered IV. 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.

Special caution is required for the indication of conscious sedation in patients with impaired respiratory function (See Warnings and Precautions).

Adults

The IV injection of Midazolam should be given slowly at a rate of approximately 1 mg in 30 seconds.

In adults below the age of 60 the initial dose is 2 to 2.5 mg given 5 to 10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3.5 to 7.5 mg. A total dose greater than 5 mg is usually not necessary.

In adults over 60 years of age, critically ill patients, high risk patients the initial dose must be reduced to 0.5 to 1.0 mg and given 5 to 10 minutes before the beginning of the procedure.

Further doses of 0.5 to 1 mg 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 3.5 mg is usually not necessary.

Paediatrics

IV administration:

Midazolam should be titrated slowly to the desired clinical effect. The initial dose of Midazolam should be administered over 2 to 3 minutes and it is recommended to 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 month 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 unless the benefits outweigh the risks. In such cases, titration with small increments to clinical effect and careful monitoring are essential.
- *Paediatric patients >6 months to 5 years of age:* initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint, but the total dose should not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses (see Warnings and Precautions).
- *Paediatric patients 6 to 12 years of age:* initial dose 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
- *Paediatric patients 13 to 16 years of age:* should be dosed as adults.

Rectal administration (paediatrics >6 months):

The total dose of Midazolam ranges from 0.3 to 0.5 mg/kg.

Total dose should be administered at once and repeated rectal administration avoided. The use in paediatrics less than 6 months of age is not recommended, as available data in this population are limited.

IM administration (paediatrics 1 to 16 years):

The recommended dose range is 0.05 to 0.15 mg/kg given 5 to 10 minutes before the beginning of the procedure. A total dose greater than 10.0 mg is not usually necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as IM injection may be painful.

In paediatrics less than 15 kg of body weight, Midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

ANAESTHESIA - PREMEDICATION

Premedication with Midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory. Midazolam can also be administered in combination with anticholinergics. For this indication Midazolam should be administered IV or IM (deep into a large muscle mass 20 to 60 minutes before induction of Anaesthesia), or preferably via the rectal route in paediatrics (see below). Adequate observation of the patients after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Adults

For preoperative sedation and to impair memory of preoperative events, the recommended dose for adults of ASA Physical Status I & II and below 60 years is 1 to 2 mg IV repeated as needed, or 0.07 to 0.1 mg/kg administered IM. The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, critically ill, high-risk patients. The recommended initial IV dose is 0.5 mg and should be slowly uptitrated as needed. Allow 2 to 3 minutes to fully evaluate the effect between doses. An IM dose of 0.025 to 0.05 mg/kg is recommended if there is no concomitant administration of narcotics. The usual dose is 2 to 3 mg.

Paediatrics

Rectal administration (paediatrics >6 months):

The total dose of Midazolam, usually 0.4 mg/kg, ranging from 0.3 to 0.5 mg/kg, should be administered 20 to 30 minutes before induction of anaesthesia.

The use in paediatrics less than 6 months of age is not recommended as available data are limited.

IM administration (1 to 15 years):

As IM injection may be painful this route should be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08 to 0.2 mg/kg of Midazolam administered IM has been shown to be effective and safe.

In paediatrics between ages 1 and 15, proportionally higher doses are required than in adults in relation to body weight. It is recommended that Midazolam should be administered deep into a large muscle mass 30 to 60 minutes prior to the induction of anaesthesia.

In paediatrics less than 15 kg of body weight, Midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

INDUCTION OF ANAESTHESIA

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 IV or inhalation agents for induction of anaesthesia, the initial dose of each agent may 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 IV induction dose of Midazolam should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.

Adults below the age of 60 years

- A dose of 0.2 mg/kg, administered IV over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice.
- In non-premedicated patients the dose may be higher (0.3 to 0.35 mg/kg), administered IV over 20 to 30 seconds and allowing about 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with volatile liquid inhalational anaesthetics. In resistant cases, a total dose of up to 0.6 mg/kg may be used for induction, but such larger doses may prolong recovery.

Adults above the age of 60 years, critically ill and high risk patients

- In non-premedicated patients the lowest initial dose of 0.15 to 0.2 mg/kg is recommended.
- In premedicated patients a dose of 0.05 to 0.15 mg/kg administered IV over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice.

Paediatrics

The use of Midazolam for the induction of anaesthesia is limited to adults only as there is very limited experience in children.

SEDATIVE COMPONENT IN COMBINED Anaesthesia

Adults

Midazolam can be given as a sedative component in combined anaesthesia by either further intermittent small IV doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of IV Midazolam (range between 0.03 and 0.1 mg/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, critically ill, high-risk patients, lower maintenance dose will be required.

Paediatrics

The use of Midazolam as sedative component in combined anaesthesia is limited to adults only as there is very limited experience in children.

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 Drug interactions).

Adults

IV loading dose: 0.03 to 0.3 mg/kg should be given slowly in increments. Each increment of 1 to 2.5 mg 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.

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

Paediatrics

In preterm new-born infants, term new-born infants and paediatrics less than 15 kg of body weight, Midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

Paediatrics up to 6 months of age

Midazolam should be given as a continuous IV infusion:

- Paediatrics <32 weeks of gestational age: starting dose at 0.03 mg/kg/hr (0.5 µg/kg/min)
- Paediatrics >32 weeks of gestational age up to 6 months of age: starting dose 0.06 mg/kg/hr (1 µg/kg/min).

Intravenous loading doses should not be used 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.

Paediatrics over 6 months of age

In intubated and ventilated paediatric patients, a loading dose of 0.05 to 0.2 mg/kg IV 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 IV infusion at 0.06 to 0.12 mg/kg/h (1 to 2 µg/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 IV 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.

Contraindications

Midazolam-hameln Injection should not be administered to patients known to suffer from:

- Myasthenia gravis
- Hypersensitivity to the active substance, other benzodiazepines or to one or more of the excipients of Midazolam-hameln Injection
- Acute intoxication with alcohol, hypnotics, neuroleptics, antidepressants or lithium.
- Acute narrow-angle glaucoma.

Use of this drug for conscious sedation in patients with severe respiratory failure or acute respiratory depression is contraindicated.

Warnings and Precautions

IV Midazolam has been associated with severe respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy resulted. IV Midazolam should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory and cardiac functions. Assure immediate availability of resuscitative drugs, equipments, appropriate antidote and personnel trained in their use.

Dosage of IV Midazolam must be individualized for each patient. Lower doses are usually required for elderly, debilitated or higher risk surgical patients. When Midazolam is administered intravenously for conscious sedation, it should be injected slowly (over at least 2 minutes); it should not be administered by rapid or single bolus IV injection because of respiratory depression and/or arrest, especially in elderly or debilitated patients. The initial dose may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult; administer over at least 2 minutes and allow additional 2 or more minutes to fully evaluate sedative effect. If further titration is necessary, use small increments to the appropriate level of sedation, allowing an additional 2 or more minutes after each increment to fully evaluate sedative effect. See Recommended Dosage for complete dosing information.

Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) can occur as early as the first time the product is administered.

When Midazolam is used for premedication, adequate observation of the patient after administration is mandatory as interindividual 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
- paediatric patients especially those with cardiovascular instability.

These high-risk patients require lower dosages (see Dosage administration) and should be continuously monitored for early signs of alterations of vital functions.

Benzodiazepines should be used with caution in patients with a history of alcohol or drug abuse.

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.

Complex sleep-related behaviour can occur which may include sleep driving, making phone calls, preparing and eating food while asleep.

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 (see Side Effects).

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 the 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 have 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 (see Drug Interactions).

Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see Pharmacokinetics).

Risks from Concomitant Use with Opioids

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Midazolam with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use. If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Midazolam is used with opioids. Advice patients not to drive or operate heavy machinery until the effects of concomitant use of opioids have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (See Drug Interactions).

Paediatric population

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.

Paediatric patients less than 6 months:

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 titrati-

on with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential (see also section 'Preterm infants' above).

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 (see Drug Interactions).

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.

Criteria for discharge:

After receiving Midazolam, patients should be discharged from the hospital or consulting room only when recommended by the treating physician and only if accompanied by an attendant. It is recommended that the patient is accompanied when returning home after discharge.

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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- *The medicine is likely to affect your ability to drive*
- *Do not drive until you know how the medicine affects you*
- *It is an offence to drive while under the influence of this medicine*

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*
- *It was not affecting your ability to drive safely*

Drug interactions

Pharmacokinetic Interactions

Midazolam is metabolized by CYP3A4.

Inhibitors and inducers of CYP3A have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of Midazolam requiring dose adjustments accordingly.

Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral than for IV Midazolam, as CYP3A4 is also present in the upper gastrointestinal tract. For the oral route both systemic clearance and availability will be altered while for the parenteral route only the change in the systemic clearance is affected.

After a single dose of IV Midazolam, the impact on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. However, after prolonged dosing of Midazolam, both the magnitude and duration of effect will be increased in the presence of CYP3A4 inhibition.

There are no available studies of 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 gastrointestinal tract is bypassed whereas after IM administration the effects of CYP3A4 modulation should not substantially differ from those seen with IV Midazolam.

It is therefore recommended to carefully monitor clinical effects and vital signs during the use of Midazolam, taking into account that they may be stronger and last longer after co-administration of a CYP3A4 inhibitor, even if given only once. Notably, administration of high doses or long-term infusions of Midazolam to patients receiving potent 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. Short term treatment with an inducer (unlike treatment of several days with an inducer) is expected to result in less apparent DDI with Midazolam. However, for strong potent inducers a relevant induction even after short-term treatment cannot be excluded.

Midazolam is not known to alter the pharmacokinetics of other drugs.

Drugs that inhibit CYP3A

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 co-administered with the strong CYP3A 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 IV dose of Midazolam is administered. The same recommendation may apply also for other azole antifungals (see further), since increased sedative effects of IV Midazolam, although lesser, are reported.
- Voriconazole increased the exposure (plasma concentration) of intravenous Midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.
- Fluconazole and itraconazole both increased the plasma concentrations of intravenous Midazolam by 2 – 3fold associated with an increase in terminal half-life by 2.4fold for itraconazole and 1.5-fold for fluconazole, respectively.
- Posaconazole increased the plasma concentrations of intravenous Midazolam by about 2-fold.
- It should be kept in mind that if Midazolam is given orally, its exposure will be significantly higher than discussed above, notably with ketoconazole, itraconazole and voriconazole. Midazolam ampoules are not indicated for oral administration.

Macrolide antibiotics

- Erythromycin resulted in an increase in 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.
- 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

- Roxithromycin: While no information on roxithromycin with IV Midazolam is available, the mild effect on the terminal half-life of oral Midazolam tablet, increasing by 30%, indicates that the effects of roxithromycin on intravenous Midazolam may be minor.

HIV Protease inhibitors

- Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of Midazolam. Upon co-administration with the ritonavir-booster 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, the 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

- 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

- 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.

Other medicines

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

Additional information from oral Midazolam

- Nefazodone increased the plasma concentrations of oral Midazolam by 4.6-fold with an increase of its terminal half-life by 1.6-fold.
- 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 approximately 2-fold.

Drugs that induce CYP3A

- Rifampicin decreased the plasma concentrations of intravenous Midazolam by about 60% after 7 days of rifampicin 600 mg OD. The terminal half-life decreased by about 50-60%.

Additional information from oral Midazolam

- Rifampicin decreased the plasma concentrations of oral Midazolam by 96% in healthy subjects and its psychomotor effects where almost totally lost.
- Carbamazepine / phenytoin: Repeated dosages of carbamazepine 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%.
- Efavirenz: The 5-fold increase in the ratio of the CYP3A4 generated metabolite α-hydroxyMidazolam to Midazolam confirms its CYP3A4-inducing effect.

Herbal medicines

- St John's Wort decreased plasma concentrations of Midazolam by about 20 to 40% associated with a decrease in terminal half-life of about 15 to 17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

Opioids

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death. The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of the actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at the μ-receptors, and the benzodiazepines interact at the GABAA sites.

When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid related respiratory depression exists. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Pharmacodynamic Drug-Drug Interactions (DDI)

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 opiates 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 H1antihistamines and centrally acting antihypertensive drugs.

Alcohol may markedly enhance the sedative effect of Midazolam. It is strongly advised that alcohol intake should be avoided in case of Midazolam administration (see Warnings and Precautions).

Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

Pregnancy and Lactation

Pregnancy

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 same risk of developing withdrawal symptoms in the postnatal period.

Consequently, Midazolam should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean.

The risk for neonate should be taken into account in case of administration of Midazolam for any surgery near the term.

Lactation

Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breastfeeding for 24 hours following administration of Midazolam.

Side Effects

The following undesirable effects (with frequencies) have been reported to occur when Midazolam is injected:

Immune system disorders:

Not known: Generalized hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylactic shock, angioedema.

Psychiatric disorders:

Not known: Confusional state, euphoric mood, hallucinations, delirium.

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Dependence: Use of Midazolam even in therapeutic doses may lead to the development of physical dependence. After prolonged IV administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions (see Warnings and Precautions).

Nervous system disorders:

Not known: Involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity.

Prolonged sedation, decreased alertness, somnolence, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Convulsions have been reported in premature infants and neonates.

Drug withdrawal convulsions.

Uncommon: Euphoria, confusion, quarrelsome behaviour, nervousness, anxiety, feeling of drunkenness, restlessness, prolonged waking from anaesthesia and dreams, sleep disturbances, insomnia, nightmares, athetotic movements, muscle twitching, dysphoria, unclear speech, dysphonia, paraesthesia.

Cardiac disorders:

Not known: Severe cardiorespiratory adverse events have occurred. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects. 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 (see Warnings and Precautions).

Uncommon: Bigeminal pulse, premature ventricular contractions, vasovagal episodes, tachycardia, nodal rhythm.

Respiratory, thoracic and mediastinal disorders:

Not known: Severe cardiorespiratory adverse events including respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm have been reported. 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 (see Warnings and Precautions). Hiccup.

Gastrointestinal disorders:

Not known: Nausea, vomiting, constipation, dry mouth.

Uncommon: Sour taste in mouth, increased salivation.

Skin and subcutaneous tissue disorders:

Not known: Skin rash, urticaria, pruritus.

Other sensory organs:

Uncommon: Blurred vision, double vision, nystagmus, miosis, fluttering of the eyelids, impaired vision, convergence disorders, impaired hearing, loss of balance, disorientation.

General and administration site conditions:

Not known: Fatigue, erythema and pain on injection site, thrombophlebitis, thrombosis.

Injury, poisoning and procedural complications:

Not known: An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Overdose

Symptoms

Like other benzodiazepines, Midazolam commonly cause 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.

Treatment

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 to 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.

Pharmacodynamics

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.

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 IM or IV administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).

Pharmacokinetics

Absorption after IM injection

Absorption of Midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after IM injection is over 90%.

Absorption after rectal administration

After rectal administration Midazolam is absorbed quickly. Maximum plasma concentration is reached in about 30 minutes. The absolute bioavailability is about 50%.

Distribution

When Midazolam is injected IV, the plasma concentration time curve shows one or two distinct phases of distribution.

The volume of distribution at steady state is 0.7 to 1.2 l/kg. 96 to 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 to 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 to 2.5 hours. Plasma clearance is in the range of 300 to 500 ml/min. Midazolam is excreted mainly by renal route (60 to 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-hydroxyMidazolam is shorter than 1 hour. When Midazolam is given by IV infusion, its elimination kinetics do not differ from that 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 rate of rectal absorption in children is similar to that in adults but the bioavailability is lower (5 to 18%).

The elimination half-life after IV and rectal administration is shorter in children 3 to 10 years old (1 to 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 to 12 hours, probably due to liver immaturity and the clearance is reduced (see Warning and Precautions).

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 (see Warnings and Precautions).

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 (see Warnings and Precautions).

Instructions for Use and Handling

The injection is for single patient use and should be used immediately after opening. The injection should not be used if particles are present. Any unused portion should be discarded.

With continuous intravenous infusion, Midazolam injection solution may be diluted in a ratio of 15 mg Midazolam to 100 to 1000 ml with one of the following infusion solutions: 0.9% NaCl, 5% and 10% dextrose and Ringer's solution. These solutions remain stable for 3 days at room temperature.

Incompatibilities

This medicinal product must not be diluted with other solutions for parenteral use than those mentioned in section 'Instructions for use and handling'.

Compatibility must be checked before administration, if intended to be mixed with other drugs.

Midazolam precipitates in solutions containing bicarbonate. Theoretically, the midazolam injection solution is likely to be unstable in solutions of neutral or alkaline pH. If midazolam is mixed with albumin, amoxicillin sodium, ampicillin sodium, bumetamide, dexamethasone sodium phosphate, dimenhydrinate, floxacillin sodium, furosemide, hydrocortison sodium succinate, pentobarbital sodium, perphenazine, prochlorperazine edisylate, ranitidine or thiopental sodium or trimethoprim-sulfamethoxazole, a white precipitate forms immediately.

A haze is formed immediately followed by a white pre-cipitate with nafcillin sodium. With ceftazidime a haze is formed.

With methotrexate sodium a yellow precipitate forms. With clonidine hydrochloride an orange discoloration forms. With omeprazole sodium a brown discoloration forms, followed by a brown precipitate. With forscarnet sodium a gas is produced.

Further midazolam should not be mixed with aciclovir, albumin, alteplase, acetazolam disodium, diazepam, enoximone, flecainide acetate, fluorouracil, imipenem, mezlocillin sodium, phenobarbital sodium, phenytoin sodium, potassium canrenoate, sulbactam sodium, theophylline, trometamol, urokinase.

Shelf Life

Shelf-life before first opening

3 years.

Shelf-life after dilution

Chemical and physical in-use stability of the dilutions (see Instructions for Use and Handling) has been demonstrated for 72 hours at 30°C.

From the microbiological point of view, the dilutions should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Storage Conditions

Please refer to outer carton.

Keep ampoules inside the outer carton to protect from light.

Keep out of reach of children.

Jauhi daripada kanak-kanak

Date of revision:
20.06.2022