Directions for Use

B. Braun Melsungen AG, 34209 Melsungen, Germany

Midazolam B. Braun 5 mg/ml

1. NAME OF THE MEDICINAL PRODUCT

Midazolam B. Braun 5 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains	5 mg midazolam (as midazolam hydrochloride, 5.56 mg)
Each ampoule of 1 ml contains	5 mg midazolam (as midazolam hydrochloride, 5.56 mg)
Each ampoule of 10 ml contains	50 mg midazolam (as midazolam hydrochloride, 55.6 mg)

Excipient with known effect: sodium 2.2 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion
Clear, colourless aqueous solution
pH: 2.9 to 3.7

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Midazolam B. Braun is a short-acting sleep-inducing medicinal product that is indicated:

In adults:

- **Conscious sedation** before and during diagnostic or therapeutic procedures with or without local anaesthesia
- **General anaesthesia**
  - premedication before induction of general anaesthesia
  - induction of general anaesthesia
  - 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
- **General anaesthesia**
  - premedication before induction of general anaesthesia
- **Sedation in intensive care units**

4.2 Posology and method of administration

Standard posology

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

Table 1: Standard dosages

Indication	Adults < 60 y	Adults ≥ 60 y / debilitated or chronically ill	Children
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 patients 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 **rectal in patients > 6 months** 0.3 – 0.5 mg/kg **IM in patients 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 in patients > 6 months** 0.3 – 0.5 mg/kg **IM in patients 1 – 15 years** 0.08 – 0.2 mg/kg
Anaesthesia induction	**IV** 0.15 – 0.2 mg/kg (0.3 – 0.35 mg/kg without premedication)	**IV** 0.05 – 0.15 mg/kg (0.15 – 0.3 mg/kg without premedication)	
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	
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 newborn infants ≤ 32 weeks gestational age** 0.03 mg/kg/h **IV in newborn infants > 32 weeks and infants 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

Conscious sedation dosage

For conscious sedation prior to diagnostic or surgical intervention, midazolam is administered intravenously.

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 intravenous 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, debilitated or chronically ill patients, start by administering a dose of 0.5 to 1 mg 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.

Paediatric population

Intravenous 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 period of time of 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 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 0.1 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.
- 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 12 to 16 years of age: should be dosed as adults.

Rectal administration: The total dose of midazolam usually ranges from 0.3 to 0.5 mg/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 10 ml. 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.

Intramuscular administration: The doses used range between 0.05 and 0.15 mg/kg. A total dose greater than 10.0 mg is usually not necessary. This route should only be used in exceptional cases. Rectal administration should be preferred to intramuscular injection as this route of administration is painful.

In children 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.

General anaesthesia premedication dosage

Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of anxiety), muscle relaxation and anterograde amnesia.

Midazolam can also be administered in combination with anticholinergics.

For this indication midazolam should be administered intravenously or intramuscularly, deep into a large muscle mass, 20 to 60 minutes before induction of anaesthesia, or preferably via the rectal route in children (see below).

Adequate observation of the patient after administration of premedication is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Adults

For preoperative sedation and to promote amnesia of preoperative events, the recommended dose for adults of ASA physical status I and II and below 60 years is 1 to 2 mg intravenously repeated as needed, or 0.07 to 0.1 mg/kg administered intramuscularly.

The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, debilitated, or chronically ill patients. The recommended intravenous dose is 0.5 mg and should be slowly up titrated as needed. The recommended intramuscular dose is 0.025 to 0.05 mg/kg, and the usual dose is 2 to 3 mg. In case of concomitant administration of anaesthetics, the midazolam dose should be reduced.

Paediatric population

Neonates and children up to 6 months of age

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 0.5 mg/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 10 ml.

Intramuscular administration: As intramuscular 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 0.2 mg/kg of midazolam, administered intramuscularly, has been shown to be effective and safe.

In paediatric patients between ages 1 and 15 years, proportionally higher doses are required than in adults in relation to body weight.

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

Induction of general anaesthesia

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 intravenous 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 intravenous 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.

- In premedicated adults below the age of 60 years, an intravenous dose of 0.15 to 0.2 mg/kg will usually suffice.
- In non-premedicated adults below the age of 60 the dose may be higher (0.3 to 0.35 mg/kg intravenously). 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 0.6 mg/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 be significantly reduced, e.g. down to 0.05 to 0.15 mg/kg administered intravenously over 20 to 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 0.3 mg/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 0.25 mg/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 intravenous doses (range between 0.03 and 0.1 mg/kg) or continuous intravenous infusion of 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, 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

Intravenous 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.

Intravenous 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.

With long-term sedation, tolerance may develop and the dose may have to be increased.

Children over 6 months of age

In intubated and ventilated paediatric patients, a loading dose of 0.05 to 0.2 mg/kg should be administered slowly intravenously 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 intravenous infusion at 0.06 to 0.12 mg/kg/h (1 to 2 micrograms/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 intravenous 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.

Neonates and children up to 6 months of age

Midazolam should be given as a continuous intravenous infusion, starting at 0.03 mg/kg/h (0.5 microgram/kg/min) in neonates with a gestational age ≤ 32 weeks or 0.06 mg/kg/h (1 microgram/kg/min) in neonates with a gestational age > 32 weeks and children up to 6 months.

Intravenous loading doses are 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.

In premature infants, neonates and children 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.

Use in special populations

Patients with renal impairment

In patients with severe renal impairment 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).

Patients with hepatic impairment

Hepatic impairment reduces the clearance of intravenous midazolam with a subsequent increase in terminal half-life. Therefore the clinical effects may be stronger and prolonged. The required dose of midazolam may be reduced and proper monitoring of vital signs should be established (see section 4.4).

4.3 Contraindications

- Hypersensitivity to midazolam, benzodiazepines or to any of the excipients listed in section 6.1.
- 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 (see section 4.8).

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Special caution is required for the indication of conscious sedation in patients with impaired respiratory function.

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 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,
  - patients with impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment),
  - patients with impaired cardiac function,
  - paediatric patients especially those with cardiovascular instability.

These high-risk patients require lower dosages (see section 4.2) 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 (see section 4.8).

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, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability, sleep disturbances, mood changes, hallucinations and convulsions. In severe cases, the following symptoms may occur: depersonalisation, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact.
Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

Amnesia

Anterograde amnesia may occur with therapeutic doses (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, with the risk increasing at higher dosages.
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.

Paradoxical reactions

Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, 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. In the event of these reactions discontinuation of the drug should be considered.

Sleep Apnoea

Midazolam should be used with extreme caution in patients with sleep apnoea syndrome and patients should be regularly monitored.

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 section 4.5).
Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see section 5.2).

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 the dose must be uptitrated in small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are required (see also section 'Preterm infants and neonates' above).

Concomitant use of alcohol / CNS depressants

The concomitant use of midazolam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam possibly including severe sedation that could result in coma or death, or clinically relevant respiratory depression (see section 4.5).

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 the 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.

Special warnings/precautions regarding excipients

This medicinal product contains 2.19 mg sodium per 1 ml ampoule, equivalent to 0.11% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 21.94 mg sodium per 10 ml ampoule, equivalent to 1.01% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Midazolam is metabolised by cytochrome P450 3A4 enzymes (CYP3A4 and CYP3A5). Inhibitors and inducers of CYP3A 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 intravenous 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 intravenously administered midazolam, the consequence 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 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 intramuscular administration the effects of CYP3A4 modulation should not substantially differ from those seen with intravenously administered midazolam.

Close monitoring of clinical effect and vital parameters during midazolam use is therefore recommended, and it should be taken into account that they may be more pronounced and prolonged following concomitant administration of a CYP3A4 inhibitor even after a single dose. It should be taken into account that administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors 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 drug-drug interactions 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.

Table 2: Interactions between midazolam and medicinal products that inhibit CYP3A

Medicinal product	Interaction with intravenous Midazolam[a]
Azole antifungals[b]	
Ketoconazole, Voriconazole	Ketoconazole and voriconazole increased the plasma concentrations of intravenous midazolam by 5-fold and 3-4-fold respectively, while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with these strong CYP3A inhibitors, it should be done in an 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 intravenous dose of midazolam is administered. The same recommendation may apply also for other azole antifungals, since increased sedative effects of intravenously administered midazolam, although lesser, are reported.
Fluconazole, Itraconazole	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.
Posaconazole	Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

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Macrolide antibiotics	
Erythromycin	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	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.
Telithromycin, Roxithromycin	*Information from oral midazolam* Telithromycin increased the plasma levels of oral midazolam 6-fold. While no information on roxithromycin with intravenously administered 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.
Intravenous anaesthetics	
Propofol	Intravenous propofol increased the AUC and half-life of intravenous midazolam by 1.6-fold.
Protease inhibitors[c]	
Saquinavir and other HIV (human immunodeficiency virus) protease inhibitors	Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration 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, the advice given above for the azole antifungals, ketoconazole and voriconazole should be followed.
Hepatitis C virus (HCV) protease inhibitors	Boceprevir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of midazolam AUC after intravenous administration and prolonged its elimination half-life 4-fold.
Calcium channel blockers	
Diltiazem	A single dose of diltiazem given to patients undergoing coronary artery bypass grafting increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%. This was less than the 4-fold increase seen after oral administration of midazolam.
Verapamil	*Information from oral midazolam* Verapamil increased the plasma concentrations of oral midazolam by 3-fold. The terminal half-life of midazolam was increased by 41%.
Various drugs/herbs	
Atorvastatin	Atorvastatin resulted in a 1.4-fold increase in plasma concentrations of intravenously administered midazolam compared to control group.
Fentanyl	Intravenous fentanyl is a weak inhibitor of midazolam elimination: AUC and half-life of intravenously administered midazolam were increased by 1.5-fold in the presence of fentanyl.
Nefazodone	*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	*Information from oral midazolam* Aprepitant at doses of 80 mg/day and above dose-dependently increased the plasma concentrations of oral midazolam by about 3.3-fold and increased terminal half-life by approximately 2-fold.
Tyrosine kinase inhibitors	*Information from oral midazolam* Tyrosine kinase inhibitors have been shown to be potent inhibitors of CYP3A4 in vitro (imatinib, lapatinib) or in vivo (idelalisib). After concomitant administration of idelalisib, oral midazolam exposure was increased on average 5.4-fold.
NK1 receptor antagonists	*Information from oral midazolam* NK1 receptor antagonists (aprepitant, netupitant, casopreptitant) dose dependently increased the plasma concentrations of oral midazolam up to about 2.5-3.5-fold and increased terminal half-life by approximately 1.5-2-fold.
Other	*Information from oral midazolam* For a number of drugs or herbal medicines, a weak interaction with midazolam's elimination was observed with concomitant changes in its exposure (< 2-fold change in AUC) (everolimus, cyclosporine, simeprevir, propiverine). These weak interactions are expected to be further attenuated after intravenous administration.

[a] For some interactions, additional information using orally administered midazolam is provided. Interactions with CYP3A inhibitors are more pronounced for oral as compared to intravenous midazolam. Midazolam B. Braun is not indicated for oral administration.

[b] If midazolam is given orally with an azole antifungal (particularly ketoconazole, itraconazole or voriconazole), its exposure will be drastically higher compared to intravenous administration.

[c] 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.

Table 3: Interactions between midazolam and medicinal products that induce CYP3A

Medicinal product	Interaction with intravenous Midazolam[a]
Rifampicin	Rifampicin decreased the plasma concentrations of intravenous midazolam by about 60% after 7 days of rifampicin 600 mg/day. The terminal half-life decreased by about 50-60%. Information from oral midazolam Rifampicin decreased the plasma concentrations of oral midazolam by 96% in healthy subjects and its psychomotor effects were almost totally lost.
Carbamazepine, phenytoin	*Information from oral midazolam* Repeat 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%.
Mitotane, enzalutamide	*Information from oral midazolam* The very strong CYP3A4 induction seen after mitotane or enzalutamide resulted in a profound and long-lasting decrease of midazolam levels in cancer patients. AUC of orally administered midazolam was reduced to 5% and 14% of normal values respectively.
Ticagrelor	Ticagrelor is a weak CYP3A inducer and has only small effects on intravenously administered midazolam (-12%) and 4-hydroxymidazolam (-23%) exposures.
Clobazam, efavirenz	*Information from oral midazolam* Clobazam and Efavirenz are weak inducers of midazolam metabolism and reduce the AUC of the parent compound by approximately 30%. There is a resulting 4-5-fold increase in the ratio of the active metabolite (1'-hydroxymidazolam) to the parent compound but the clinical significance of this is unknown.
Vemurafenib	*Information from oral midazolam* Vemurafenib modulates CYP isozymes and induces CYP3A4 mildly: Repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 39% (up to 80% in individuals).
Herbs and food	
St John's Wort	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.
Quercetin	*Information from oral midazolam* Quercetin (also contained in ginkgo biloba) and panax ginseng both have weak enzyme inducing effects and reduced exposure to midazolam after its oral administration by approximately 20-30%.
Acute protein displacement	
Valproic acid	Increased free midazolam concentrations due to displacement from the plasma protein binding sites by valproic acid cannot be ruled out. The clinical relevance of such an interaction is not known.

[a] For some interactions, additional information using orally administered midazolam is provided. Interactions with CYP3A inducers are more pronounced for oral as compared to intravenous midazolam. Midazolam B. Braun is not indicated for oral administration.

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 cardio-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 and centrally acting antihypertensive drugs.

Alcohol may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration.

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

4.6 Fertility, 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 are available from exposed pregnancies during the first two trimesters. It is assumed that the use of benzodiazepines during the first trimester of pregnancy is associated with an increased risk of congenital abnormalities.

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 events (aspiration 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 postnatal period.

Consequently, midazolam may be used during pregnancy if clearly necessary but 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.

Breast-feeding

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

Fertility

No data available.

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.

If insufficient sleep occurs or alcohol is consumed, the likelihood of impaired alertness is increased.

4.8 Undesirable effects

Undesirable effects are ranked with regard to their frequency using the following convention:
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).

The following undesirable effects have been reported (frequency not known, cannot be estimated from the available data) to occur when midazolam is injected:

Immune system disorders

Hypersensitivity, angioedema, anaphylactic shock

Psychiatric disorders

Confusional state, disorientation, emotional and mood disturbances, changes in libido

Agitation*, hostility*, anger*, aggressiveness*, excitement*

Physical drug dependence and withdrawal syndrome, abuse

Nervous system disorders

Sedation (prolonged and postoperative), alertness decreased, somnolence, headache, dizziness, ataxia, 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 (see section 4.4).

Convulsions have been reported more frequently in premature infants and neonates.

Drug withdrawal convulsions.

Involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity*.

Cardiac disorders

Cardiac arrest, bradycardia, Kounis syndrome**

Vascular disorders

Hypotension, vasodilation, thrombophlebitis, thrombosis

Respiratory, thoracic and mediastinal disorders

Respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm, hiccups

Gastrointestinal disorders

Nausea, vomiting, constipation, dry mouth

Skin and subcutaneous tissue disorders

Rash, urticaria, pruritus

General disorders and administration site conditions

Fatigue, erythema and pain on injection site

Injury, poisoning and procedural complications

Falls, fractures. The risk of falls and bone fractures is increased in patients taking sedatives concomitantly (including alcoholic beverages) and in elderly patients.

Social circumstances

Assault*

*Such paradoxical drug reactions have been reported particularly among children and the elderly (see section 4.4).

**particularly after parenteral administration

Renal impairment: There is a greater likelihood of adverse drug reactions in patients with severe renal impairment (see section 4.2).

Dependence: Use of midazolam – even in therapeutic doses – may lead to the development of physical dependence. After prolonged intravenous administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions (see section 4.4). 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 (see section 4.4).

Note

Patients should inform their doctor if they notice any of these reactions or other adverse reactions.

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, hypotension, cardiorespiratory depression, apnoea and in rare cases to coma.

Coma, if it occurs, usually lasts a few hours. The effect may be prolonged and clinically significant, particularly in elderly patients. The effects of benzodiazepines on respiratory depression are far more serious in patients with respiratory system diseases.

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

Treatment

In most cases, only monitoring of vital functions is required. In the management of overdose special attention should be paid to the respiratory and cardiovascular functions in intensive care unit. The benzodiazepine antagonist flumazenil is indicated in case of severe intoxication accompanied with coma or respiratory depression. It has a short half-life, therefore patients administered flumazenil will require monitoring after its effects have worn off.

Caution must be taken when using flumazenil in case of mixed drug overdose and in patients with epilepsy already treated with benzodiazepines.

Flumazenil should not be used in patients treated with tricyclic antidepressant medicinal products, epileptogenic medicinal products, or patients with ECG abnormalities (QRS or QT prolongation).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives – benzodiazepine derivatives, ATC code: N05CD08.

Midazolam has hypnotic and sedative effects characterised by a rapid onset and short duration. It also exerts anxiolytic, anticonvulsant and muscle-relaxant effects. Midazolam impairs psychomotor function after single and/or multiple doses but causes minimal haemodynamic changes.

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

Chemically, midazolam is a derivative of the imidazobenzodiazepine group. Although 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, producing a stable and well tolerated injection solution. This, together with rapid metabolic transformation, is the reason for rapid onset and short duration of effects. Due to its low toxicity, midazolam has a broad therapeutic spectrum.

After intramuscular or intravenous 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 intramuscular injection*
Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after intramuscular injection is over 90%.

– *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 intravenously, 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.

Metabolism

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 P450 CYP3A4 and CYP3A5 isozymes 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 young healthy volunteers, the elimination half-life of midazolam ranges from 1.5 to 2.5 hours. The elimination half-life of the metabolite is shorter than 1 hour; therefore, after midazolam administration, the concentration of the parent compound and the main metabolite decline in parallel.
Plasma clearance of midazolam is in the range of 300–500 ml/min.
Midazolam's metabolites are excreted mainly by the renal route: 60–80% of the dose is excreted in the urine as glucuroconjugated alpha-hydroxymidazolam.
Less than 1% of the dose is recovered in urine as unchanged drug.

When midazolam is given by intravenous infusion, its elimination kinetics do not differ from those following bolus injection. Repeated administrations of midazolam do not induce drug-metabolising enzymes.

Pharmacokinetics in special populations

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

Children
The rate of rectal absorption in children is similar to that in adults but the bioavailability is lower (5–18%). The elimination half-life after intravenous and rectal 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 12 hours, probably due to liver immaturity, and the clearance is reduced (see section 4.4). Neonates with asphyxia-related hepatic and renal impairment are at risk of generating unexpectedly high serum midazolam concentration due to a significantly decreased and variable clearance.

Obese
The mean half-life is greater in obese than in non-obese patients (5.9 vs 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

Patients with hepatic impairment
The clearance in cirrhotic patients may be reduced and the elimination may be longer when compared to those in healthy volunteers (see section 4.4).

Patients with renal impairment
The pharmacokinetics of unbound midazolam are not altered in patients with severe renal impairment. The pharmacologically mildly active major midazolam metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in patients with severe renal impairment. This accumulation may produce a prolonged sedation. Midazolam should therefore be administered carefully and titrated to the desired effect (see section 4.4).

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 section 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Neonatal studies in mice suggest that midazolam may trigger apoptotic neurodegeneration in the developing mouse brain specially when combined with other anaesthetics. However, these effects have not been reproduced in humans and the dose used in mice was higher than the recommended dose for midazolam in the neonatal population.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid 10%
Water for injections

6.2 Incompatibilities

Midazolam B. Braun may be incompatible with alkaline parenteral preparations, including solutions for parenteral nutrition with an alkaline pH.

Midazolam must not be mixed with solutions containing bicarbonate or other alkaline solutions, aminoglycosides, amoxicillin, aminophylline, phosphates or phenothiazines because of chemical incompatibility and occurrence of precipitation.

This medicinal product must not be diluted in dextran solutions.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Incompatibility of midazolam preparations with injectable preparations of the following active substances has been reported in the literature:

aciclovir
albumin
alteplase (human plasminogen activator)
amoxicillin sodium
acetazolamide sodium
bumetanide
dexamethasone-21-dihydrogen phosphate
diazepam
dimenhydrinate
disodium methotrexate
enoximone
flecainide acetate
fluorouracil
folic acid
foscarnet sodium
furosemide sodium
imipenem
mezlocillin sodium
omeprazole sodium
phenobarbitone sodium
phenytoin sodium
perphenazine enanthate
potassium canrenoate
ranitidine hydrochloride
sodium hydrocortisone-21-hydrogen succinate
sulbactam sodium/ampicillin sodium
theophylline
thiopental sodium
trimethoprim/sulfamethoxazole
trometamol
urokinase

6.3 Shelf life

– unopened
Glass ampoules: 3 years
Polyethylene ampoules: 2 years

– after first opening the container
This medicinal product should be used immediately after opening.

– after dilution
Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and for 3 days at 5 °C.
From a microbiological point of view, dilutions should be used immediately after preparation. 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.

6.4 Special precautions for storage

Do not store above 30 °C.
Keep the containers in the outer carton in order to protect from light.
For storage conditions of the opened and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

- Ampoules of colourless glass type I,
  Contents: 1 ml, Pack sizes: packs of 10 ampoules
- Ampoules of colourless glass type I,
  Contents: 10 ml, Pack sizes: packs of 5 or 10 ampoules
- Transparent polyethylene ampoules (low-density polyethylene, LDPE),
  Contents: 10 ml, Pack sizes: packs of 4, 10 or 20 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

The product is supplied in single-dose containers. Unused contents of opened containers must be discarded immediately.

Midazolam B. Braun may be diluted in
- 9 mg/ml (0.9%) sodium chloride solution,
- 50 mg/ml (5%) glucose solution,
- Ringer's solution and
- Hartmann's solution,

to a resulting concentration of 15 mg midazolam per 100 - 1000 ml of infusion solution.

The compatibility with other solutions should be checked prior to mixing.

Only to be used if solution is clear and colourless and the container and its closure are undamaged.

7. DATE OF REVISION OF THE TEXT

03/2024

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