SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Midazolam B. Braun 1 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains	1mg of midazolam (as midazolam hydrochloride, 1.112 mg)
One ampoule of 5 ml contains	5 mg of midazolam (as midazolam hydrochloride, 5.56 mg)
One bottle of 50 ml contains	50 mg of midazolam (as midazolam hydrochloride, 55.6 mg)
One bottle of 100 ml contains	100 mg of midazolam (as midazolam hydrochloride, 111.2 mg)

Excipients with known effect: sodium 3.5 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 – 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

- **Anaesthesia**
  - premedication before induction of anaesthesia,
  - induction of 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

- **Anaesthesia**

– for premedication before induction of anaesthesia

- **Sedation in intensive care units**

4.2 Posology and method of administration

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.

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 > 6 months*** 0.3 – 0.5 mg/kg ***IM 1 – 15 years*** 0.05 – 0.15mg/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*** 0.15 – 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 new-born infants < 32 weeks gestational age*** 0.03 mg/kg/h ***IV in new-born infants > 32 weeks and infants up to 6 months*** 0.06 mg/kg/h ***IV in patients > 6 months of age***

Indication	Adults < 60 y	Adults ≥ 60 y / debilitated or chronically ill	Children
			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 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, debilitated or chronically ill patients**, start by administering a dose of 0.5 to 1 mg. 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

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. 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 young children less than 6 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.

- 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 ampoule 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.

IM 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 IM 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.

Anaesthesia dosage

Premedication

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 IV or IM, 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 & II and below 60 years is 1-2 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, debilitated, or chronically ill patients**. The recommended IV dose is 0.5 mg and should be slowly uptitrated as needed. A dose of 0.025 to 0.05 mg/kg, administered IM, is recommended. The usual dose is 2 to 3 mg.

Paediatric population

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 ampoule 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.

IM administration: As IM 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 IM, 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 bodyweight.

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

In paediatric patients 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

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 IV or inhalation agents for induction of anaesthesia, the initial dose of each agent should be significantly reduced. 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.

- In adults below the age of 60 years, an IV 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 IV). 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 adults over 60 years of age, debilitated or chronically ill patients, the dose is 0.05 to 0.15 mg/kg administered IV. 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 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, 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

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. 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 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 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 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.

Neonates and children up to 6 months of age

Midazolam should be given as a continuous IV 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.

Patients with renal impairment
In patients with renal impairment (creatinine clearance < 10 ml/min) the pharmacokinetics of unbound midazolam following a single IV dose is similar to that reported in healthy volunteers. However, after prolonged infusion in intensive care unit (ICU) patients, the mean duration of the sedative effect in the renal failure population was considerably increased most likely due to accumulation of α-hydroxymidazolam glucuronide.

There is no specific data in patients with severe renal impairment (creatinine clearance below 30 ml/min) receiving midazolam for induction of anaesthesia.

Patients with hepatic impairment
Hepatic impairment reduces the clearance of IV 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 only be administered by experienced physicians, trained in the recognition and management of expected adverse events, when age- and size-appropriate resuscitation facilities are available, as IV administration of midazolam may depress myocardial contractility and cause apnoea. Severe cardiorespiratory adverse events have occurred on rare occasions. 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. 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.

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 specially 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.

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.

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 history of episodes 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, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

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

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

Delayed 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).

Pre-term newborn infants and newborn infants
Due to an increased risk of apnoea, extreme caution is advised when sedating preterm and former preterm patients. Careful monitoring of respiratory rate and oxygen saturation is required. Rapid injection should be avoided in the neonatal population.

New-born infants have reduced and/or immature organ function and are also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Special warnings/precautions regarding excipients

This medicinal product contains 3.5 mg sodium per millilitre, equivalent to 0.2 % 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

The metabolism of midazolam is almost exclusively mediated by the isoenzyme CYP3A4 of the cytochrome P450 (CYP450). CYP3A4 inhibitors (see section **4.4**) and inducers, but also other active substances (see below), may lead to drug-drug interactions with midazolam. Dose adjustments may be needed.

Since midazolam undergoes significant first pass effect, parenteral midazolam would theoretically be less affected by metabolic interactions and clinical relevant consequences should be limited. After a single dose of IV 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 IM administration the effects of CYP3A4 modulation should not substantially differ from those seen with IV midazolam.

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

CYP3A4 inhibitors

Azole antifungals
Co-administration of oral midazolam and some azole antifungals (itraconazole, fluconazole, ketokonazole) increased markedly midazolam plasma levels and prolonged its elimination half-life, leading to major impairment of psychosedative tests. After concomitant midazolam IV administration the elimination half-lives were not as high as with oral administration, however they increased from 3 to 8 hours approximately.
When a single bolus dose of midazolam was given for short-term sedation, the effect of midazolam was not enhanced or prolonged to a clinically significant degree by itraconazole, and dosage reduction is therefore not required. However, administration of high doses or long-term infusions of midazolam to patients receiving azole antifungals such as itraconazole, fluconazole and especially ketoconazole, e.g. during intensive care treatment, may result in long-lasting hypnotic effects, possible delayed recovery, and possible respiratory depression, thus requiring dose adjustments and close monitoring.

Calcium channel blockers
A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25 % and the terminal half-life was prolonged by 43 %.
However, as expected, oral midazolam pharmacokinetics varied in a clinically significant way when combined to verapamil and diltiazem, notably with almost a doubling of half-life value and peak plasma level, resulting in a strongly reduced performance in co-ordination and cognitive function tests while producing profound sedation. When oral midazolam is used, dosage adjustment is usually recommended. Although no clinically significant interaction is expected with midazolam used for short-term sedation, caution should be exercised if intravenous midazolam is concomitantly given with verapamil or diltiazem.

Macrolide Antibiotics: Erythromycin and clarithromycin
Co-administration of oral midazolam and erythromycin or clarithromycin significantly increased the AUC of midazolam about 4-fold and more than doubled the elimination half- life of midazolam, depending on the study. Marked changes in psychomotor tests were observed and it is advised to adjust doses of midazolam, if given orally, due to significantly delayed recovery.
When single bolus doses of midazolam were given for short-term sedation, the effect of midazolam was not enhanced or prolonged to a clinically significant degree by erythromycin, although a significant decrease in plasma clearance was recorded. Caution should be exercised if intravenous midazolam is concomitantly given with erythromycin or clarithromycin. No clinical significant interaction has been shown with midazolam and other macrolide antibiotics.

Cimetidine and ranitidine
Co-administration of cimetidine (at doses equal or higher than 800 mg/day) and intravenous midazolam slightly increased the steady-state plasma concentration of midazolam, which could possibly lead to a delayed recovery, whereas co-administration of ranitidine had no effect. Cimetidine and ranitidine did not affect oral midazolam pharmacokinetics. These data indicate that intravenous midazolam can be administered at usual doses of cimetidine (i.e. 400 mg/day) and ranitidine without dosage adjustment.

Protease inhibitors

Saquinavir
Co-administration of a single intravenous dose of 0.05 mg/kg midazolam after 3 or 5 days of saquinavir dosing (1200 mg three times daily) to 12 healthy volunteers decreased the midazolam clearance by 56 % and increased the elimination half-life from 4.1 to 9.5 h. Only the subjective effects to midazolam (visual analogue scales with the item “overall drug effect”) were intensified by saquinavir.
Therefore, a single bolus dose of intravenous midazolam can be given in combination with saquinavir. Nevertheless, during a prolonged midazolam infusion, a total dose reduction is recommended to avoid delayed recovery (see section 4.4).

Other protease inhibitors
Considering that saquinavir has the weakest CYP3A4 inhibitory potency among all protease inhibitors, the dosage of midazolam should be systematically reduced during prolonged infusion when administered in combination with other protease inhibitors. Patients should also be closely monitored.

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

Inducers of CYP3A4
Rifampicin decreased the plasma concentrations of intravenous midazolam by about 60 % after 7 days of rifampicin 600 mg o.d. The terminal half-life decreased by about 50-60 %.
Rifampicin decreased the plasma concentrations of oral midazolam by 96 % in healthy subjects and its psychomotor effects were almost totally lost.
Carbamazepine / phenytoin: Repeat dosages of carbamezepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 90 % and a shortening of the terminal half-life by 60 %.

Saint-John’s-wort
Long-term use of herbal medicinal products containing Saint-John’s-wort *(Hypericum perforatum)* leads to a decrease of the plasma concentration of midazolam by selective induction of CYP3A4. This may cause reduced therapeutic activity of midazolam. After intravenous administration this effect is considerably less pronounced than after oral use of midazolam.

CNS depressants
Other sedative active substances may potentiate midazolam effects.

The pharmacological classes of CNS depressants include opiates (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, phenobarbital, sedative antidepressants, antihistaminics and centrally acting antihypertensive active substances.
An additional sedative effect should be taken into account when midazolam is combined with other sedative active substances.
Moreover, additional increase of respiratory depression should be particularly monitored in case of concomitant treatment with opiates, phenobarbital or benzodiazepines.
Alcohol may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration.

Other interactions
The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics required for general anaesthesia.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of midazolam in pregnant women. 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 (aspiration risk in the mother, irregularities in the fetal 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 should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean section.

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

Lactation

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

Fertility

No data 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.

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

Generalised hypersensitivity reactions: skin reactions, cardiovascular reactions, bronchospasm, anaphylactic shock.

Psychiatric disorders

Confusional state, euphoric mood, hallucinations

Agitation*, hostility*, rage*, aggressiveness* and excitement*

Physical drug dependence and withdrawal syndrome

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.

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

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

Skin 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

Offensive behaviour

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

Use of midazolam – even in therapeutic doses – may lead to the development of physical dependence after prolonged intravenous administration, abrupt discontinuation may be accompanied by withdrawal symptoms including withdrawal convulsions.

Life-threatening cardiac, vascular and respiratory 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**)

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Symptoms

The symptoms of overdose are mainly an intensification of the pharmacological effects; drowsiness, mental confusion, lethargy and muscle relaxation or paradoxical excitation. More serious symptoms would be areflexia, hypotension, cardio-respiratory depression, apnoea and 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.

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 overdosage 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

Pharmacotherapeutic group: Hypnotics and sedatives – benzodiazepine derivatives
ATC code: N05C D08

Description

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water.

The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of midazolam to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

Mechanism of action, therapeutic effect

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, anticonvulsant and muscle-relaxant effect.

Other pharmacological effects

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).

5.2 Pharmacokinetic properties

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 %.

- *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 0.7-1.2 1/kg. 96 – 98 % of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter fetal 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 – 60 %. Midazolam is hydroxylated by the cytochrome P450

3A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxymidazolam. Plasma concentrations of alpha-hydroxymidazolam are 12 % of those of the parent compound. Alpha-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

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

Pharmacokinetics in other special populations

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

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 of midazolam is also reduced in 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 section 4.4).

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 section 4.4).

Paediatric population

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 IV 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 6 – 12 hours, probably due to liver immaturity and the clearance is reduced (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, amoxicilline, 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)
amoxicilline sodium
acetazolamide sodium
bumetanide
dexamethasone-21-dihydrogenphosphate
diazepam
dimenhydrinate
disodium methotrexate
enoximone
flecainide acetate
fluorouracil
folic acid
foscarnet sodium
furosemide sodium
imipenem
mezlocilline sodium
omeprazol sodium
phenobarbitone sodium
phenytoin sodium
perphenazine enantate
potassium canrenoate
ranitidine hydrochloride
sodium hydrocortisone-21-hydrogensuccinate
sulbactam sodium / ampicilline sodium
theophylline
thiopental sodium
trimethoprim/sulfamethoxazole
trometamol
urokinase

6.3 Shelf life

- unopened

Glass ampoules:	3 years
Polyethylene ampoules:	2 years
Polyethylene bottles:	3 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

[To be completed nationally]

Do not store above 25 °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

[To be completed nationally]

- Ampoules of colourless glass type I.,
  contents: 5 ml, Pack sizes: Packs of 10 ampoules

- Transparent polyethylene plastic ampoules,
  contents: 5 ml, Pack sizes: Packs of 4, 10 or 20 ampoules

- Transparent polyethylene bottles (low-density polyethylene, LDPE),
  contents: 50 ml and 100 ml, Pack sizes: Packs of 10 bottles

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 ampoules 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 ampoule is undamaged.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: <[To be completed nationally]>

Date of latest renewal: <[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

Internal revision date: 09/2020