SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Midazolam Kalceks 5 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5 mg of midazolam.
Each ampoule with 1 ml of solution contains 5 mg of midazolam.
Each ampoule with 3 ml of solution contains 15 mg of midazolam.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear, colourless or yellowish liquid.
Osmolality 275 – 305 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

In adults
- CONSCIOUS SEDATION before or 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 paediatric
- CONSCIOUS SEDATION before or during diagnostic or therapeutic procedures with or without local anaesthesia
- ANAESTHESIA
  - Premedication before induction of anaesthesia
- SEDATION IN INTENSIVE CARE UNITS

For dosage recommendation in specific age range see section 4.2 below, Table 1.

4.2 Posology and method of administration

Midazolam is a potent sedative agent that requires slow administration and individualization of dosage.
The dose should be individualized and 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 of age, critically ill patients, high-risk patients and paediatric patients, the dose should be determined with caution and risk factors related to each patient should be taken into account.

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

Standard dosages are provided in the Table 1 below. Additional details are given in the text following the table.

Table 1 Standard dosage

Indication	Adults <60 y	Adults ≥60 y / critically ill, high-risk patients	Paediatrics
Conscious sedation	***i.v.*** Initial dose: 2-2.5 mg Titration doses: 1 mg Total dose: 3.5-7.5 mg	***i.v.*** Initial dose: 0.5-1 mg Titration doses: 0.5-1 mg Total dose: <3.5 mg	***i.v. 6 months–5 years:*** Initial dose: 0.05-0.1 mg/kg Total dose: <6 mg ***i.v. 6–12 years:*** Initial dose: 0.025-0.05 mg/kg Total dose: <10 mg ***13–16 years:*** As adult ***Rectal >6 months:*** 0.3-0.5 mg/kg ***i.m. 1–15 years:*** 0.05-0.15 mg/kg
Anaesthesia premedication	***i.v.*** 1-2 mg repeated ***i.m.*** 0.07-0.1 mg/kg	***i.v.*** Initial dose: 0.5 mg Slow uptitration as needed ***i.m.*** 0.025-0.05 mg/kg	***Rectal >6 months:*** 0.3-0.5 mg/kg ***i.m. 1–15 years:*** 0.08-0.2 mg/kg
Anaesthesia induction	***i.v.*** 0.2 mg/kg (0.2-0.35 mg/kg without premedication)	***i.v.*** 0.05-0.15 mg/kg (0.15-0.2 mg/kg without premedication)	Not indicated in paediatrics
Sedative component in combined anaesthesia	***i.v.*** intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	***i.v.*** Lower doses than recommended for adults <60 years	Not indicated in paediatrics
Sedation in ICU	***i.v.*** Loading dose: 0.03-0.3 mg/kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		***i.v. <32 weeks gestational age:*** 0.03 mg/kg/h ***i.v. >32 weeks gestational age up to 6 months:*** 0.06 mg/kg/h ***i.v. >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 basal (conscious) sedation prior to diagnostic or surgical intervention, midazolam is administered i.v. The dose must be individualized 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 individual need. Special caution is required for the indication of conscious sedation in patients with impaired respiratory function, see section 4.4 Special warnings and precautions for use.

Adults
The i.v. 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 5-10 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 3.5-7.5 mg. A total dose greater than 5 mg is usually not necessary.
In adults over 60 years of age, critically ill patients, high-risk patients the initial dose must be reduced to 0.5-1 mg, given 5-10 minutes before the beginning of the procedure. Further doses of 0.5-1 mg of midazolam 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 not usually necessary.

Paediatrics
i.v. administration:
Midazolam should be titrated slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes, and it is recommended to wait an additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. Infants and young children less than 5 years of age may require substantially higher doses 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 unless the benefits outweigh the risks. In such cases titration with small increments to clinical effect and careful monitoring are essential.
- *Paediatric patients> 6 months to 5 years of age:* initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but the total dose should not exceed 6 mg. Prolonged sedation and risk of hyperventilation may be associated with the higher doses (see section 4.4).
- *Paediatric patients 6 to 12 years of age:* initial dose 0.025 to 0.05 mg/kg. A total dose up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hyperventilation may be associated with the higher doses (see section 4.4).
- *Paediatric patients 13 to 16 years of age:* should be dosed as adults.

Rectal administration (paediatrics > 6 months):
The total dose of midazolam, ranges from 0.3-0.5 mg/kg.
Total dose should be administered at once and repeated rectal administration avoided. The use in paediatrics less than 6 months of age is not recommended, as available data in this population are limited. The solution contained in the ampoule is administered rectally by means of a plastic applicator attached to a syringe. If the volume to be administered is too small, water may be added for a total volume of 10 ml.

i.m. administration (paediatrics 1-16 years):
The recommended dose range is 0.05 to 0.15 mg/kg given 5-10 minutes before the beginning of the procedure. A total dose greater than 10 mg is not usually necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as i.m. injection may be painful.
In paediatrics less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

ANAESTHESIA-PREMEDICATION
Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory.

Midazolam can also be administered in combination with anticholinergics. For this indication midazolam should be administered i.v. or i.m. (deep into a large muscle mass 20-60 minutes before induction of anaesthesia), or preferably via the rectal route in paediatrics (see below). Adequate observation of the patient after administration is mandatory as inter-individual sensitivity varies and symptoms of overdose may occur.

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

Paediatrics
Rectal administration (>6 months): The total dose of midazolam, usually 0.4 mg/kg, ranging from 0.3-0.5 mg/kg, should be administered 20-30 minutes before induction of anaesthesia. The solution contained in the ampoule is administered rectally by means of a plastic applicator attached to a syringe. If the volume to be administered is too small, water may be added for a total volume of 10 ml. The use in paediatrics less than 6 months of age is not recommended as available data are limited.

i.m. administration(1-15 years):
As i.m. injection may be painful this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08-0.2 mg/kg of midazolam administered i.m. has been shown to be effective and safe.
In children between ages 1 and 15, proportionally higher doses are required than in adults in relation to body-weight. It is recommended that midazolam should be administered deep into a large muscle mass 30-60 minutes prior to the induction of anaesthesia.
In paediatrics less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

INDUCTION OF ANAESTHESIA

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

Adults below the age of 60 years
- A dose of 0.15-0.2 mg/kg, administered i.v. over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.
- In non-premedicated patients the dose may be higher (0.3-0.35 mg/kg), administered i.v. over 20-30 seconds and allowing about 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with volatile liquid inhalational anaesthetics. In resistant cases, a total dose of up to 0.6 mg/kg may be used for induction, but such larger doses may prolong recovery.

Adults above the age of 60 years and/or critically ill and/or high-risk patients
- In non-premedicated patients the lowest initial dose of 0.15-0.2 mg/kg is recommended.

- In premedicated patients a dose of 0.05-0.15 mg/kg administered i.v. over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.

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

SEDATIVE COMPONENT IN COMBINED ANAESTHESIA
Adults
Midazolam can be given as a sedative component in combined anaesthesia by either further intermittent small i.v. doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of i.v. midazolam (range between 0.03 and 0.1 mg/kg/h) typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction.
In adults over 60 years of age, critically ill and/or high-risk patients lower maintenance doses will be required.

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

SEDATION IN THE INTENSIVE CARE UNIT
The desired level of sedation is reached by stepwise titration of midazolam followed by either continuous infusion or intermittent bolus, according to the clinical need, physical status, age and concomitant medication (see section 4.5).

Adults
i.v. loading dose: 0.03-0.3 mg/kg should be given slowly in increments. Each increment of 1-2.5 mg should be injected over 20-30 seconds allowing 2 minutes between successive increments.
In hypovolemic, vasoconstricted or hypothermic patients the loading dose should be reduced or omitted.
When midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of midazolam can be safely titrated on top of any sedation caused by the analgesic.
i.v. maintenance dose: doses can range from 0.03-0.2 mg/kg/h. In hypovolemic, vasoconstricted or hypothermic patients the maintenance dose should be reduced. The level of sedation should be assessed regularly if the patient's condition permits. With long-term sedation, tolerance may develop and the dose may have to be increased.

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

Paediatrics up to 6 months of age
Midazolam should be given as a continuous i.v. infusion:
- Paediatrics ≤32 weeks of gestational age: starting dose at 0.03 mg/kg/hr (0.5 µg/kg/min)
- Paediatrics >32 weeks of gestational age up to 6 months of age: starting dose 0.06 mg/kg/hr (1 µg/kg/min)

Intravenous loading doses should not be used rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation.
Careful monitoring of respiratory rate and oxygen saturation is required.

Paediatrics over 6 months of age
In intubated and ventilated patients, a loading dose of 0.05 to 0.2 mg/kg i.v. should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. Midazolam should not be

administered as a rapid intravenous dose. The loading dose is followed by a continuous i.v. infusion at 0.06 to 0.12 mg/kg/h (1 to 2 µg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental i.v. doses of midazolam can be administered to increase or maintain the desired effect.
When initiating an infusion with midazolam in hemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for hemodynamic 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.

Special dosage instructions
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 4.2, 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetics in special populations and Use in special populations).

Hepatic impairment
The clinical effects in patients with hepatic impairment may be stronger and prolonged. The dose of midazolam may have to be reduced and vital signs should be monitored (see section 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetics in special populations).

Route of administration
Ampoules for intravenous infusion, intravenous injection, intramuscular and rectal administration.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to midazolam, benzodiazepines or to any of the excipients listed in section 6.1.
Use of this drug for conscious sedation in patients with severe respiratory failure or acute respiratory depression

4.4 Special warnings and precautions for use

i.v. midazolam has been associated with severe respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy resulted.
i.v. midazolam should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory and cardiac functions. Assure immediate availability of resuscitative drugs, equipments, appropriate antidote and personnel trained in their use. Dosage of i.v. midazolam must be individualized for each patient. Lower doses are usually required for elderly, debilitated or higher risk surgical patients. When Midazolam is administered intravenously for conscious sedation, it should be injected slowly (over at least 2 minutes); it should not be administered by rapid or single bolus i.v. injection because of respiratory depression and/or arrest, especially in elderly or debilitated patients. The initial dose may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult; administer over at least 2 minutes and allow additional 2 or more minutes to fully evaluate sedative effect. If further titration is necessary, use small increments to the appropriate level of sedation, allowing an additional 2 or more minutes after each increment to fully evaluate sedative effect. See section 4.2 Posology and method of administration for complete dosing information.

Midazolam should be administered only by experienced physicians in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function, or by persons specifically trained in the recognition and management of adverse reactions, including resuscitation. Severe cardiorespiratory adverse reactions have been reported, including respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening complications are more likely to occur when the injection is given too rapidly or when a high dosage is administered (see section 4.8).

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

Paediatric patients under 6 months of age are especially predisposed to develop airway obstruction and hypoventilation. Therefore it is essential to titrate the dosage with small increments to clinical effect and to carefully monitor respiratory rate and oxygen saturation.
After midazolam is administered as premedication, the patient should be kept under careful observation as individual sensitivity varies and symptoms of overdose may occur.

Special caution is required when administering midazolam to high-risk patients:
- adult patients over 60 years of age
- chronically ill or debilitated patients, e.g.:
    - patients with chronic respiratory insufficiency
    - patients with chronic renal failure, impaired hepatic function or impaired cardiac function
    - paediatric patients, especially those with cardiovascular instability.

Lower doses should be administered to high-risk patients (see section 4.2) and they should be continuously monitored for early signs of alterations of vital functions.
As with any medicine that has CNS depressant and/or muscle-relaxant properties, special caution is required when administering midazolam to patients with myasthenia gravis.

Tolerance
Some loss of efficacy has been reported when using midazolam as long-term sedation in intensive care unit.

Dependence
When midazolam is used in long-term sedation in intensive care, possible development of physical dependence should be taken into account. The risk of developing dependence increases with higher doses and longer duration of treatment; it is also higher in patients with a medical history of alcohol and/or drug abuse (see section 4.8).

Withdrawal symptoms
Physical dependence may develop during prolonged treatment with midazolam in intensive care. Therefore, abrupt termination of treatment leads to 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 higher after abrupt termination of treatment, it is recommended to decrease doses gradually.

Amnesia
Midazolam causes anterograde amnesia (in some situations this effect is very desirable, primarily prior and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged amnesia may cause problems in outpatients who are discharged after the procedure. After receiving midazolam parenterally, patients should be discharged from the hospital or sent to a 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 with midazolam use. Such reactions may occur when high doses are used and/or the medicine is administered rapidly. Such reactions are more prevalent in children and elderly patients.

Altered elimination of midazolam
Altered elimination of midazolam may be caused by compounds that inhibit or induce isoenzyme CYP3A4, and the midazolam dose may need to be adjusted accordingly (see section 4.5).

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

Preterm infants and neonates
Due to an increased risk of apnoea, extreme caution is required when sedating preterm and former preterm non-intubated children. Careful monitoring of breathing rate and oxygen saturation is required.

Rapid injection should be avoided in neonates.
Neonates have immature organs and/or reduced organ function and are therefore more sensitive to profound and/or prolonged respiratory effects of midazolam.
Adverse haemodynamic reactions have been reported in children with cardiovascular instability; rapid intravenous administration should be avoided in these patients.

Paediatric patients less than 6 months
For these patients, midazolam is indicated for sedation in the intensive care unit only.
Children under 6 months of age are especially predisposed to developing airway obstructions and hypoventilation. Therefore titration with small increments until the clinical effect is reached, and careful monitoring of respiratory rate and oxygen saturation are required (see also the section 'Preterm infants' above).

Concomitant use of alcohol / CNS depressants
The concomitant use of midazolam with alcohol or/and CNS depressants should be avoided. Concomitant use may increase the clinical effect of midazolam, causing profound sedation or clinically relevant respiratory depression (see section 4.5).

Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken.
Complex sleep – related behaviors which may include sleep driving, making phone calls, preparing and eating food while asleep.

Risks from Concomitant Use with Opioids
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Midazolam Kalceks with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.
If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.
If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.
Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Midazolam Kalceks is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

Discharging criteria
After receiving midazolam, patients may be discharged from hospital or sent to a consulting room only when it is recommended by the attending physician and if accompanied by an attendant. The patient should not be left unattended after discharge.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Midazolam is metabolized by CYP3A4.
Inhibitors and inducers of CYP3A have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam requiring dose adjustments accordingly.

Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to intravenous administration of midazolam, in particular since CYP3A4 also exist 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 intravenous dose of midazolam the change in maximal clinical effect will be minor due to inhibition of CYP3A4, while the duration of the effect may be prolonged. However, after prolonged administration of midazolam, both the magnitude and duration of the effect will be increased with CYP3A4 inhibition.

There are no available studies on the effect of CYP3A4 modulation on the pharmacokinetics of midazolam after rectal and intramuscular administration. It is expected that these interactions are less pronounced for rectal than for 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 intravenous administration.

Therefore it is recommended to carefully monitor the clinical effect and vital signs during the use of midazolam, taking into account that the clinical effect of midazolam may be stronger and last longer after co-administration of a CYP3A4 inhibitor, even if it is administered only once. In particular, administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors (e.g. during intensive care) may cause long-lasting hypnotic effects, delayed recovery from anaesthesia and respiratory depression, thus requiring dose adjustments.

With CYP3A4 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, short-term treatment results in less apparent interactions with midazolam. However, for strong inducers a significant induction even after short-term treatment cannot be excluded.
Midazolam is not known to change the pharmacokinetics of other drugs.

Drugs that inhibit CYP3A:
Azole antifungals:
- Ketoconazole increased the plasma concentrations of intravenously administered midazolam 5-fold while the terminal half-life increased approximately 3-fold. If parenteral midazolam is co-administered with the strong CYP3A inhibitor ketoconazole, it should be done in an intensive care unit or similar setting which ensures close clinical monitoring and appropriate treatment in case of respiratory depression and/or prolonged sedation. Staggered dosing or dosage adjustment should be considered, especially if more than a single intravenous dose of midazolam is administered. The same recommendation may also apply for other azole antifungals (see further), since increased sedative effects of intravenously administered midazolam, although to a lesser extent, are reported.
- Voriconazole increased the plasma concentrations of intravenously administered midazolam 3-fold while the elimination half-life also increased approximately 3-fold.

- Both fluconazole and itraconazole increased the plasma concentrations of intravenously administered midazolam 2-3-fold, associated with terminal half-life extension 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.
- Posaconazole increased the plasma concentrations of intravenously administered midazolam approximately 2-fold.

It should be kept in mind that after oral administration the exposure of midazolam will be significantly higher than that of the above-mentioned ones, especially with ketoconazole, itraconazole and voriconazole.

Midazolam ampoules are not indicated for oral administration.

Macrolide antibiotics
- Erythromycin increased the plasma concentrations of intravenously administered midazolam approximately 1.6-2-fold, associated with terminal half-life extension of midazolam 1.5-1.8-fold.
- Clarithromycin increased the plasma concentrations of midazolam up to 2.5-fold, and the terminal half-life was extended 1.5–2-fold.

Additional information from oral midazolam
- Roxithromycin: Although there is no data available on the effect of roxitromycin on intravenously administered midazolam, the mild effect on the terminal half-life of an oral midazolam tablet (extension by approximately 30%) indicates that the effect of roxithromycin on intravenously administered midazolam may be minor.

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

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

Calcium-channel blockers
- Diltiazem: Administration of a single dose of diltiazem increased the plasma concentration of intravenously administered midazolam by approximately 25% and the terminal half-life was extended by 43%.

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

Various medicines/Herbal substances
- Co-administration of atorvastatin increased the plasma concentrations of intravenously administered midazolam 1.4-fold compared to the control group.

Additional information from oral midazolam
- Nefazodone increased the plasma concentrations of oral midazolam 4.6-fold and the terminal half-life was extended 1.6-fold.
- Aprepitant increased the plasma concentration of midazolam dose-dependently (3.3-fold with a daily dose of 80 mg) and the terminal half-life was extended 2-fold.

Drugs that induce CYP3A

- Rifampicin decreased the plasma concentrations of intravenously administered midazolam by 60% after administration of rifampicin 600mg/day for 7 days. Terminal half-life was shortened by approximately 50 to 60%.

Additional information from oral midazolam

- Rifampicin decreased the plasma concentrations of oral midazolam by 96% in healthy individuals and its psychomotor effects where almost totally lost.
- Carbamazepine / phenytoin: Repeated doses of carbamazepine or phenytoin decreased the plasma concentration of oral midazolam by up to 90% and the terminal half-life was shortened by 60%.
- Efavirenz: The 5-fold increase in the ratio of the CYP3A4 generated metabolite α-hydroxymidazolam to midazolam confirms its CYP3A4-inducing effect.

Herbal substances and food

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

Pharmacodynamic interactions

Co-administration of midazolam with other sedative / hypnotic agents and CNS depressants (including alcohol) is likely to result in enhanced sedation and respiratory depression.
These include opiates derivatives (be they used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate, sedative antidepressants, 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 (see section 4.4).
Midazolam decreases the minimum alveolar concentration of inhalational anaesthetics.

Opioids

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see section 4.4).
Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

4.6 Fertility, pregnancy and lactation

Pregnancy

Insufficient data are available to assess safety of midazolam during pregnancy.
Animal studies do not indicate a teratogenic effect, but foetotoxicity has been observed with use of other benzodiazepines. There are no data about the use of the drug during the first two trimesters of pregnancy.
The administration of high doses of midazolam in the last trimester of pregnancy, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or foetal adverse effects (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).

Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at same risk of developing withdrawal symptoms in the postnatal period.
Consequently, midazolam should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean section.
The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

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

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

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

Immune system disorders	
frequency not known	Hypersensitivity, angioedema, anaphylactic shock
Psychiatric disorders	
frequency not known	Confused state, euphoric mood, hallucinations Agitation*, hostility*, rage*, aggressiveness*, excitement* Physical drug dependence and withdrawal syndrome Abuse
Nervous system disorders	
frequency not known	Involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity* Sedation (prolonged and postoperative), alertness decreased, somnolence, headache, dizziness, ataxia, anterograde amnesia**, the duration of which is directly related to the administered dose Convulsions have been reported in premature infants and neonates Drug withdrawal convulsions
Cardiac disorders	
frequency not known	Cardiac arrest, bradycardia
Vascular disorders	
frequency not known	Hypotension, vasodilation, thrombophlebitis, thrombosis
Respiratory disorders	
frequency not known	Respiratory depression, apnoea, respiratory arrest, dyspnea, laryngospasm, hiccups
Gastrointestinal disorders	
frequency not known	Nausea, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders	

frequency not known	Skin rash, urticaria, pruritus
General disorders and administration site reactions	
frequency not known	Fatigue, injection site erythema, injection site pain
Injury, poisoning and procedural complications	
frequency not known	Falls, fractures***
Social circumstances	
frequency not known	Assault*

* Paradoxical reactions have been reported among children and the elderly, in particular (see section 4.4).
** Anterograde amnesia may persist until the end of the procedure and a few isolated cases prolonged amnesia have been reported (see section 4.4).
*** The risk of falls and fractures is higher for those taking concomitant sedatives (including alcoholic beverages) and in elderly patients.

Dependence: midazolam may cause development of physical dependence, even if used in therapeutic doses. Discontinuation (especially abrupt discontinuation) of treatment after prolonged intravenous administration may cause withdrawal symptoms, including drug withdrawal convulsions (see section 4.4). Cases of drug abuse have been reported.
Severe cardiorespiratory adverse reactions have occurred. Life-threatening complications are more prevalent in adults over 60 years of age and patients with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the administration rate is too rapid or the dose is high (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 Centre for Adverse Drug Reaction Monitoring by visiting the website portal.npra.gov.my

4.9 Overdose

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

Treatment
A patient's vital signs should be monitored and supportive treatment started according to the patient's clinical status. In particular, patients may require symptomatic treatment for cardiorespiratory or central nervous system effects.
If taken orally further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.
If central nervous system depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance and has a low solubility in water.
The basic nitrogen in position 2 of the imidazobenzodiazepine ring enables midazolam to form water-soluble salts with acids, producing a stable and-well tolerated solution for injection or infusion.
The pharmacological effect of midazolam is characterised by short duration because of a rapid metabolic transformation over a short time. Midazolam has a potent sedative and sleep-inducing effect. Furthermore, it has the effect of relieving anxiety and convulsions and of relaxing muscles.
After intramuscular or intravenous administration, anterograde amnesia of short duration occurs; (the patient does not remember events occurring at the time of the substance's maximal activity).

5.2 Pharmacokinetic properties

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

Absorption after rectal administration
Midazolam is rapidly absorbed after rectal administration. The peak plasma concentration is reached within approximately 30 minutes. The absolute bioavailability is approximately 50%.

Distribution
After intravenous administration of midazolam one or two distinct distribution phases form on the plasma concentration time curve. The steady-state distribution volume is 0.7 to 1.2 l/kg.
96-98% of midazolam binds to plasma proteins, mostly albumin. Midazolam passes slowly and in small quantities into the cerebrospinal fluid. It has been shown in humans that midazolam crosses the placental barrier slowly and enters foetal circulation. Midazolam has been found in human breast milk in small quantities.

Metabolism
Midazolam is almost entirely eliminated by biotransformation. It has been estimated that the fraction of the dose metabolised through the liver is 30 - 60%. Midazolam is hydroxylated by cytochrome P4503A4 isoenzyme. The main metabolite in plasma and urine is alpha-hydroxymidazolam.
The plasma concentrations of alpha-hydroxymidazolam are 12% of the parent compound.
Alpha-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

Elimination
In healthy individuals the midazolam elimination half-life ranges between 1.5 and 2.5 hours.
Plasma clearance is 300 to 500 ml/min. Midazolam is mostly eliminated through the kidneys (60-80% of the dose injected) and is recovered as glucuronide-conjugated alpha-hydroxymidazolam. Less than 1% of the dose is recovered as an unmodified substance in the urine. The elimination half-life of alpha-hydroxymidazolam is under one hour. The elimination kinetics of intravenously administered midazolam are similar to that of bolus injection.

Pharmacokinetics in special populations
Elderly

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

Paediatric population
While the absorption rate of rectally administered midazolam is similar in children and adults, the bioavailability is lower in children (5-18%). Compared to adults, the elimination half-life after intravenous and rectal administration is shorter (1 - 1.5 hours) in children 3 to 10 years of age. This difference corresponds to the elevated 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).

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 insufficiency
The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared to those in healthy individuals (see section 4.4).

Patients with renal insufficiency
The elimination half-life in patients with chronic renal failure is similar to that in healthy individuals.

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

Patients with cardiac insufficiency
The elimination half-life in patients with congestive heart failure is longer than that in healthy individuals (see section 4.4).

5.3 Preclinical safety data

There are no further relevant preclinical data for the prescribing doctor beyond the information set out in other sections of the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid concentrated
Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Midazolam Kalceks solution for injection/infusion must not be diluted with Dextran 6% solution in glucose.
Midazolam Kalceks solution for injection/infusion must not be mixed with alkaline solutions for injection.
Midazolam precipitates in solutions containing hydrogen carbonate.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years

Shelf life after dilution
Chemical and physical in-use stability has been demonstrated 40 hours at 25 °C and 3 days at 2-8 °C temperature with following infusion solutions: sodium chloride 0.9 %, glucose 5 % and 10 % and Ringers`s solution.
From a microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30 °C.
Keep the ampoules in the outer carton in order to protect from light. Do not freeze.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I colourless glass ampoules with one point cut containing 1 ml and 3 ml solution.
5 ampoules are packed in a liner. Two liners together are packed into an outer carton.

Pack size: 10 ampoules.

6.6 Special precautions for disposal and other handling

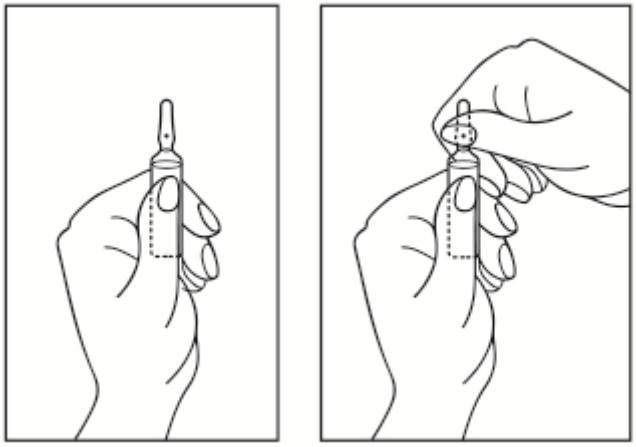
Compatible with the following solutions for infusion
- sodium chloride 0.9 % solution
- glucose 5 % solution
- glucose 10 % solution
- Ringer's solution

After dilution with sodium chloride 0.9 % solution, glucose 5 % solution, glucose 10 % solution or Ringer's solution, the diluted solutions are clear, colourless or yellowish and free from particles.

For intravenous infusion, the content of Midazolam Kalceks ampoules may be diluted with one of the solutions mentioned above in a ratio of 15 mg midazolam per 100 to 1000 ml of infusion solution.

Midazolam Kalceks solution for injection/infusion is for single use only.
The solution should be examined visually before administration. Only clear solution without visible particles should be used.

Instruction of ampoule opening:
1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



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

7. PRODUCT REGISTRATION HOLDER AND MANUFACTURER

Product Registration Holder:
Eucogen Sdn Bhd
6A, Jalan Sungai Burung U
32/U, Bukit Rimau, 40460 Shah
Alam, Selangor, Malaysia

Brunei Darussalam Product Licence Holder:
Nova Borneo Company Sdn Bhd
Unit 4GF Bangunan Zainuddin & Azizah, Simpang 501
Jalan Tutong, Kg Telanai, Brunei-Muara BA2312

Manufacturer:
HBM Pharma s.r.o.
Sklabinska str., 30, Martin, 036 80
Slovakia

8. DATE OF REVISION OF THE TEXT

01/2023