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 (as hydrochloride).
One ampoule with 1 ml of solution contains 5 mg of midazolam.
One ampoule with 3 ml of solution contains 15 mg of midazolam.
One ampoule with 10 ml of solution contains 50 mg of midazolam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless solution.
pH 2.9 – 3.7
Osmolality 275 – 305 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Midazolam Kalceks is a short-acting hypnotic with the following indications for use:

Adults
- CONSCIOUS SEDATION with or without local anaesthesia before or during diagnostic or therapeutic procedures
- ANAESTHESIA
  - premedication before the induction of anaesthesia
  - induction of anaesthesia
  - as a sedative component in maintenance of anaesthesia
- SEDATION IN THE INTENSIVE CARE UNIT

Children
- CONSCIOUS SEDATION with or without local anaesthesia before or during diagnostic or therapeutic procedures
- ANAESTHESIA
  - premedication before the induction of anaesthesia
- SEDATION IN THE INTENSIVE CARE UNIT

4.2 Posology and method of administration

Posology

STANDARD DOSAGES
Midazolam is a potent sedative agent that requires slow administration and titration. Titration is strongly recommended to safely obtain the desired level of sedation according to clinical needs, physical status, age, and concomitant medication. For patients over 60 years of age, debilitated patients or chronically

ill patients and children the medicine should be administered with care and the risk factors related to each patient should be evaluated on an individual basis. Standard dosages are provided in the table below. Additional information is provided in the text following the table.

Indication	**Adults <60 years**	**Adults ≥60 years/ debilitated or chronically ill patients**	**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. 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*** 0.05-0.15 mg/kg
Anaesthesia premedication	***iv.*** 1-2 mg repeated ***im.*** 0.07-0.1 mg/kg	***iv.*** Initial dose: 0.5 mg Slow uptitration as needed ***im.*** 0.025-0.05 mg/kg	***Rectal >6 months*** 0.3-0.5 mg/kg ***im. 1-15 years*** 0.08-0.2 mg/kg
Anaesthesia induction	***iv.*** 0.15-0.2 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 the intensive care unit (ICU)	***iv.*** Loading dose: 0.03-0.3 mg/kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		***iv.*** ***in neonates ≤ 32 weeks gestational age*** 0.03 mg/kg/h ***iv. in neonates >32 weeks and children < 6 months*** 0.06 mg/kg/h ***iv. in patients over 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 sedation required for diagnostic and surgical procedures midazolam is administered intravenously. The suitable dose is determined on an individual basis. The medicine should not be administered rapidly or as a bolus injection, but by titrating the dose. The onset of the sedative effect may vary individually, depending on the physical status of the patient and the dosage method used (e.g. rate of administration, dose level). If necessary, additional doses may be administered according to individual needs. The onset of action is approximately 2 minutes after the injection. The maximum effect is obtained in approximately 5 to 10 minutes.

Adults
Midazolam should be administered slowly as an intravenous injection at a rate of approximately 1 mg/30 seconds. In adults under 60 years of age 2 to 2.5 mg is administered 5 to 10 minutes before the beginning of the procedure as an initial dose. The initial dose may be followed by additional 1 mg doses as necessary. The average total dosage is 3.5 to 7.5 mg. Administration of a total dosage higher than 5 mg is usually not necessary.
The initial dose for patients over 60 years of age, debilitated patients or chronically ill patients is 0.5 to 1 mg, administered 5 to 10 minutes before the beginning of the procedure. Additional doses of 0.5 to 1 mg of midazolam may be administered as necessary. In these patients it may take more time to reach the peak effect; therefore additional doses of midazolam should be titrated very slowly and carefully. Administration of a total dosage higher than 3.5 mg is usually not necessary.

Paediatric population
Iv. administration: doses of midazolam are titrated slowly until the desired clinical effect is reached. The initial dose is administered in 2 to 3 minutes. To fully evaluate the sedative effect, one should wait another 2 to 5 minutes before beginning with the procedure or repeating the dose. If it is necessary to increase the sedative effect, continue to administer additional low doses until the appropriate sedation level is reached. For infants and children under 5 years of age, significantly higher doses may be required (mg/kg) compared to older children and adolescents.

- Children under 6 months of age: children under 6 months of age are especially predisposed to develop airway obstruction and hypoventilation. Therefore, conscious sedation is not recommended in children under 6 months of age.
- Patients 6 months to 5 years of age: the initial dose is 0.05 to 0.1 mg/kg. To reach the desired effect, it may be necessary to administer a dose up to 0.6 mg/kg. However, the total dosage should not exceed 6 mg. Higher doses may cause prolonged sedation and risk of hypoventilation.
- Children 6 to 12 years of age: the initial dose is 0.025 to 0.05 mg/kg. It may be necessary to administer a total dosage of 0.4 mg/kg (10 mg as the maximum dosage). Higher doses may cause prolonged sedation and risk of hypoventilation.
- Children 12 to 16 years of age: use the recommended dosages for adults.

Rectal administration: the total dosage of midazolam is usually 0.3 to 0.5 mg/kg. 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 whole dose should be administered at once. Avoid repeated rectal administration.
Rectal administration is not recommended in children under 6 months, due to limited data concerning this age group.

Im. administration: doses range from 0.05 to 0.15 mg/kg. Usually the total dose greater than 10.0 mg is not required. The intramuscular route should only be used in exceptional cases.
Rectal administration should be preferred, as intramuscular injection is painful.
In children weighing less than 15 kg midazolam solutions with a concentration higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

ANAESTHESIA DOSAGE
PREMEDICATION
Administration of midazolam immediately before the procedure causes sedation (hypnotic or anaesthetic effect and depressed level of consciousness) and preoperative impairment of memory. Midazolam can also be administered in combination with anticholinergics. In such case midazolam is administered intravenously or intramuscularly (deep into the muscle mass, 20 to 60 minutes before the induction of anaesthesia), and in children rectal administration should be preferred (see below). The patient should be carefully and constantly monitored after administration of the premedication, as sensitivity towards the medication varies and symptoms of overdose may occur.

Adults
The recommended dose used for preoperative sedation and to impair memory of preoperative events for patients belonging to ASA Physical Status Class I and II, and patients under 60 years of age is 1 to 2 mg intravenously, repeated as necessary, or 0.07 to 0.1 mg/kg intramuscularly. For patients over 60 years of age, debilitated patients or chronically ill patients the dosage should be decreased and adjusted based on the specific case. The recommended intravenous initial dose is 0.5 mg and this should be slowly increased as needed. The recommended intramuscular initial dose is 0.025 to 0.05 mg/kg. In the case of concomitant administration of narcotics, midazolam dosage should be reduced. The usual dosage is 2 to 3 mg.

Paediatric population
Neonates and children up to 6 months of age:
This medicine is not recommended in children under 6 months of age, due to limited data.

Children over 6 months of age
Rectal administration: The total dosage of midazolam (usually in the range of 0.3 to 0.5 mg/kg) should be administered 15 to 30 minutes before the 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.

Im. administration: Intramuscular administration is painful; therefore this method of administration should only be used in exceptional cases. Rectal administration is preferred. The proven and safe dosage range for intramuscular administration is 0.08 to 0.2 mg/kg. Children between 1 to 15 years of age require proportionally higher dosages per body weight than adults.

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

INDUCTION
Adults
If midazolam is used before other anaesthetic agents for induction of anaesthesia, the patients' individual response is variable. The dosage should be increased by titrating until the desired effect is reached. The dosage is increased based on the patient's age and clinical status. If midazolam is used before or in combination with other intravenous or inhalational medicines used for induction of anaesthesia, the initial doses of all these medicines should be significantly reduced, sometimes to as low as 25% of the usual initial dose.
The desired level of anaesthesia is reached by gradually increasing the dose. For intravenous induction of anaesthesia midazolam is administered at a slow rate in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds, with 2-minute intervals between the doses.

- *For premedicated adults under 60 years of age* usually a 0.15 to 0.2 mg/kg dose administered intravenously is sufficient.
- *For non-premedicated adults under 60 years of age* higher doses (0.3 to 0.35 mg/kg iv) may be used. If full induction is sought, the additional doses may comprise approximately 25% of the patient's initial dose. Induction may also be conducted with inhalational anaesthetics. In refractory cases a total dosage of up to 0.6 mg/kg may be used for induction, but such higher doses may cause prolong recovery from anaesthesia.
- *For premedicated adults over 60 years of age, debilitated patients or chronically ill patients* the dosage should be significantly reduced, e.g. up to 0.05 to 0.15 mg/kg administered intravenously over 20 to 30 seconds, with 2 minutes waiting time for the drug to take effect.
- *For non-premedicated adults over 60 years of age* usually higher midazolam doses are required for induction: the recommended initial dose is 0.15 to 0.3 mg/kg. For non-premedicated debilitated patients or patients with a severe systemic disease less midazolam should usually be administered for induction. An initial dose of 0.15 to 0.25 mg/kg is generally sufficient.

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 patients or chronically ill patients lower doses are required for maintenance.

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. Midazolam is administered according to clinical need and the patient's condition, age, and concomitant medications (see section 4.5).

Adults

Iv. loading dose: 0.03 to 0.3 mg/kg administered slowly in increments. Every 1 to 2.5 mg dose should be administered over 20 to 30 seconds, with 2-minute intervals between the doses. For patients with hypovolaemia, vasoconstriction or hypothermia, the loading dose should be reduced or omitted. If midazolam is administered together with strong analgesics, the analgesics should be administered first. This enables safe titration of the sedative effect of midazolam, so it is not affected by analgesic sedation.

Iv. maintenance dose: ranging from 0.03 to 0.2 mg/kg/h. For patients with hypovolaemia, vasoconstriction or hypothermia, the maintenance dose should be reduced. The sedation level should be assessed on a regular basis. Long-term sedation may lead to tolerance, which may require increasing the dose.

Paediatric population

Neonates and children up to 6 months of age:
Midazolam is administered as an intravenous continuous infusion. The initial dose for neonates born before 32 weeks of gestation is 0.03 mg/kg/h (0.5 µg/kg/min), and in neonates born after 32 weeks of gestation as well as children up to 6 months of age 0.06 mg/kg/h (1 µg/kg/min).
Intravenous loading doses are not recommended in preterm infants, neonates and children up to 6 months of age; rather the infusion rate should be higher during the first hours to reach therapeutic concentrations. The infusion rate should be frequently and carefully re-evaluated to select the lowest possible effective dose and to prevent accumulation of the drug, especially over the first 24 hours. Careful monitoring of breathing rate and oxygen saturation is required.

Children over 6 months of age:
Intubated and ventilated children should be administered a loading dose of 0.05 to 0.2 mg/kg iv, slowly over 2 to 3 minutes, to achieve the desired clinical effect.
Midazolam should not be administered as a rapid intravenous injection. Following the loading dose, midazolam is administered as continuous infusion at a rate of 0.06 to 0.12 mg/kg/h (1 to 2 µg/kg/min). As necessary, the infusion rate can be increased or reduced (generally, 25% of the initial or following infusion rate), or additional doses of midazolam are intravenously administered to maintain or increase the desired effect.
If the midazolam infusion is initiated in haemodynamically unstable patients, the usual loading dose should be titrated with low doses and the patient should be monitored for haemodynamic alterations (e.g. hypotension). These patients are more sensitive towards midazolam's depressive effect on respiration, and careful monitoring of respiratory rate and oxygen saturation is required.

In premature infants, neonates and children with body weight below 15 kg it is not recommended to use midazolam solutions with a concentration above 1 mg/ml. Higher concentrations should be diluted to 1 mg/ml.

Special populations
Renal impairment
In patients with severe renal impairment (creatinine clearance below 30 ml/min) midazolam may be accompanied by more pronounced and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression.
Midazolam should therefore be dosed carefully in this patient population and titrated for the desired effect (see section 4.4).

In patients with renal failure (creatinine clearance <10 ml/min) the pharmacokinetics of unbound midazolam following a single intravenous 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 1'-hydroxymidazolam glucuronide (see sections 4.4 and 5.2).

Hepatic impairment
Hepatic impairment reduces the clearance of intravenously administered midazolam with a subsequent increase in terminal half-life. This may lead to a stronger and prolonged clinical effect. The required dose of midazolam may be reduced and vital signs should be properly monitored. (See section 4.4).

Paediatric population
See above and section 4.4.

Method of administration
For intravenous, intramuscular and rectal use.
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

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 respiratory and cardiac 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).

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

Special caution is required for conscious sedation in patients with impaired respiratory function (see section 4.3).

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

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

Amnesia
Anterograde amnesia may occur with therapeutic doses, with the risk increasing at higher dosages (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 restlessness, agitation, irritability, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault have been reported 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. In the event of these reactions discontinuation of the drug should be considered.

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).

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

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 and neonates' 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 (that could result in coma or death) or clinically relevant respiratory depression (see section 4.5).

Risk from concomitant use of opioids
Concomitant use of Midazolam Kalceks and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Midazolam Kalceks with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Midazolam Kalceks concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

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 1 ml, i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Midazolam is metabolized by CYP3A4 and CYP3A5.
Inhibitors and inducers of CYP3A have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam 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. The effect of midazolam may be weaker and last shorter when co-administered with a CYP3A inducer and a higher dose may be required.

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 3-4-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

- Telithromycin increased the plasma levels of oral midazolam 6-fold.
- 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.

Intravenous anaesthetics

- Disposition of intravenous midazolam was also changed by intravenous propofol (AUC and half-life increased by 1.6-fold).

HIV protease inhibitors

- Saquinavir and other HIV (human immunodeficiency virus) 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.
- Hepatitis C virus (HCV) protease inhibitors: boceprevir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of midazolam AUC after IV administration and prolonged its elimination half-life 4-fold.

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 given to patients undergoing coronary artery bypass grafting increased the plasma concentration of intravenously administered midazolam by approximately 25% and the terminal half-life was extended by 43%. This was less than the 4-fold increase seen after oral administration of midazolam.

Additional information from oral midazolam

- Verapamil increased the plasma concentrations of oral midazolam 3-fold. The terminal- half-life of midazolam was extended by 41%.

Various medicines/Herbal substances

- Co-administration of atorvastatin increased the plasma concentrations of intravenously administered midazolam 1.4-fold compared to the control group.
- Intravenous fentanyl is a weak inhibitor of midazolam elimination: AUC and half-life of IV midazolam were increased by 1.5-fold in the presence of fentanyl.

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.

- Tyrosine kinase inhibitors have been shown to be potent inhibitors of CYP3A *in vitro* (imatinib, lapatinib) or *in vivo* (idelalisib). After concomitant administration of idelalisib, oral midazolam exposure was increased on average 5.4-fold.
- NK1 receptor antagonists (aprepitant, netupitant, casoprepitant) dose-dependently increased the plasma concentrations of oral midazolam up to about 2.5-3.5-fold and increased terminal half-life by approximately 1.5-2-fold.
- For a number of drugs or herbal medicines, a weak interaction with midazolam's elimination was observed with concomitant changes in its exposure (< 2-fold change in AUC) (everolimus, cyclosporine, simeprevir, propiverine). These weak interactions are expected to be further attenuated after IV administration.

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%.
- Ticagrelor is a weak CYP3A inducer but has only small effects on intravenously administered midazolam (-12%) and 4-hydroxymidazolam (-23%) exposures.

Additional information from oral midazolam

- Rifampicin decreased the plasma concentrations of oral midazolam by 96% in healthy subjects and its psychomotor effects where almost totally lost.
- Carbamazepine / phenytoin: Repeated 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%.
- The very strong CYP3A4 induction seen after mitotane or enzalutamide resulted in a profound and long-lasting decrease of midazolam levels in cancer patients. AUC of orally administered midazolam was reduced to 5% and 14% of normal values respectively.
- Clobazam and efavirenz are weak inducers of midazolam metabolism and reduce the AUC of the parent compound by approximately 30%. There is a resulting 4-5-fold increase in the ratio of the active metabolite (1'-hydroxymidazolam) to the parent compound but the clinical significance of this is unknown.
- Vermurafenib modulates CYP isozymes and induces CYP3A4 mildly: repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 39% (up to 80% in individuals).

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.

Additional information from oral midazolam

- Quercetin (also contained in Ginkgo biloba) and Panax ginseng both have weak enzyme inducing effects and reduced exposure to midazolam after its oral administration by approximately 20-30%.

Acute protein displacement

- Valproic acid: increased concentration of free midazolam due to displacement from plasma protein binding sites by valproic acid cannot be excluded although the clinical relevance of such an interaction is not known.

Pharmacodynamic interactions

Co-administration of midazolam with other sedative / hypnotic agents and CNS depressants (including alcohol) is likely to result in enhanced sedation and cardiorespiratory 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.

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Midazolam Kalceks with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

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.

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.
An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested. The administration of high doses of midazolam in the last trimester of pregnancy, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or foetal adverse effects (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).
Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the 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

Midazolam has a major influence on the ability to drive and use machines.

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

If insufficient sleep occurs or alcohol is consumed, the likelihood of impaired alertness may be increased (see section 4.5).

4.8 Undesirable effects

Frequency categories are as follows:
very common: (≥ 1/10)
common: (≥ 1/100 to < 1/10)
uncommon: (≥ 1/1000 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 to occur when midazolam is injected:

Immune system disorders	
Frequency not known	Hypersensitivity, angioedema, anaphylactic shock
Psychiatric disorders	
Frequency not known	Confusional state, disorientation, emotional and mood disturbances, changes in libido Paradoxical reactions* including restlessness, agitation, irritability, nervousness, hostility, anger, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal 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, vasodilatsioon, 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).

*** There have been reports of falls and fractures in benzodiazepine users. The risk of falls and fractures is higher for those taking concomitant sedatives (including alcoholic beverages) and in elderly patients.

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

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 reporting system listed in Appendix V.

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.

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

Pharmacodynamic effects
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. Midazolam impairs psychomotor function after single and/or multiple doses, but causes minimal haemodynamic changes.
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. Midazolam is not a substrate for drug transporters.

Biotransformation
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 P450 CYP3A4 and CYP3A5 isoenzymes. The main metabolite in plasma and urine is 1'-hydroxymidazolam.
The plasma concentrations of 1'-hydroxymidazolam are 12% of the parent compound.
1'-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

Elimination
In healthy test subjects 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 1'-hydroxymidazolam. Less than 1% of the dose is recovered as an unmodified substance in the urine. The elimination half-life of 1'-hydroxymidazolam is under one hour. The elimination kinetics of midazolam when given by intravenous infusion are similar to that of bolus injection. Repeated administration of midazolam does not induce drug-metabolising enzymes.

Pharmacokinetics in special populations

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

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. Neonates with asphyxia-related hepatic and renal impairment are at risk of generating unexpectedly high serum midazolam concentration due to a significantly decreased and variable clearance (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 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 pharmacokinetics of unbound midazolam are not altered in patients with severe renal impairment. The pharmacologically mildly active major midazolam metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in patients with severe renal impairment. This accumulation produces a prolonged sedation. Midazolam should therefore be administered carefully and titrated to the desired effect (see section 4.4).

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

Patients with cardiac insufficiency
The elimination half-life in patients with congestive heart failure is longer than that in healthy subjects (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 Macrodex 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 24 hours at 25 °C and 3 days at 2–8°C temperature with following infusion solutions: sodium chloride 0.9 %, glucose 5 % and 10 %, Ringer`s solution and Hartmann`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 2–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. 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, 3 ml or 10 ml solution.

Pack size: 5 or 10 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Midazolam Kalceks solution for injection or infusion is compatible with the following solutions for infusion:
- sodium chloride 0.9 % (9 mg/ml) solution;
- glucose 5 % (50 mg/ml) solution;
- glucose 10 % (100 mg/ml) solution;
- Ringer's solution;
- Hartmann's solution.

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.

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

Note: ⊠ (an empty cross)
Classification: Group II / 2 (5 mg / 1 ml)
Medicinal product subject to restricted medical prescription, requiring special supervision by a specialist throughout the treatment after a diagnosis made by a specialist or in a hospital (Sz).

Classification: Group II / 3 (15 mg / 3 ml)
Medicinal product subject to restricted medical prescription defined in Act CLIV of 1997 on Health. Medicinal product can be used under out-patient provided conditions and in-patient medical care in accordance with Section 3(ga) of the Act (I).

Classification: Group II / 3 (50 mg / 10 ml)
Medicinal product subject to restricted medical prescription defined in Act CLIV of 1997 on Health. Medicinal product can be used under out-patient provided conditions and in-patient medical care in accordance with Section 3(ga) of the Act (I).

7. MARKETING AUTHORISATION HOLDER

AS KALCEKS
Krustpils iela 53
Rīga, LV-1057
Latvia

8. MARKETING AUTHORISATION NUMBER(S)

OGYI-T-23404/01	5×1 ml
OGYI-T-23404/02	10×1 ml
OGYI-T-23404/03	5×3 ml
OGYI-T-23404/04	10×3 ml
OGYI-T-23404/05	5×10 ml
OGYI-T-23404/06	10×10 ml

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 July 2018

10. DATE OF REVISION OF THE TEXT

3 September 2020