SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Midazolam Sandoz 1 mg/ml, oplossing voor injectie of infusie
Midazolam Sandoz 5 mg/ml, oplossing voor injectie of infusie

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection or infusion contains 1 mg of midazolam (as hydrochloride).

Each ampoule of 5 ml solution for injection or infusion contains 5 mg of midazolam (as hydrochloride).

Each ml of solution for injection or infusion contains 5 mg of midazolam (as hydrochloride).

Each ampoule of 1 ml solution for injection or infusion contains 5 mg of midazolam (as hydrochloride).
Each ampoule of 3 ml solution for injection or infusion contains 15 mg of midazolam (as hydrochloride).
Each ampoule of 10 ml solution for injection or infusion contains 50 mg of midazolam (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear, slightly yellow solution.

pH 2.9 – 3.7.
Osmolality 280 – 330 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is indicated for i.v. use, i.m. use and rectal use only.

Midazolam is a short-acting sleep-inducing medicinal product that is indicated for:

In adults:

- CONSCIOUS SEDATION before and during diagnostic or therapeutic procedures with or without local anaesthesia
- ANAESTHESIA
  - Premedication before induction of anaesthesia
  - Induction of anaesthesia
  - As a sedative component in combined anaesthesia

- SEDATION IN INTENSIVE CARE UNITS

In children:

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

4.2 Posology and method of administration

STANDARD DOSE

Midazolam is a potent sedative agent that requires titration and slow administration. Titration is strongly recommended to safely obtain the desired level of sedation according to the clinical need, physical status, age and concomitant medication. In adults over 60 years, debilitated or chronically ill patients and paediatric patients, dose should be determined with caution and risk factors related to each patient should be taken into account. Standard doses are provided in the table below. Additional details are provided in the text following the table.

Indication	**Adults < 60 years**	**Adults ≥ 60 years / debilitated or chronically ill**	**Children**
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. in patients 6 months - 5 years*** Initial dose: 0.05 - 0.1 mg/kg Total dose: < 6 mg ***i.v. in patients 6-12 years*** Initial dose: 0.025 - 0.05 mg/kg Total dose: < 10 mg ***rectal> 6 months*** 0.3 - 0.5 mg/kg ***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.*** 0.15 - 0.2 mg/kg (0.3 -0.35 without premedication)	***i.v.*** 0.05-0.15 mg/kg (0.15 -0.3 without premedication)	
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	
Sedation in ICU	***i.v.*** Loading dose: 0.03 - 0.3mg/kg in increments of 1 - 2.5 mg Maintenance dose: 0.03 - 0.2 mg/kg/h		***i.v. in neonates ≤ 32 weeks gestational age*** 0.03 mg/kg/h ***i.v. in neonates> 32 weeks and children up to 6 months*** 0.06 mg/kg/h ***i.v. in patients> 6 months*** Loading dose: 0.05 - 0.2 mg/kg Maintenance dose: 0.06 - 0.12 mg/kg/h

CONSCIOUS SEDATION DOSE

For conscious sedation prior to diagnostic or surgical intervention, midazolam is administered i.v. The dose must be individualised and titrated, and should not be administered by rapid or single bolus injection. The onset of sedation may vary individually depending on the physical status of the patient and the detailed circumstances of dosing (e.g. speed of administration, amount of dose). If necessary, subsequent doses may be administered according to the individual need. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes.

Adults
The 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 to10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3.5 to 7.5 mg. A total dose greater than 5 mg is usually not necessary.
In adults over 60 years of age, debilitated or chronically ill patients, the initial dose must be reduced to 0.5-1.0 mg and given 5-10 minutes before the beginning of the procedure. Further doses of 0.5 to 1 mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional midazolam should be titrated very slowly and carefully. A total dose greater than 3.5 mg is usually not necessary.

Paediatric population
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. One must wait an additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. Infants and young children less than 5 years of age may require substantially higher doses (mg/kg) than older children and adolescents.

- Paediatric patients less than 6 months of age: paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation. For this reason, the use in conscious sedation in children less than 6 months of age is not recommended.
- Paediatric patients 6 months to 5 years of age: initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint, but the total dose should not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
- Paediatric patients 6 to 12 years of age: initial dose 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
- Paediatric patients 12 to 16 years of age: should be dosed as adults.

Rectal administration:
The total dose of midazolam usually ranges from 0.3 to 0.5 mg/kg. Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10 ml. Total dose should be administered at once and repeated rectal administration avoided.
The use in children less than 6 months of age is not recommended, as available data in this population are limited.

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

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

ANAESTHESIA DOSE

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 to 60 minutes before induction of anaesthesia, or preferably via the rectal route in children (see below). Close and continuous monitoring of the patients after administration of premedication is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Adults:
For preoperative sedation and to impair memory of preoperative events, the recommended dose for adults of ASA Physical Status I & II and below 60 years is 1-2 mg i.v. repeated as needed, or 0.07 to 0.1 mg/kg administered i.m. The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, debilitated or chronically ill patients. The recommended initial i.v. dose is 0.5 mg and should be slowly uptitrated as needed. A dose of 0.025 to 0.05 mg/kg administered i.m. is recommended. In case of concomitant administration of narcotics the midazolam dose should be reduced**.** The usual dose is 2 to 3 mg.

Paediatric population:
Neonates and children up to 6 months of age:
The use in children less than 6 months of age is not recommended as available data are limited.

Children over 6 months of age:
Rectal administration: The total dose of midazolam, usually ranging from 0.3 to 0.5 mg/kg should be administered 15 to 30 minutes before induction of anaesthesia. Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.
I.M. administration: As i.m. injection is painful, this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08 to 0.2 mg/kg of midazolam administered i.m. has been shown to be effective and safe. In children between ages 1 and 15 years, proportionally higher doses are required than in adults in relation to body-weight.

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

Induction
Adults
If midazolam is used for induction of anaesthesia before other anaesthetic agents have been administered, the individual response is variable. The dose should be titrated to the desired effect according to the patient's age and clinical status. When midazolam is used before or in combination with other i.v. or inhalation agents for induction of anaesthesia, the initial dose of each agent should be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.
The desired level of anaesthesia is reached by stepwise titration. The 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 to 30 seconds allowing 2 minutes between successive increments.

- In premedicated adults below the age of 60 years, an i.v. dose of 0.15 to 0.2 mg/kg will usually suffice.
- In non-premedicated adults below the age of 60 the dose may be higher (0.3 to 0.35 mg/kg i.v.). If needed to complete induction, increments of approximately 25% of the patient's initial

dose may be used. Induction may instead be completed with inhalational anaesthetics. In resistant cases, a total dose of up to 0.6 mg/kg may be used for induction, but such larger doses may prolong recovery.

- In premedicated adults over 60 years of age, debilitated or chronically ill patients, the dose should significantly be reduced, e.g., down to 0.05- 0.15 mg/kg administered i.v. over 20 -30 seconds and allowing 2 minutes for effect.
- Non-premedicated adults over 60 years of age usually require more midazolam for induction; an initial dose of 0.15 to 0.3 mg/kg is recommended. Non-premedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.15 to 0.25 mg/kg will usually suffice.

SEDATIVE COMPONENT IN COMBINED ANAESTHESIA
Adults
Midazolam can be given as a sedative component in combined anaesthesia by either further intermittent small 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, debilitated or chronically ill patients, lower maintenance doses will be required.

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

Adults
I.V. loading dose: 0.03 to 0.3 mg/kg should be given slowly in increments. Each increment of 1 to 2.5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments. In hypovolaemic, vasoconstricted, or hypothermic patients the loading dose should be reduced or omitted. When midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of midazolam can be safely titrated on top of any sedation caused by the analgesic.

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

Paediatric population:
Neonates and children up to 6 months of age:
Midazolam should be given as a continuous i.v. infusion, starting at 0.03 mg/kg/h (0.5 μg/kg/min) in neonates with a gestational age ≤32 weeks, or 0.06 mg/kg/h (1 μg/kg/min) in neonates with a gestational age >32 weeks and children up to 6 months.
Intravenous loading doses is not recommended in premature infants, neonates and children up to 6 months, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation.
Careful monitoring of respiratory rate and oxygen saturation is required.

Children over 6 months of age:
In intubated and ventilated paediatric 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 haemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for haemodynamic instability, e.g., hypotension. These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.

In premature infants, neonates and children less than 15 kg of body weight, midazolam solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

USE IN SPECIAL POPULATIONS
Patients with renal impairment
In patients with severe renal impairment midazolam may be accompanied by more ronounced 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.

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

Paediatric population
See above and section 4.4.

METHOD OF ADMINISTRATION
This medicinal product is for i.v. administration, i.m. administration and also for rectal administration according to the instructions given above.
For instructions on dilution of the medicinal product with infusion solutions before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance (midazolam), to benzodiazepines or to any of the excipients listed in section 6.1.
- Conscious sedation in patients with severe respiratory failure or acute respiratory depression.

4.4 Special warnings and precautions for use

Midazolam should be administered only by experienced physicians in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.

Severe cardiorespiratory adverse events have been reported. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dose is administered (see section 4.8).

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

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

When midazolam is used for premedication, adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Special caution should be exercised when administering midazolam to high-risk patients:
- adults over 60 years of age
- chronically ill or debilitated patients, e.g.
  - patients with chronic respiratory insufficiency (see also section 4.3)
  - patients with chronic renal failure, impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment) or with impaired cardiac function
  - paediatric patients especially those with cardiovascular instability.

These high-risk patients require lower doses (see section 4.2) and should be continuously monitored for early signs of alterations of vital functions.

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering midazolam to a patient with myasthenia gravis.

Tolerance
Some loss of efficacy has been reported when midazolam was used as long-term sedation in intensive care units (ICU).

Dependence
When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on midazolam may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse (see section 4.8).

Withdrawal symptoms
During prolonged treatment with midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. In severe cases, the following symptoms may occur: depersonalisation, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact. Since the risk of withdrawal

symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

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

Paradoxical reactions
Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, delusions, rage reaction, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects paroxysmal excitement and assault, have been reported to occur with midazolam. These reactions may occur with high doses and/or when the injection is given rapidly. The highest incidence to such reactions has been reported among children and the elderly. In the event of these reactions discontinuation of the drug should be considered.

Altered elimination of midazolam
Midazolam elimination may be altered in patients receiving compounds that inhibit or induce CYP3A4 and the dose of midazolam may need to be adjusted accordingly (see section 4.5*)*.
Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see section 5.2*)*.

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

Paediatric population
Adverse haemodynamic events have been reported in paediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.

Preterm infants and neonates
Due to an increased risk of apnoea, extreme caution is advised when sedating preterm and former preterm non intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required.
Rapid injection should be avoided in the neonatal population.
Neonates have reduced and/or immature organ function and are also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Paediatric patients less than 6 months
In this population, midazolam is indicated for sedation in ICU only. Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential (see also paragraph 'Preterm infants and neonates' above).

Concomitant use of alcohol or/and CNS depressants

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

Medical history of alcohol or drug abuse
Midazolam as other benzodiazepines should be avoided in patients with a medical history of alcohol or drug abuse.

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

Additional information
This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic Interactions
Midazolam is metabolised by CYP3A4 and CYP3A5. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to i.v. midazolam, in particular since CYP3A4 also exists in the upper gastro-intestinal tract. This is because for the oral route both systemic clearance and availability will be altered while for the parenteral route only the change in the systemic clearance becomes effective. After a single dose of i.v. midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect will be increased in the presence of CYP3A4 inhibition.

There are no available studies on CYP3A4 modulation on the pharmacokinetics of midazolam after rectal and intramuscular administration. It is expected that these interactions will be less pronounced for the rectal than for the oral route because the gastro-intestinal tract is by-passed whereas after i.m. administration the effects of CYP3A modulation should not substantially differ from those seen with i.v. midazolam.

It is therefore recommended to carefully monitor the clinical effects and vital signs during the use of midazolam, taking into account that they may be stronger and last longer after co-administration of a CYP3A4 inhibitor, be it given only once. Notably, administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors, e.g. during intensive care, may result in long-lasting hypnotic effects, delayed recovery and respiratory depression, thus requiring dose adjustments.

With respect to induction, it should be considered that the inducing process needs several days to reach its maximum effect and also several days to dissipate. Contrary to a treatment of several days with an inducer, a short-term treatment is expected to result in less apparent DDI with midazolam. However, for strong inducers a relevant induction even after short-term treatment cannot be excluded.

Midazolam is not known to change the pharmacokinetics of other medicinal products.

Medicinal products that inhibit CYP3A4

Azole antifungals

- *Ketoconazole* increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with the strong CYP3A4 inhibitor ketoconazole, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dose adjustment should be considered, especially if more than a single i.v. dose of midazolam is administered. The same recommendation may apply also for other azole antifungals (see further), since increased sedative effects of i.v. midazolam, although lesser, are reported.
- *Voriconazole* increased the exposure of intravenous midazolam by 3-4 fold whereas its elimination half-life increased by about 3-fold.
- *Fluconazole and itraconazole* both increased the plasma concentrations of intravenous midazolam by 2 – 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.
- *Posaconazole* increased the plasma concentrations of intravenous midazolam by about 2-fold.

It should be kept in mind that if midazolam is given orally, its exposure will drastically be higher than the above-mentioned ones, notably with ketoconazole, itraconazole, voriconazole.

Midazolam ampoules are not indicated for oral administration.

Macrolide antibiotics

- *Erythromycin* resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 – 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 – 1.8-fold.
- *Clarithromycin* increased the plasma concentrations of midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 – 2-fold.

Additional information from oral midazolam:

- Telithromycin increased the plasma levels of oral midazolam 6-fold.
- *Roxithromycin:* While no information on roxithromycin with i.v. midazolam is available, the mild effect on the terminal half-life of oral midazolam tablet, increasing by 30%, indicates that the effects of roxithromycin on intravenous midazolam may be minor.

Intravenous anaesthetics

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

Protease inhibitors

- *Saquinavir and other HIV protease inhibitors:* Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral midazolam is

coadministered with HIV protease inhibitors, 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 i.v. 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 given orally. Therefore protease inhibitors should not be co-administered with orally administered midazolam.

Calcium-channel blockers

- *Diltiazem:* A single dose of diltiazem given to patients undergoing coronary artery bypass grafting increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%. This was less than the 4-fold increase seen after oral administration of midazolam.

Additional information from oral midazolam:

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

Various medicinal products/Herbs

- *Atorvastatin* showed a 1.4-fold increase in plasma concentrations of i.v. midazolam compared to control group.
- *Intravenous fentanyl* is a weak inhibitor of midazolam elimination: AUC and half-life of i.v. 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 by 4.6-fold with an increase of its terminal half-life by 1.6-fold.
- *Aprepitant* dose dependently increased the plasma concentrations of oral midazolam by 3.3-fold after 80 mg/day associated with an increase in terminal half-life by ca. 2-fold.

Medicinal products that induce CYP3A4

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

Herbs 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 concentrations 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 Drug-Drug Interactions (DDI)
The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.
Examples include opiate derivatives (be they used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non recent H1-antihistamines and centrally acting antihypertensive drugs.

Alcohol may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.
The administration of high doses of midazolam in the last trimester of pregnancy, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or foetal adverse effects (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).
Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Consequently, midazolam may be used during pregnancy if clearly necessary but it is preferable to avoid using it for caesarean.
The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

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

Fertility
Animal studies did not show an impairment of fertility (see section 5.3).

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.

4.8 Undesirable effects

The following frequency estimates are used in assessing adverse events:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000
Not known	cannot be estimated from the available data

Summary of the safety profile
The most serious (frequency not known) occurring adverse reactions using midazolam are:
Anaphylactic shock and severe cardiorespiratory adverse reactions including

- cardiac arrest
- hypotension
- bradycardia,
- vasodilating effects
- respiratory depression
- apnoea
- respiratory arrest
- dyspnea
- laryngospasm.

Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4).

Tabulated summary of adverse reactions

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

Adverse Drug Reactions (ADRs) by System Organ Class and Frequency		
MedDRA System Organ Class	**Frequency**	**ADRs**
Immune system disorders	**Not known**	Hypersensitivity, angioedema, anaphylactic shock
Psychiatric disorders	**Not known**	Confusional state, disorientation, emotional and mood disturbances, hallucinations, changes in libido, agitation*, hostility*, anger*, aggressiveness*, excitement* physical drug dependence and withdrawal syndrome, abuse
Nervous system disorders	**Not known**	Involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity*, sedation (prolonged and postoperative), decreased alertness, 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	**Not known**	Cardiac arrest, bradycardia, kounis syndrome****
Vascular disorders	**Not known**	Hypotension, vasodilation, thrombophlebitis, thrombosis
Respiratory, thoracic and mediastinal disorders	**Not known**	Respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm, hiccup
Gastrointestinal disorders	**Not known**	Nausea, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders	**Not known**	Skin rash, urticaria, pruritus

General disorders and administration site conditions	**Not known**	Fatigue, injection site erythema, pain on injection site
Injury, poisoning and procedural complications	**Not known**	Falls and fractures ***
Social circumstances	**Not known**	Assault*

* Such paradoxical drug reactions have been reported particularly among children and the elderly (see section 4.4).
** Anterograde amnesia may still be present at the end of the procedure and in few cases prolonged amnesia has been reported (see section 4.4).
*** The risk of falls and fractures is increased in patients taking concomitant sedatives (including alcoholic beverages) and in the elderly.
**** Particularly after parenteral administration.

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

Midazolam is not a substrate for drug transporters.

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

Management
Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.
If taken orally further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative

for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.
If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of medicinal products that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of it.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Midazolam has hypnotic and sedative effects that occur quickly and are of short duration. It also has anxiolytics, anticonvulsant and muscle relaxing properties. Midazolam reduces the psychomotor functions after a single and/or repeated dose but causes very few hemodynamic changes.

Central activity of benzodiazepines is mediated by increasing the gamma-aminobutyric acid neurotransmission (GABA-neurotransmission) at inhibitory synapses. In the presence of benzodiazepines, the affinity of the GABA-receptor for GABA is increased by positive allosteric modulation. This leads to an increased activity of the released GABA on the postsynaptic transmembrane chloride ions flux.

Chemically, Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water.
The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of midazolam to form water-soluble salts with acids. These produce a stable and well tolerated solution for injection or infusion.

In combination with the rapid metabolization this will result in a rapid action and short duration of the effects. Because of its low toxicity, midazolam has a wide therapeutic range.

After i.m. or i.v. administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).

5.2 Pharmacokinetic properties

<u>Absorption after i.m. injection</u>
Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after i.m. injection is over 90%.

<u>Absorption after rectal administration</u>
After rectal administration midazolam is absorbed quickly. Maximum plasma concentration is reached in about 30 minutes. The absolute bioavailability is about 50%.

Distribution
When midazolam is injected i.v., the plasma concentration-time curve shows one or two distinct phases of distribution. The volume of distribution at steady state is 0.7 - 1.2 l/kg. 96 - 98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk. Midazolam is not a substrate for drug transporters.

Biotransformation
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30 - 60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxymidazolam. Plasma concentrations of alpha-hydroxymidazolam are 12% of those of the parent compound. Alpha-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

Elimination
In young healthy volunteers, the elimination half-life of midazolam is between 1.5 - 2.5 hours. Elimination half-life of the metabolite is less than 1 hours and therefore the concentrations of the original substance and its main metabolite decrease simultaneously after administration of midazolam. Plasma clearance of midazolam is in the range of 300 – 500 ml/min. Midazolam is excreted mainly by renal route (60 - 80% of the injected dose) and recovered as glucuroconjugated alpha-hydroxymidazolam. Less than 1% of the dose is recovered in urine as unchanged drug.
When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection. Repeated administration of midazolam does not induce enzymes that are involved in the biotransformation.

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
The rate of rectal absorption in children is similar to that in adults but the bioavailability is lower (5 - 18%). The elimination half-life after i.v. and rectal administration is shorter in children 3 - 10 years old (1 - 1.5 hours) as compared with that in adults. The difference is consistent with an increased metabolic clearance in children.
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).
Neonates with an asphyxia-related impaired hepatic or renal function are at risk of unexpectedly high serum concentrations of midazolam as the result of a significantly reduced and variable clearance.

Obese
The mean half-life is greater in obese than in non-obese patients (5.9 versus 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
Pharmacokinetics of unbound midazolam is no different in patients with a severely impaired renal function. The pharmacologically slightly active and main metabolite of midazolam (alpha-hydroxy-midazolam glucuronide), which is excreted by the kidneys, accumulates in patients with severely impaired renal function. This accumulation causes a prolonged sedation.
Midazolam must therefore be administered carefully and titrated to the desired effect.

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

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

5.3 Preclinical safety data

In rat fertility study, animals dosed up to 10 times the clinical dose, no adverse effects on fertility were observed.
There are no other preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[1 mg/ml solution for injection or infusion]:
Sodium chloride
Hydrochloric acid
Water for injections

[5 mg/ml solution for injection or infusion]:
Sodium chloride
Hydrochloric acid
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

[Nationally completed name] is **not compatible** with the following solutions for infusion:

- dextran 6% w/v (with 0.9% sodium chloride) in dextrose
- alkaline solutions for injection. Midazolam precipitates in sodium bicarbonate.

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

6.3 Shelf life

[1 mg/ml solution for injection or infusion]:
3 years

[5 mg/ml solution for injection or infusion]:
5 years

After opening of the ampoule
From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After dilution:
Chemical and physical in-use stability of the dilutions has been demonstrated for 24 hours at room temperature (15 – 25°C) or for 3 days at +2 °C to +8 °C.
From a microbiological point of view, the product should be used immediately after dilution. 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 in the original packaging in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless glass type I ampoules

Pack sizes:
[1 mg/ml solution for injection or infusion]:
5 ml: carton box with 5 ampoules

[5 mg/ml solution for injection or infusion]:
1 ml: carton box with 5 ampoules
3 ml: carton box with 5 ampoules
10 ml: carton box with 5 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

[Nationally completed name] 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 solution

- Hartmann's solution

In case of continuous intravenous infusion, the content of the [nationally completed name] ampoules can be diluted with Sodium chloride 0.9 % (9 mg/ml) solution, Glucose 5 % (50 mg/ml) solution, Glucose 10 % (100 mg/ml) solution, Ringer solution or Hartmann's solution in a ratio of 15 mg midazolam per 100 to 1000 ml of infusion solution (see below).

Ampoule presentation	Strength (mg/ ml)	Number of ampoules needed	Total ampoule volume needed (ml)	Dilution solution	Final volume (ml)	Final concentration (mg/ ml)
5mg/ 5ml	1	3	15	• Sodium chloride 0.9 % (9mg/ ml) solution • Glucose 5 % (50mg/ ml) solution • Glucose 10 % (100mg/ ml) solution • Ringer solution • Hartmann's solution.	100 to 1000	0.015 to 0.15
5mg/ ml	5	3	3			
15mg/ 3ml	5	1	3			
50mg/ 10ml	5	1	3			

[Nationally completed name] ampoules are for single use only. Discard any unused solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The ampoule and the solution should be examined visually before administration.
Do not use this medicinal product if you notice that the ampoule is found leaking, or if the solution is not clear, or not free from particles or if you notice any discoloration of the solution.

7. MARKETING AUTHORISATION HOLDER

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 110832
RVG 110837

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 12 november 2012
Datum van laatste verlenging: 2 oktober 2017

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 7: 8 februari 2024