SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Senozam 1 mg/ml, solution for infusion
Senozam 5 mg/ml, solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Senozam 1 mg/ml, solution for infusion
1 ml of solution contains 1 mg of midazolam.
1 bag with 100 ml solution for infusion contains 100 mg midazolam.

Senozam 5 mg/ml, solution for infusion
1 ml of solution contains 5 mg of midazolam.
1 bag with 100 ml solution for infusion contains 500 mg midazolam.

Excipients with known effect:
The 1 mg/ml strength contains 357 mg sodium per 100 ml.
The 5 mg/ml strength contains 220 mg sodium per 100 ml.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

The solution is a clear and (almost) colourless solution. The pH is 2.9 – 3.7.

Senozam 1 mg/ml, solution for infusion
The osmolality is 270 – 320 mOsmol/kg.

Senozam 5 mg/ml, solution for infusion
The osmolality is 180 – 230 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Senozam is a short-acting sleep-inducing drug that is indicated:

In adults
• **Conscious sedation** before and during diagnostic or therapeutic procedures with or without local anaesthesia
• **Anaesthesia**
  - Premedication before induction of anaesthesia
  - 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 for children aged 2 years and older
• **Sedation in intensive care units** in combination with the analgesic morphine or fentanyl for children and infants aged 28 days and older

4.2 Posology and method of administration

Posology

Standard Dosage

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

Indication	**Adults <60 years**	**Adults ≥ 60 years / debilitated or chronically ill**	**Children**
Conscious sedation	**I.V.** Initial dose: 2-2.5mg Titration doses: 1mg Total dose : 3.5-7.5mg	**I.V.** Initial dose : 0.5-1mg Titration doses : 0.5- 1mg Total dose : <3.5mg	**I.V. in patients 2-5 years** Initial dose: 0.05-0.1mg/kg Total dose: <6mg **I.V. in patients 6-12 years** Initial dose: 0.025-0.05mg/kg Total dose: <10mg **I.M. 2-15 years** 0.05-0.15mg/kg
Anaesthesia premedication	**I.V.** 1-2mg repeated **I.M.** 0.07-0.1mg/kg	**I.V.** Initial dose: 0.5mg Slow up titration as needed **I.M.** 0.025-0.05mg/kg	
Sedative component in combined anaesthesia	**I.V.** intermittent doses of 0.03-0.1mg/kg or continuous infusion of 0.03-0.1mg/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 1-2.5mg Maintenance dose: 0.03-0.2mg/kg/h		**I.V. in infants ≥28 days up to 6 months** 0.06mg/kg/h **I.V. in patients >6 months of age** Loading dose: 0.05-0.2mg/kg Maintenance dose: 0.06-0.12mg/kg/h

Method of administration

Conscious sedation

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 intravenous injection of midazolam should be given slowly at a rate of approximately 1 mg/ 30 seconds.

Adults below the age of 60
In adults below the age of 60 the initial dose is 2 to 2.5 mg given 5 to 10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3.5 to 7.5 mg. A total dose greater than 5 mg is usually not necessary.

In adults over 60 years of age,
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. Young children less than 5 years of age may require substantially higher doses (mg/kg) than older children and adolescents.

- Paediatric patients <2 years of age: the use of midazolam in paediatric patients <2 years of age is not recommended as available data are limited.
- Paediatric patients 2 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.

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.

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

Anaesthesia dosage

Premedication

Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of 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 0.5mg 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.

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 preterm infants: midazolam is not recommended in neonates as available data are limited.
Children aged 28 days to 6 months:
Midazolam should be given as a continuous I.V. infusion of 0.06 mg/kg/h (1 µg/kg/min) in children ≥28 days up to 6 months. Combination with morphine or fentanyl is usually required.

Intravenous loading doses are not recommended in 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. Midazolam will be administered in combination with the analgesic morphine or fentanyl.

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 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.

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 <10ml/min) the pharmacokinetics of unbound midazolam following a single IV dose is similar to that reported in healthy volunteers. However, after prolonged infusion in intensive care unit (ICU) patients, the mean duration of the sedative effect in the renal failure population was considerably increased most likely due to accumulation of 1'-hydroxymidazolam glucuronide (see sections 4.4 and 5.2).

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

Paediatric population
See above and section 4.4

Each bag is for single use only (see section 6.6). For administration of low volumes other midazolam products filled in smaller packages are recommended to be used.

4.3 Contraindications

Hypersensitivity to the active substance, 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 and by persons specifically trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.

Severe cardiorespiratory adverse events have been reported. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered (see section 4.8). Special caution is required for the indication of '*conscious sedation*" in patients with impaired respiratory function.

Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential.

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

Special caution should be exercised when administering midazolam to high- risk patients:

• adults over 60 years of age

• chronically ill or debilitated patients, e.g.

• patients with chronic respiratory insufficiency

• patients with chronic renal failure,

• patients with impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment)

• patients with impaired cardiac function

• paediatric patients especially those with cardiovascular instability.

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

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

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

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

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

Amnesia:
Anterograde amnesia may occur at therapeutic doses (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose, with the risk increasing at higher dosages. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied 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 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 injection 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 advised when sedating preterm and former preterm non intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required. Rapid injection should be avoided in the neonatal population.

Neonates have reduced and/or immature organ function and are also vulnerable to profound and/or prolonged respiratory effects of midazolam.

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

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

Risk from concomitant use of opioids:

Concomitant use of midazolam 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 with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe midazolam 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:
Midazolam as other benzodiazepines should be avoided in patients with a medical history of alcohol or drug abuse.

Criteria for discharge:

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

Sodium

Senozam 1 mg/ml contains 357 mg sodium per 100 ml , equivalent to 17.85% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Senozam 5 mg/ml contains 220 mg sodium per 100 ml, equivalent to 10.96% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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 than for I.V. midazolam, as CYP3A4 is also present in the upper gastro-intestinal tract. For the oral route both systemic clearance and availability will be altered while for the parenteral route only the change in the systemic clearance is affected.

After a single dose of I.V. midazolam, the impact 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 of CYP3A4 modulation on the pharmacokinetics of midazolam after intramuscular administration. After I.M. administration the effects of CYP3A4 modulation should not substantially differ from those seen with I.V. midazolam.

When co-administered with a CYP3A4 inhibitor the clinical effects of midazolam may be stronger and also longer lasting, and a lower dose may be required. It is therefore recommended to carefully monitor 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, even if given only once. Notably, administration of high doses or long-term infusions of midazolam to patients receiving potent CYP3A4 inhibitors, e.g. during intensive care, may result in long-lasting hypnotic effects, delayed recovery 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 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. Unlike treatment of several days with an inducer) 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 alter the pharmacokinetics of other drugs.

Drugs that inhibit CYP3A

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 CYP3A 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 dosage 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 below), since increased sedative effects of I.V. midazolam, although less pronounced, have been reported.
- Voriconazole increased the exposure (plasma concentration) of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.
- Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2- to 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 be significantly higher than discussed above, notably with ketoconazole, itraconazole and voriconazole.

Senozam, solution for infusion is not indicated for oral and rectal administration.

Macrolide antibiotics

• Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6- to 2-fold with an increase of the terminal half-life of midazolam by 1.5- to 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- to 2-fold.

Intravenous anaesthetics

• Intravenous propofol increased the AUC and half-life of intravenous midazolam by 1.6-fold.

HIV protease inhibitors

• Saquinavir and other human immunodeficiency virus (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 co-administered with HIV protease inhibitors, the treatment setting should follow the description in the above section for azole antifungals, ketoconazole.

Calcium-channel blockers

• Diltiazem: A single dose of diltiazem increased plasma levels of intravenous midazolam by approximately 25% and the terminal half-life was prolonged by 43%.

Other medicines

• Atorvastatin showed a 1.4-fold increase in plasma concentrations of I.V. midazolam compared to control group.

Drugs that induce CYP3A

• 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 and has only small effects on intravenously administered midazolam (-12%) and 4-hydroxymidazolam (-23%) exposures.

Herbal medicines and food

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

Pharmacodynamic Drug-Drug Interactions (DDI)

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

Opioids:

The concomitant use of midazolam with sedative medicines such as benzodiazepines or related drugs such as 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. It is strongly advised that alcohol intake should be 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

There are no or limited amount of data from the use of midazolam in pregnant women. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines.

No data on exposed pregnancies are available for the first two trimesters of pregnancy. It has been suggested that the use of benzodiazepines during the first trimester of pregnancy is associated with an increased risk of congenital abnormalities.

The administration of high doses of midazolam in the last trimester of pregnancy, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or foetal adverse reactions (risk of aspiration of fluids and stomach contents during labour in the 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.

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

Breastfeeding

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

There are no or limited amount of data from the effect of midazolam on fertility. Animal studies are insufficient with respect to fertility.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

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

The frequency of side effects is classified into the following categories:

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

Immune System Disorders	
Not known	Hypersensitivity, angioedema, anaphylactic shock
Psychiatric Disorders	
Not known	Confusional state, disorientation, emotional and mood disturbances, changes in libido Physical drug dependence and withdrawal syndrome Abuse 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
Nervous System Disorders	
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	
Not known	Cardiac arrest, bradycardia, Kounis syndrome****
Vascular Disorders	
Not known	Hypotension, vasodilation, thrombophlebitis, thrombosis
Respiratory Disorders	
Not known	Respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm, hiccups
Gastrointestinal Disorders	
Not known	Nausea, vomiting, constipation, dry mouth
Skin and Subcutaneous Tissue Disorders	
Not known	Rash, urticaria, pruritus
General Disorders and Administration Site Conditions	
Not known	Fatigue, injection site erythema, injection site pain
Injury, Poisoning and Procedural Complications	
Not known	Falls, 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).

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

**** Particularly after parenteral administration

Dependence:

Use of midazolam – even at 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). Abuse has been reported.

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

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, 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.

Treatment

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 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

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.

Chemically midazolam is a derivative of the imidazobenzodiazepine group. Although the free base is a lipophilic substance with low solubility in water, the basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of midazolam to form water-soluble salts with acids, producing a stable and well tolerated injection solution. This together with rapid metabolic transformation is the reason for rapid onset and short duration of effects. Due to its low toxicity, midazolam has a wide therapeutic range.

Pharmacodynamic effects

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

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

Absorption

Absorption after I.M. injection

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%.

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. Midazolam is 96-98% bound to plasma proteins, primarily 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 P450 CYP3A4 and CYP3A5 isozymes and the major urinary and plasma metabolite is 1'-hydroxymidazolam (also known as alpha-hydroxymidazolam). Plasma concentrations of 1'-hydroxymidazolam are 12% of those of the parent compound. 1'-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. The elimination half-life of the metabolite is shorter than 1 hour; therefore after midazolam administration the concentration of the parent compound and the main metabolite decline in parallel. Plasma clearance is in the range of 300-500 ml/min. Midazolam metabolites are excreted mainly by renal route (60-80% of the injected dose) and recovered as glucuroconjugated 1'-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

administrations of midazolam do not induce drug metabolising enzymes involved in biotransformation.

Pharmacokinetics in special populations

Elderly

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

Children

The rate of rectal absorption in children is similar to that in adults but the bioavailability is lower (5-18%).The elimination half-life after IV and rectal administration is shorter in children 3-10 years old (1-1.5 hours) as compared with that in adults. The difference is consistent with an increased metabolic clearance in children.

Neonates

In premature and full-term 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 4.4 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Shelf-life before first opening
3 years

Use immediately after opening.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Midazolam 1 mg/ml, solution for infusion
100 ml (100 mg) in a transparent bag (polypropylene/polyolephine / SEB (Styrene-Ethylene-Buthylene) block copolymer) / TPE (ThermoPlastic Elastomer) copolymer).

There are two tubes (polypropylene/polyolephine / SEB block copolymer), one twist-off (ethylene-and propylene- monomers / Ziegler/-natta catalysts) and the other with a female Luer lock with bi-directionnal valve (Makrolon® Rx 1805 polycarbonate) to be connected to the infusion line of a Patient control Anaesthesia pump or with an injection site.

All the bags are overwrapped in outer pouches made of PET (polyester) / OPA (polyamide) / aluminium / PP (polypropene). One bag is packaged in a carton.

Midazolam 5 mg/ml, solution for infusion
100 ml (500 mg) in a transparent bag (polypropylene/polyolephine / SEB (Styrene-Ethylene-Buthylene) block copolymer) / TPE (ThermoPlastic Elastomer) copolymer).

There are two tubes (polypropylene/polyolephine / SEB block copolymer), one twist-off (ethylene-and propylene- monomers / Ziegler/-natta catalysts) and the other with a female Luer lock with bi-directionnal valve (Makrolon® Rx 1805 polycarbonate) to be connected to the infusion line of a Patient control Anaesthesia pump or with an injection site.

All the bags are overwrapped in outer pouches made of PET (polyester) / OPA (polyamide) / aluminium / PP (polypropene). One bag is packaged in a carton.

6.6 Special precautions for disposal and other handling

Each bag is for single use only.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

2023-12-12