# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

NASOLAM 5 mg nasal spray, solution in single-dose container

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NASOLAM 5 mg nasal spray, solution in single dose container
Each ml of solution contains midazolam as hydrochloride equivalent to 50 mg midazolam.
Each single-dose container holds one dose (100 microliters) of 5 mg midazolam (as hydrochloride).

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Nasal spray, solution in single-dose container
Clear, slightly yellow solution.
pH 3.3 - 3.8
Osmolarity 2400-2800 mmol/kg

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

NASOLAM is a short-acting sleep-inducing and anticonvulsive drug that is indicated in:

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia
- Premedication before induction of anaesthesia

NASOLAM must only be used by healthcare professionals for conscious sedation or premedication.

- Treatment of prolonged, acute, convulsive seizures.

NASOLAM must only be used by parents/care givers where the patient has been diagnosed to have epilepsy.

NASOLAM is indicated in adults and children ≥ 12 kg and aged 2 years and older.

## 4.2 Posology and method of administration

Posology

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

Table 1

| **Age/Body weight range** | **First dose** | **Second dose** At least 10 min after first dose |
|---|---|---|
| **Conscious sedation and premedication** | | |
| 12 kg to 43 kg | 2.5 mg | 2.5 mg |
| ≥ 44 kg and < 60 years | 5 mg | 2.5 mg or 5 mg* |
| ≥ 60 years | 2.5 mg | 2.5 mg |
| **Treatment of prolonged, acute, convulsive epileptic seizures** | | |
| 12 kg to 18 kg | 2.5 mg | 2.5 mg |
| 19 kg to 39 kg | 3.75 mg | 3.75 mg |
| ≥ 40 kg or ≥ 12 years to < 60 years | 5 mg | 5 mg |
| ≥ 60years | 3.75 mg | 3.75 mg |

* depending on desired level and duration of sedation

**Conscious sedation and premedication dosage**

- NASOLAM must only be used by healthcare professionals in conscious sedation or premedication. Adequate observation of the patient after administration is mandatory.
- NASOLAM can be administered in any position, including lying or sitting patients.

- The dose indicated in table 1 should be administered intranasally into one nostril, at 5-10 minutes before the procedure is initiated.
- The onset of action is circa 4-8 minutes after the nasal administration of the first dose. The onset of sedation may vary individually depending on the physical status of the patient.
- If required, one subsequent dose may be administered intranasally into the opposite nostril of the first dose, at least 10 minutes after the initial dose, according to the individual need.
- The maximum dose for conscious sedation purposes or premedication is 10 mg.
- If after administration of the recommended doses of midazolam (see table 1), the level of sedation is not sufficient, no further intranasal midazolam doses should be administered. Other midazolam options should be considered.

- Paediatric patients < 12 kg: The safety and efficacy of NASOLAM in this paediatric patients group have not been established. No data are available. NASOLAM should not be used in this patient group.
- The administration of a second NASOLAM dose may result in prolonged sedation.
- Paediatric patients 12 kg to 43 kg that are debilitated or chronically ill, that require conscious sedation or premedication, should only use NASOLAM in a setting with special monitoring and support facilities (see also 4.4).
- Patients $\geq$ 44 kg and < 60 years that are debilitated or chronically ill: the first dose is 2.5 mg administered intranasally 5-10 minutes before the procedure is initiated. One further dose of 2.5 mg may be given as required but at least 10 minutes after the first dose into the opposite nostril of the first dose (see also 4.4).
- Patients $\geq$ 60 years that are debilitated or chronically ill that require conscious sedation or premedication, should only use NASOLAM in a setting with special monitoring and support facilities (see also 4.4).

- Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory. Close and continuous monitoring of the patients after administration of premedication is mandatory as inter-individual sensitivity varies and symptoms of overdose may occur.

**Treatment of prolonged, acute, convulsive seizures dosage**

- NASOLAM must only be used by parents/care givers where the patient has been diagnosed to have epilepsy
- NASOLAM prescribers should consider the following prior to starting treatment:

1. for patients at increased risk of respiratory depression from benzodiazepines, administration of NASOLAM under healthcare professional supervision should be considered prior to starting treatment with NASOLAM. This administration may be performed in the absence of a seizure.
2. prior to starting treatment, the healthcare professional should instruct the patient and patient's immediate associates (e.g. parents, caregivers) on:
   - how to identify (convulsive) seizures
   - how to use NASOLAM appropriately
   - when to administer a second dose and when not
   - the risk of concomitant use of opioids/alcohol/CNS depressants/other benzodiazepines;
   - the risk of respiratory depression, the symptoms and what to do if it occurs

- NASOLAM can be administered in any position, including lying or sitting patients
- The first dose indicated in table 1 should be administered intranasally in one nostril.
- Carers should only administer a single dose of midazolam. If the seizure has not stopped within 10 minutes after administration of midazolam, emergency medical assistance must be sought, and the empty single-dose container should be given to the healthcare professional to provide information on the dose received by the patient.
- A second or repeat dose when seizures continue or re-occur after an initial response should not be given without prior medical advice. In particular, young children, patients with respiratory impairment and elderly patients should receive a second dose only in the presence of a health care professional. This second or repeat dose should be administered into the opposite nostril of the first dose

<u>Use in Special Populations</u>

Renal Impairment

In patients with severe renal impairment the pharmacological effects of midazolam can be enhanced and the duration can be prolonged, potentially with clinical relevant suppression of the cardiorespiratory system.

No dose adjustment is required, however NASOLAM should be used with caution in patients with chronic renal failure as elimination of midazolam may be delayed and the clinical effects of midazolam prolonged (see section 4.4).

Hepatic Impairment

Hepatic impairment reduces the clearance of midazolam with a subsequent increase in terminal half-life. The clinical effects may be prolonged and proper

monitoring of clinical effects and vital signs should be established (see section 4.4).
NASOLAM is contraindicated in patients with severe hepatic impairment.

Elderly
In patients from 60 years and in elderly patients NASOLAM should be used with caution and dose reduction is recommended (see Table 1). Elderly patients should receive a second dose only in the presence of a health care professional. See also the text following table 1 and section 4.4.

Paediatric patients
For children < 12 kg: NASOLAM should not be used. The safety and efficacy of midazolam in these children, has not been established. No data are available. See above and section 4.4.
For children ≥ 12 kg: NASOLAM should be used according to table 1. In particular, young children should receive a second dose only in the presence of a health care professional. See also the text following table 1 and section 4.4.

Method of administration
NASOLAM is for intranasal use only. Each NASOLAM single-dose container contains just one dose and is intended for single use only in a single nostril. In young children, the nozzle may not fit in the nostril. In this case, make sure the nozzle seals the nostril before administration. Do not test or prime the product before administration as NASOLAM only delivers one single dose. If you need a second dose, use a new single-dose container and administer the second dose in the other nostril than the one that was used for administering the first NASOLAM dose. See also section 6.6.

## 4.3 Contraindications

Use of this drug in patients with:
- known hypersensitivity to the active substance (midazolam), benzodiazepines or to any excipient of the product, listed in section 6.1.
- severe respiratory failure or acute respiratory depression,
- severe hepatic impairment,
- myasthenia gravis or sleep apnoea syndrome,
- acute angle glaucoma; benzodiazepines can be used with open-glaucoma only if they are administered according to the appropriate dose,
- cyanogen congenital heart disease,
- severe sepsis.

## 4.4 Special warnings and precautions for use

Respiratory insufficiency
Special caution is required for patients with impaired respiratory function, because midazolam may further depress respiration.

Prolonged acute convulsive seizures
All patients who are prescribed NASOLAM should be thoroughly instructed to understand the indication for use and the correct method of administration (see section 4.2). It is strongly advised also to educate the patient's immediate associates (e.g. parents, caregivers) for the correct usage of NASOLAM in case support is needed in the emergency situation.

High-risk patients in conscious sedation or premedication
Special caution should be exercised when administering midazolam to high-risk patients:

- adults ≥ 60 years of age;
- chronically ill or debilitated patients ≥ 44 kg or between 12 years to < 60 years, e.g. :
  - patients with chronic respiratory insufficiency, because midazolam may further depress respiration
  - patients with chronic renal failure
  - patients with impaired hepatic function
  - patients with impaired cardiac function

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

Special caution should be exercised when administering midazolam to paediatric patients of 12 kg to 43 kg that are chronically ill or debilitated patients, and patients > 60 years of age that are chronically ill or debilitated, e.g. patients with chronic respiratory insufficiency, patients with chronic renal failure, or with impaired hepatic- or cardiac function that require conscious sedation or premedication. These high-risk patients should only use NASOLAM 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.

Elderly patients
Patients > 60 years should be aware that the use of NASOLAM may result in prolonged sedation.

Amnesia

Anterograde amnesia could occur at therapeutical dose, with an increased risk at higher 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.

Discharge criteria following conscious sedation
After receiving midazolam, patients should be discharged from hospital or consulting room only when recommended by the treating physician. It is recommended that the patient is accompanied when returning home after discharge

Altered elimination of midazolam
Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic- or cardiac function.
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 hepatic dysfunction, low cardiac output and with chronic renal failure (see section 5.2). Midazolam may accumulate in patients with impaired hepatic function whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam.

Risk from concomitant use of opioids
Concomitant use of NASOLAM 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 NASOLAM with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe NASOLAM concomitantly with opioids, the lowest effective dose and the shortest possible duration of opioids should be used.
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).

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).

Concomitant use of other benzodiazepines
Debilitated patients are more prone to central nervous system effects of benzodiazepines and, therefore lower doses may be required.

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.

Excipients
This product contains 7.8 mg (for NASOLAM 2.5 mg nasal spray, solution in single dose container), 11.7 mg (for NASOLAM 3.75 mg nasal spray, solution in single dose container) or 15.6 mg (for NASOLAM 5 mg nasal spray, solution in single dose container) propylene glycol per dosage unit.

## 4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic Interactions
Midazolam is metabolized by cytochrome P450 (CYP3A4, CYP3A5). Inhibitors and inducers of CYP3A 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 intravenous or intranasal administration of 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- and intranasal route only the change in the systemic clearance becomes effective. After a single dose of intravenous or intranasal 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, intramuscular or intranasal administration. It is expected that the effects of CYP3A4 modulation should not substantially differ from those seen with intravenous 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, even

be it given only once.

With respect to induction of CYP3A4, 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 drug-drug interactions with midazolam. However, for strong inducers a relevant induction even after short-term treatment cannot be excluded.

**Drugs that inhibit CYP3A**
The concomitant use of drugs that inhibit CYP3A may lead to similar increases of midazolam concentrations as observed after the administration of intravenous midazolam, and may therefore prolong the pharmacologic activity of intranasal midazolam.

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 further), since increased sedative effects of i.v. midazolam, although lesser, are reported.
- Voriconazole increased the exposure 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 – 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.

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.

Intravenous anesthetics

- The disposition of intravenous midazolam 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.
- 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.

Calcium-channel blockers

- Diltiazem: A single dose of diltiazem to patients undergoing a coronary artery bypass grafting increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

Various drugs

- 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 intravenous midazolam were increased by 1.5-fold in the presence of fentanyl.

**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%)

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.

Protein binding displacement

- An increased concentration of free midazolam could be the result of protein binding displacement of valproic acid use. Clinical relevance 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. As with other benzodiazepines, foetotoxicity was observed. No data on exposed pregnancies are available for the first two trimesters of pregnancy. It has been suggested that use of benzodiazepines during the first trimester of pregnancy is associated with an increased risk of congenital malformation.

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.

Breastfeeding
Midazolam passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast-feeding following a single dose or two doses 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, ride a bicycle or use machines. Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered.

In case of conscious sedation: The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.

In case of treatment of prolonged acute epileptic seizure: After receiving midazolam, the patient should be warned not to drive a vehicle or use a machine until completely recovered.

## 4.8 Undesirable effects

Summary of safety profile
The following undesirable effects have been reported (frequency not known, cannot be estimated from the available data) to occur when midazolam is

injected:
Frequency categories are as follows:
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** | |
| frequency not known | Hypersensitivity, angioedema, anaphylactic shock |
| **Psychiatric Disorders** | |
| frequency not known<br><br><br><br>very rare | Disorientation, emotional and mood disturbances, changes in libido, excitation*, physical drug dependence and withdrawal syndrome, abuse.<br><br>Agitation*, hostility*, aggression*, anger*, confusional state, euphoric mood, hallucinations. |
| **Nervous System Disorders** | |
| common<br><br><br><br>very rare | Decreased alertness, depressed levels of consciousness, sedation (prolonged and postoperative), somnolence.<br><br>Involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity*, headache, dizziness, ataxia, paradoxical reactions, anterograde amnesia**, the duration of which is directly related to the administered dose. Drug withdrawal convulsions. |
| **Cardiac Disorders** | |
| very rare | Cardiac arrest, bradycardia |
| **Vascular disorders** | |
| very rare | Hypotension, vasodilatation |
| **Respiratory System disorders** | |
| common<br><br><br><br>very rare | Sneezing, cough, itching nose, nasal congestion, nasal dryness, rhinorrhea, yawning, respiratory depression<br><br>Apnoea, respiratory arrest, dyspnea, laryngospasm, hiccups |

| | |
|---|---|
| **Gastrointestinal Disorders** | |
| common<br><br>very rare | Nausea, vomiting<br><br>Constipation, dry mouth. |
| **Skin and subcutaneous tissue disorder** | |
| uncommon | Rash, urticarial, pruritis |
| **General Disorders and Administration Site Conditions** | |
| very rare | Fatigue |
| **Injury, Poisoning and Procedural complications** | |
| frequency unknown | Falls, fractures*** |
| **Social circumstances** | |
| very rare | Assaults* |
| **Eye disorders** | |
| frequency not known | Diplopia, blurred vision, excessive blinking |

* Such paradoxical drug reactions have been reported, particularly among children and the elderly after intravenous midazolam, which may be of relevance to intranasal administration.
** Anterograde amnesia may still be present at the end of the procedure and in few cases prolonged amnesia has been reported after the use of midazolam.
*** The risk of falls and fractures is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Severe cardiorespiratory adverse events have occurred after the administration of midazolam. Life-threating 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 a high dose 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the

Google Play or Apple App Store.

### 4.9 Overdose

Symptoms

Midazolam overdose can present a threat to life if the patient has pre-existing respiratory or cardiac insufficiency, or when combined with other CNS depressants (including alcohol).

Like other benzodiazepines, midazolam commonly causes 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

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 solution for nasal administration.

Pharmacodynamic effects

The pharmacological action of midazolam is characterized by short duration because of rapid metabolic transformation. Midazolam has a sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect.
After midazolam administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).

Clinical efficacy and safety

The data from published reports of studies in paediatric and adult patients demonstrate that intranasal midazolam acts as a sedative and an anxiolytic prior to a surgical procedure requiring anaesthesia as well as in other medical procedures requiring sedation without anaesthesia. A study in healthy adults showed a fast onset of intranasal midazolam. Onset of sedation on average was 7 minutes after administration of a 2.5 mg dose, and 4 minutes after administration of a 5 mg dose. Maximum sedation was generally reached around 15 - 40 minutes after administration of intranasal midazolam. The sedation effects were at plasma midazolam concentrations ranging from 20 to 80 ng/ml on average.

The data from published reports of studies in paediatric and adult patients demonstrate that intranasal midazolam is efficacious in the treatment of prolonged, acute, convulsive epileptic seizures in children (>2 years), adolescents and adults. A study in healthy adults showed a rapid increase of midazolam concentrations after the administration of NASOLAM. After administration of NASOLAM, midazolam concentrations increased to clinically relevant concentrations within 5 minutes, and reached a maximal concentration of 31 ng/ml at 11 minutes for the 2.5 mg dose, and 66 ng/ml at 14 minutes for the 5 mg dose.

The safety and efficacy of NASOLAM has been evaluated in adults and on the basis of in silico simulations and bibliographic data on the safety of midazolam in children aged 2 to 12 years. The safety and efficacy of intranasal midazolam in children aged less than 2 years has not been evaluated.

Therefore, intranasal midazolam is not recommended under 2 years of age

## 5.2 Pharmacokinetic properties

Simulated pharmacokinetic parameters for the recommended posology based on population pharmacokinetic study are provided in tabulated format below:

Absorption after intranasal administration
After intranasal NASOLAM administration midazolam is absorbed rapidly. Maximum plasma midazolam concentrations are reached within 11 minutes after administration of 2.5 mg NASOLAM and 14 minutes after administration of 5 mg NASOLAM in adults. The absolute bioavailability of NASOLAM in adults is circa 75% in adults.

Distribution
Midazolam is highly lipophilic and distributes extensively. The volume of distribution at steady state is 0.7-1.2 L/kg. Circa 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.

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 after NASOLAM administration in healthy adults are 17% of those of the parent compound. Alpha-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

Elimination
In healthy volunteers, the elimination half-life of midazolam after intravenous administration is between 1.5 – 2.5 hours. After intranasal administration this is 3- 6 hours. Plasma clearance is in the range of 300 - 500ml/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.

Exposure following a second dose
As midazolam pharmacokinetics is linear over the indicated dose range, a

second dose of midazolam administered to the second nostril together with a first dose in the first nostril will increase the AUC of midazolam with 100%. The administration of a second dose at 10 minutes after the first dose leads to an increase of the Cmax of approximately 1.7 to 1.9 fold as based on in silico pharmacokinetic simulations.

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 elimination half-life after intravenous and rectal administration is shorter in children 3 - 10 years old (1 - 1.5 hours) as compared with that in adults. The difference can be explained by the increased metabolic clearance in children in this age group.

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.

In obese patients, the administration of intranasal midazolam of a 2.5 mg, 3.75 mg or 5 mg dose leads to a slower decrease in midazolam concentrations at sub-clinical levels. This prolongation at sub-clinical levels is not expected to lead to the prolongation of pharmacological effect in obese patients relative to non-obese patients.

Patients with hepatic impairment

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

Patients with renal impairment

The pharmacokinetics of unbound midazolam are not altered in patients with severe renal impairment. The pharmacologically mildly active major midazolam metabolite (1'- hydroxyl-midazolam glucuronide), which is excreted through the kidney, accumulates in patients with severe renal impairment. This accumulation may prolong sedation. Midazolam should be administered carefully.

Critically ill patients

The elimination half-life of midazolam is prolonged up to 6 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).

Exposure following a second dose for conscious sedation, premedication or the treatment of prolonged, acute, convulsive seizures.
As the pharmacokinetics of midazolam is linear for the indicated dose range, the administration of a second dose increases the overall AUC with 100%. The administration of a second dose, at 10 minutes after the first dose, results in a significant increase in mean Cmax of between 1.7 - 1.9 fold. Administration of a second dose at 30 or 60 minutes leads to an increase in Cmax of 1.3 - 1.6 and 1.2 - 1.5 fold respectively, as based on in silico simulations (see section 4.2).

### 5.3 Preclinical safety data

In a rat fertility study, animals dosed up to ten times the clinical dose, no adverse effects on fertility were observed.

During local tolerance studies in animals, NASOLAM was well tolerated after intranasal administration.
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

Water
Propylene glycol
Ethanol

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

2 years

## 6.4 Special precautions for storage

This medical product does not require any special storage conditions.

## 6.5 Nature and contents of container

Single-dose container consisting of a clear glass vial with a rubber stopper, integrated in a polypropylene spray container packed in a blister.
Pack size: 4 single-dose containers of 2.5 mg, or 4 single-dose containers of 3.75 mg or 4 single-dose containers of 5 mg.

## 6.6 Special precautions for disposal

Each single-dose container contains only one dose. The single-dose container should not be tested before use. Epileptics should always have at least 2 single-dose containers available for use. Any unused product or waste material should be disposed of in accordance with local requirements or returned to the pharmacy.

Mode of administration

1. Remove the single-dose container from the blister
2. Hold the single-dose container by placing your thumb on the plunger of the device and your index- and middle finger on both sides of the nozzle
3. Insert the nozzle in one nostril until your fingers on the finger-grip, touch the nose.
   In young children, the nozzle may not fit in the nostril. In that case, place the end of the nozzle on the nostril - due to the spherical shaped top, it will always enter the nostril to some extent - and make sure the nozzle seals the nostril before administration
4. Press the plunger firmly with your thumb
5. Remove the nozzle from the nose
6. In case of epileptic seizure treatment, if possible the patient should be placed in the recovery position, on their side with their mouth open, their head tilt back
7. If required, one subsequent dose may be administered intranasally into the opposite nostril of the first dose, at least 10 minutes after the initial dose (e.g. if seizure did not stop after first dose), only after obtaining medical advice. <u>This subsequent dose should not be administered if the patient has trouble breathing or if there is excessive sedation that is uncharacteristic of the patient during a seizure, in these cases medical assistance must be sought immediately.</u>

## 7 MARKETING AUTHORISATION HOLDER

Medir Europe BV
Dorpsstraat 5
3941 JJ Doorn
The Netherlands

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 52530/0003

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/04/2022

## 10 DATE OF REVISION OF THE TEXT

26/04/2022