SUMMARY OF PRODUCT CHARACTERISTICS
SEDALAM® 15 mg/3 mL, SEDALAM® 5 mg/5 mL Solution for Intravenous or Intramuscular Injection (Midazolam)

1. NAME OF THE MEDICINAL PRODUCT

SEDALAM® 15 mg/3 mL, 5 mg/5 mL Solution for Intravenous or Intramuscular Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For SEDALAM® 15 mg/3 mL Solution for Injection: Each 1 ml of SEDALAM® solution contains 5 mg of midazolam, in packs of 3 mL vial.

For SEDALAM® 5 mg/5 mL Solution for Injection: Each 1 ml of SEDALAM® solution contains 1 mg of midazolam, in packs of 5 mL vial.

Excipient with Known Effect:
For SEDALAM® 15 mg/3 mL Solution for Injection: Each vial contains 9.44 mg of sodium.
For SEDALAM® 5 mg/5 mL Solution for Injection: Each vial contains 15.76 mg of sodium.

3. PHARMACEUTICAL FORM

Solution for Intravenous or Intramuscular Injection. Clear, colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

SEDALAM® is a short-acting hypnotic with the following indications for use:

Adults:

- Conscious sedation with or without local anaesthesia before or during diagnostic or therapeutic procedures.
- Anaesthesia.
- Premedication before the induction of anaesthesia.
- Induction of anaesthesia.
- As a sedative component in maintenance of anaesthesia.
- Sedation in the intensive care unit.

Children:

- Conscious sedation with or without local anaesthesia before or during diagnostic or therapeutic procedures.
- Anaesthesia.

- Premedication before the induction of anaesthesia.
- Sedation in the intensive care unit.

4.2 Posology and Method of Administration

Standard Dosages: SEDALAM® is a potent sedative agent that requires slow administration and titration. Titration is strongly recommended to safely obtain the desired level of sedation according to clinical needs, physical status, age, and concomitant medication. For patients over 60 years of age, debilitated patients or chronically ill patients and children, the medicine should be administered with care and the risk factors related to each patient should be evaluated on an individual basis. Standard dosages are provided in the table below; additional information follows the table.

Indication	**Adults <60 years**	**Adults ≥60 years / debilitated or chronically ill patients**	**Children**
Conscious sedation	IV: Initial dose: 2–2.5 mg Titration doses: 1 mg Total dose: 3.5–7.5 mg	IV: Initial dose: 0.5–1 mg Titration doses: 0.5–1 mg Total dose: <3.5 mg	IV in patients 6 months–5 years: Initial dose: 0.05–0.1 mg/kg Total dose: <6 mg IV 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 IM 1–15 years: 0.05–0.15 mg/kg
Anaesthesia premedication	IV: 1–2 mg repeated IM: 0.07–0.1 mg/kg	IV: Initial dose 0.5 mg, slow up-titration as needed IM: 0.025–0.05 mg/kg	Rectal >6 months: 0.3–0.5 mg/kg IM 1–15 years: 0.08–0.2 mg/kg
Anaesthesia induction	IV: 0.15–0.2 mg/kg (0.3–0.35 mg/kg without premedication)	IV: 0.05–0.15 mg/kg (0.15–0.3 mg/kg without premedication)	—
Sedative component in combined anaesthesia	IV: intermittent doses of 0.03–0.1 mg/kg OR continuous infusion of 0.03–0.1 mg/kg/h	IV: lower doses than recommended for adults <60 years	—
Sedation in the intensive care unit (ICU)	IV: Loading dose: 0.03–0.3 mg/kg in increments of 1–2.5 mg Maintenance dose: 0.03–0.2 mg/kg/h	—	IV: Neonates <32 weeks gestational age: 0.03 mg/kg/h Neonates >32 weeks and children up to 6 months: 0.06 mg/kg/h Patients >6 months: Loading dose 0.05–0.2 mg/kg; Maintenance dose 0.06–0.12 mg/kg/h

(IM: intramuscular; IV: intravenous)

Conscious Sedation Dosage

For sedation required for diagnostic and surgical procedures, SEDALAM® is administered intravenously. The suitable dose is determined on an individual basis. The medicine should not be administered rapidly or as a bolus injection, but by titrating the dose. The onset of the sedative effect may vary individually, depending on the physical status of the patient and the dosage method used. If necessary, additional doses may be administered according to individual needs. The onset of action is approximately 2 minutes after the injection. The maximum effect is obtained in approximately 5 to 10 minutes.

Adults: SEDALAM® should be administered slowly as an intravenous injection at a rate of approximately 1 mg/30 seconds. In adults under 60 years of age, 2 to 2.5 mg is administered 5 to 10 minutes before the beginning of the procedure as an initial dose. The initial dose may be followed by additional 1 mg doses as necessary. The average total dosage is 3.5 to 7.5 mg. Administration of a total dosage higher than 5 mg is usually not necessary.

The initial dose for patients over 60 years of age, debilitated patients or chronically ill patients is 0.5 to 1 mg, administered 5 to 10 minutes before the beginning of the procedure. Additional doses of 0.5 to 1 mg of SEDALAM® may be administered as necessary. In these patients it may take more time to reach the peak effect; therefore, additional doses of SEDALAM® should be titrated very slowly and carefully. Administration of a total dosage higher than 3.5 mg is usually not necessary.

Paediatric Population:

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

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

Rectal administration: the total dosage of midazolam is usually 0.3 to 0.5 mg/kg. The solution contained in the vial is administered rectally by means of a plastic applicator attached to a syringe. If the volume to be administered is too small, water may be added for a total volume of 10 ml. The whole dose should be administered at

once. Avoid repeated rectal administration. Rectal administration is not recommended in children under 6 months, due to limited data concerning this age group.

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

Anaesthesia Dosage – Premedication

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

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

Paediatric Population – Neonates and Children up to 6 Months of Age: This medicine is not recommended in children under 6 months of age, due to limited data.

Children over 6 Months of Age:

Rectal administration: The total dosage of SEDALAM® (usually in the range of 0.3 to 0.5 mg/kg) should be administered 15 to 30 minutes before the induction of anaesthesia. The solution contained in the vial is administered rectally by means of a plastic applicator attached to a syringe. If the volume to be administered is too small, water may be added for a total volume of 10 ml.

Intramuscular administration: Intramuscular administration is painful; therefore, this method of administration should only be used in exceptional cases. Rectal administration is preferred. The proven and safe dosage range for intramuscular administration is 0.08 to 0.2 mg/kg. Children between 1 to 15 years of age require proportionally higher dosages per body weight than adults. In children less than 15 kg of body weight, SEDALAM® solutions with a concentration higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

Induction Dosage

Adults: If SEDALAM® is used before other anaesthetic agents for induction of anaesthesia, the patient's individual response is invariable. The dosage should be increased by titrating until the desired effect is reached, based on the patient's age and clinical status. If SEDALAM® is used before or in combination with other intravenous or inhalational medicines used for induction of anaesthesia, the initial doses of all these medicines should be significantly reduced, sometimes to as low as 25% of the usual initial dose.

The desired level of anaesthesia is reached by gradually increasing the dose. For intravenous induction of anaesthesia, SEDALAM® is administered at a slow rate in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds, with 2-minute intervals between the doses.

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

Sedative Component in Combined Anaesthesia

Adults: SEDALAM® can be given as a sedative component in combined anaesthesia by either further intermittent small IV doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of IV SEDALAM® (range between 0.03 and 0.1 mg/kg/h), typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction. In adults over 60 years of age, debilitated patients or chronically ill patients, lower doses are required for maintenance.

Sedation in the Intensive Care Unit

The desired level of sedation is reached by stepwise titration of SEDALAM® followed by either continuous infusion or intermittent bolus. SEDALAM® is administered according to clinical need and the patient's condition, age, and concomitant medications (see section 4.5).

Adults: Intravenous loading dose: 0.03 to 0.3 mg/kg administered slowly in increments. Every 1 to 2.5 mg dose should be administered over 20 to 30 seconds, with 2-minute intervals between the doses. For patients with hypovolaemia, vasoconstriction or hypothermia, the loading dose should be reduced or omitted. If SEDALAM® is administered together with strong analgesics, the analgesics should be administered first.

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

Paediatric Population – Neonates and Children up to 6 Months of Age: SEDALAM® is administered as an intravenous continuous infusion. The initial dose for neonates born before 32 weeks of gestation is 0.03 mg/kg/h (0.5 µg/kg/min), and in neonates born after 32 weeks of gestation as well as children up to 6 months of age, 0.06 mg/kg/h (1 µg/kg/min). Intravenous loading doses are not recommended in preterm infants, neonates and children up to 6 months of age; rather the infusion rate should be higher during the first hours to reach therapeutic concentrations. Careful monitoring of breathing rate and oxygen saturation is required.

Children over 6 Months of Age: Intubated and ventilated children should be administered a loading dose of 0.05 to 0.2 mg/kg IV, slowly over 2 to 3 minutes, to achieve the desired clinical effect. SEDALAM® should not be administered as a rapid intravenous injection. Following the loading dose, SEDALAM® is administered as continuous infusion at a rate of 0.06 to 0.12 mg/kg/h (1 to 2 µg/kg/min). As necessary, the infusion rate can be increased or reduced, or additional doses are intravenously administered to maintain or increase the desired effect.

If SEDALAM® infusion is initiated in haemodynamically unstable patients, the usual loading dose should be titrated with low doses and the patient monitored for haemodynamic alterations. In premature infants, neonates and children with body weight below 15 kg, it is not recommended to use SEDALAM® solutions with a concentration above 1 mg/ml. Higher concentrations should be diluted to 1 mg/ml.

Special Populations

Renal Impairment: In patients with severe renal impairment (creatinine clearance below 30 ml/min), SEDALAM® may be accompanied by more pronounced and prolonged sedation, possibly including clinically relevant respiratory and cardiovascular depression. SEDALAM® should therefore be dosed carefully in this patient population and titrated for the desired effect (see section 4.4). In patients with renal failure (creatinine clearance <10 ml/min), the pharmacokinetics of unbound SEDALAM® following a single intravenous dose is similar to that reported in healthy volunteers. However, after prolonged infusion in ICU patients, the mean duration of the sedative effect in the renal failure population was considerably increased, most likely due to accumulation of 1'-hydroxy-midazolam glucuronide (see sections 4.4 and 5.2).

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

Paediatric Population: See above and section 4.4.

Method of Administration

For intravenous, intramuscular and rectal use. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

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

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

Special caution is required for conscious sedation in patients with impaired respiratory function. Paediatric patients under 6 months of age are especially predisposed to develop airway obstruction and hypoventilation. Therefore, it is essential to titrate the dosage with small increments to clinical effect and to carefully monitor respiratory rate and oxygen saturation.

After SEDALAM® is administered as premedication, the patient should be kept under careful observation as individual sensitivity varies and symptoms of overdose may occur.

Special caution is required when administering SEDALAM® to high-risk patients:

- Adult patients over 60 years of age.
- Chronically ill or debilitated patients, e.g. patients with chronic respiratory insufficiency.
- Patients with chronic renal failure.
- Patients with impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment).

- Patients with impaired cardiac function.
- Paediatric patients, especially those with cardiovascular instability.

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

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

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

Withdrawal Symptoms: Physical dependence may develop during prolonged treatment with SEDALAM® in intensive care. Abrupt termination of treatment leads to withdrawal symptoms, which may include headaches, diarrhoea, muscle pain, anxiety, tension, restlessness, confusion, irritability, sleep disturbances, mood changes, hallucinations and convulsions. In severe cases: depersonalisation, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact. It is recommended to decrease doses gradually.

Amnesia: Anterograde amnesia may occur with therapeutic doses, with the risk increasing at higher dosages, the duration of which is directly related to the administered dose. Prolonged amnesia may cause problems in outpatients who are discharged after the procedure. After receiving midazolam parenterally, patients should be discharged from the hospital or sent to a consulting room only if accompanied by an attendant.

Paradoxical Reactions: Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault have been reported with SEDALAM® use. Such reactions may occur when high doses are used and/or the medicine is administered rapidly, and are more prevalent in children and elderly patients. In the event of these reactions, discontinuation of the drug should be considered.

Altered Elimination of Midazolam: Altered elimination of midazolam may be caused by compounds that inhibit or induce isoenzyme CYP3A4, and the SEDALAM® dose may need to be adjusted accordingly (see section 4.5). Midazolam elimination time may also be extended in patients with liver dysfunction and low cardiac output and in neonates (see section 5.2).

Sleep Apnoea: SEDALAM® vials should be used with extreme caution in patients with sleep apnoea syndrome and patients should be regularly monitored.

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

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

Paediatric Patients Less Than 6 Months: For these patients, SEDALAM® is indicated for sedation in the intensive care unit only. Children under 6 months of age are especially predisposed to developing airway obstructions and hypoventilation. Titration with small increments until the clinical effect is reached, and careful monitoring of respiratory rate and oxygen saturation, are required.

Concomitant Use of Alcohol/CNS Depressants: The concomitant use of SEDALAM® with alcohol and/or CNS depressants should be avoided. Concomitant use may increase the clinical effect of midazolam, causing profound sedation that could result in coma or death, or clinically relevant respiratory depression (see section 4.5).

Risk from Concomitant Use of Opioids: Concomitant use of SEDALAM® and opioids may result in sedation, respiratory depression, coma and death. Concomitant prescribing should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe SEDALAM® concomitantly with opioids, the lowest effective dose should be used and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

Medical History of Alcohol or Drug Abuse: Use of SEDALAM® as well as other benzodiazepines should be avoided in patients with a history of alcohol or drug abuse.

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

Excipients:

For SEDALAM® 15 mg/3 mL Solution for Injection: Each vial contains 9.44 mg of sodium.

For SEDALAM® 5 mg/5 mL Solution for Injection: Each vial contains 15.76 mg of sodium.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Pharmacokinetic Interactions: Midazolam is metabolised by cytochrome P450 3A4 (CYP3A4, CYP3A5). Inhibitors and inducers of CYP3A have the potential to respectively increase and decrease the plasma concentrations, and subsequently the effects, of SEDALAM®, requiring dose adjustments accordingly.

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

It is recommended to carefully monitor the clinical effect and vital signs during the use of midazolam, taking into account that the clinical effect may be stronger and last longer after co-administration of a CYP3A4 inhibitor. Administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors may cause long-lasting hypnotic effects, delayed recovery from anaesthesia and respiratory depression, 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. Midazolam is not known to change the pharmacokinetics of other drugs.

Drugs that Inhibit CYP3A – Azole Antifungals:

- Ketoconazole increased the plasma concentrations of intravenously administered midazolam 5-fold, while the terminal half-life increased approximately 3-fold. If parenteral midazolam is co-administered with ketoconazole, it should be done in an intensive care unit or similar setting ensuring close clinical monitoring.
- Voriconazole increased the plasma concentrations of intravenously administered midazolam 3–4-fold, while the elimination half-life also increased approximately 3-fold.
- Both fluconazole and itraconazole increased the plasma concentrations of intravenously administered midazolam 2–3-fold, with terminal half-life extension of 2.4-fold for itraconazole and 1.5-fold for fluconazole.
- Posaconazole increased the plasma concentrations of intravenously administered midazolam approximately 2-fold.

It should be kept in mind that after oral administration the exposure of midazolam will be significantly higher than the above, especially with ketoconazole, itraconazole and voriconazole. Midazolam vials are not indicated for oral administration.

Macrolide Antibiotics:

- Erythromycin increased the plasma concentrations of intravenously administered midazolam approximately 1.6–2-fold, with terminal half-life extension of 1.5–1.8-fold.
- Clarithromycin increased the plasma concentrations of midazolam up to 2.5-fold; the terminal half-life was extended 1.5–2-fold.
- Telithromycin increased the plasma levels of oral midazolam 6-fold.

- Roxithromycin: no data on intravenous administration is available, but the mild effect on the terminal half-life of an oral midazolam tablet suggests the effect on intravenous midazolam may be minor.

Intravenous Anaesthetics:

- Propofol changed the disposition of intravenous midazolam (AUC and half-life increased by 1.6-fold).

HIV Protease Inhibitors:

- Saquinavir and other HIV protease inhibitors may cause a significant increase in midazolam concentration. Co-administration of ritonavir-boosted lopinavir increased the plasma concentrations of intravenously administered midazolam 5.4-fold, with a similar increase in terminal half-life.
- Hepatitis C virus (HCV) protease inhibitors boceprevir and telaprevir reduce midazolam clearance, resulting in a 3.4-fold increase of midazolam AUC after IV administration and prolonging its elimination half-life 4-fold.

Calcium-Channel Blockers:

- Diltiazem: a single dose increased the plasma concentration of intravenously administered midazolam by approximately 25% and the terminal half-life was extended by 43%.
- Verapamil increased the plasma concentrations of oral midazolam 3-fold; the terminal half-life was extended by 41%.

Various Medicines/Herbal Substances:

- Atorvastatin increased the plasma concentrations of intravenously administered midazolam 1.4-fold.
- Intravenous fentanyl is a weak inhibitor of midazolam elimination (AUC and half-life increased by 1.5-fold).
- Nefazodone increased the plasma concentrations of oral midazolam 4.6-fold; the terminal half-life was extended 1.6-fold.
- Tyrosine kinase inhibitors (imatinib, lapatinib, idelalisib) have been shown to be potent inhibitors of CYP3A; idelalisib increased oral midazolam exposure on average 5.4-fold.
- NK1 receptor antagonists (aprepitant, netupitant, casoprepitant) dose-dependently increased plasma concentrations of oral midazolam up to about 2.5–3.5-fold and increased terminal half-life by approximately 1.5–2-fold.
- Weak interactions (<2-fold change in AUC) were observed with everolimus, cyclosporine, simeprevir and propiverine; these are expected to be further attenuated after IV administration.

Drugs that Induce CYP3A:

- Rifampicin decreased the plasma concentrations of intravenously administered midazolam by 60% after 600 mg/day for 7 days; terminal half-life was shortened by approximately 50–60%. Orally, rifampicin decreased plasma concentrations of midazolam by 96%.
- Ticagrelor is a weak CYP3A inducer with only small effects on intravenously administered midazolam (–12%) and 4-hydroxymidazolam (−23%) exposures.

- Carbamazepine/phenytoin: repeated doses decreased the plasma concentration of oral midazolam by up to 90%; terminal half-life was shortened by 60%.
- Mitotane or enzalutamide caused profound, long-lasting decreases of midazolam levels in cancer patients (AUC reduced to 5% and 14% of normal values, respectively).
- Clobazam and efavirenz are weak inducers, reducing AUC by approximately 30%, with a resulting 4–5-fold increase in the ratio of active metabolite to parent compound; clinical significance unknown.
- Vemurafenib mildly induces CYP3A4: repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 39% (up to 80% in individuals).

Herbal Substances and Food:

- St John's Wort decreased plasma concentrations of midazolam by about 20–40%, with a decrease in terminal half-life of about 15–17%.
- Quercetin (also in Ginkgo biloba) and Panax ginseng have weak enzyme-inducing effects, reducing oral midazolam exposure by approximately 20–30%.

Acute Protein Displacement: Valproic acid: increased concentration of free midazolam due to displacement from plasma protein binding sites by valproic acid cannot be excluded, although the clinical relevance is not known.

Pharmacodynamic Interactions: Co-administration of midazolam with other sedative/hypnotic agents and CNS depressants (including alcohol) is likely to result in enhanced sedation and cardiorespiratory depression. These include opiate derivatives, antipsychotics, other benzodiazepines, barbiturates, propofol, ketamine, etomidate, sedative antidepressants, H1-antihistamines, and centrally acting antihypertensive drugs.

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

Alcohol may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4). Midazolam decreases the minimum alveolar concentration of inhalational anaesthetics.

4.6 Fertility, Pregnancy and Lactation

Pregnancy: Insufficient data are available to assess the safety of midazolam during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity has been observed with use of other benzodiazepines. There are no data about use of the drug during the first two trimesters of pregnancy. An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester has been suggested.

The administration of high doses of midazolam in the last trimester of pregnancy, during labour, or when used as an induction agent of anaesthesia for caesarean section, has been reported to produce maternal or foetal adverse effects (inhalation risk

in mother, irregularities in foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate). Infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at risk of developing withdrawal symptoms postnatally.

Consequently, SEDALAM® should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean section. The risk for the neonate should be taken into account in case of administration of SEDALAM® for any surgery near 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 SEDALAM®.

Fertility: No data on fertility are available.

4.7 Effects on Ability to Drive and Use Machines

Midazolam has a major influence on the ability to drive and use machines. Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge. If insufficient sleep occurs or alcohol is consumed, the likelihood of impaired alertness may be increased (see section 4.5).

4.8 Undesirable Effects

Frequency categories according to the MedDRA convention 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.

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

Immune system disorders

Frequency not known: Hypersensitivity, angioedema, anaphylactic shock.

Psychiatric disorders

Frequency not known: Confusional state, disorientation, emotional and mood disturbances, changes in libido. Paradoxical reactions* including restlessness, agitation, irritability, nervousness, hostility, anger, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement. Physical drug dependence and withdrawal syndrome. Abuse.

Nervous system disorders

Frequency not known: Involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity*. Sedation (prolonged and postoperative), 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

Frequency not known: Cardiac arrest, bradycardia, Kounis syndrome***.

Vascular disorders

Frequency not known: Hypotension, vasodilatation, thrombophlebitis, thrombosis.

Respiratory, thoracic and mediastinal disorders

Frequency not known: Respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm, hiccups.

Gastrointestinal disorders

Frequency not known: Nausea, vomiting, constipation, dry mouth.

Skin and subcutaneous tissue disorders

Frequency not known: Skin rash, urticaria, pruritus.

General disorders and administration site conditions

Frequency not known: Fatigue, injection site erythema, injection site pain.

Injury, poisoning and procedural complications

Frequency not known: Falls, fractures****.

Social circumstances

Frequency not known: Assault*.

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

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

Dependence: SEDALAM® may cause development of physical dependence, even if used in therapeutic doses. Discontinuation (especially abrupt discontinuation) of treatment after prolonged intravenous administration may cause withdrawal symptoms, including drug withdrawal convulsions (see section 4.4). Cases of drug abuse have been reported.

Severe cardiorespiratory adverse reactions have occurred. Life-threatening complications are more prevalent in adults over 60 years of age and patients with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the administration rate is too rapid or the dose is high (see section 4.4).

Health care professionals are asked to report any suspected adverse reactions via the https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms: Like other benzodiazepines, midazolam commonly causes drowsiness, ataxia, dysarthria and nystagmus. Overdose of SEDALAM® is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and, in rare cases, coma. Coma usually lasts a few hours but 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: A patient's vital signs should be monitored and supportive treatment started according to the patient's clinical status. Patients may require symptomatic treatment for cardiorespiratory or central nervous system effects. If taken orally, further absorption should be prevented using an appropriate method, e.g. treatment within 1–2 hours with activated charcoal; airway protection is imperative for drowsy patients. In case of mixed ingestion, gastric lavage may be considered, though not as a routine measure.

If central nervous system depression is severe, consider the use of flumazenil, a benzodiazepine antagonist, only under closely monitored conditions. It has a short half-life (about an hour); 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 its correct use.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Hypnotics and sedatives, benzodiazepine derivatives.

ATC Code: N05CD08

SEDALAM® is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance and has a low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring enables midazolam to form water-soluble salts with acids, producing a stable and well-tolerated solution for injection or infusion.

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

Pharmacodynamic Effects: The pharmacological effect of midazolam is characterised by rapid onset and short duration because of rapid metabolic transformation over a short time. Midazolam has a potent sedative and sleep-inducing effect, and has the effect of relieving anxiety and convulsions and of relaxing muscles. Midazolam impairs psychomotor function after single and/or multiple doses, but causes minimal

haemodynamic changes. After intramuscular or intravenous administration, anterograde amnesia of short duration occurs.

5.2 Pharmacokinetic Properties

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

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

Distribution: After intravenous administration of midazolam, one or two distinct distribution phases form on the plasma concentration time curve. The steady-state distribution volume is 0.7 to 1.2 l/kg. 96–98% of midazolam binds to plasma proteins, mostly albumin. Midazolam passes slowly and in small quantities into the cerebrospinal fluid, crosses the placental barrier slowly and enters foetal circulation, and has been found in human breast milk in small quantities. Midazolam is not a substrate for drug transporters.

Biotransformation: Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose metabolised through the liver is estimated at 30–60%. Midazolam is hydroxylated by cytochrome P450 CYP3A4 and CYP3A5 isoenzymes. The main metabolite in plasma and urine is 1'-hydroxymidazolam. The plasma concentrations of 1'-hydroxymidazolam are 12% of the parent compound; it is pharmacologically active but contributes only minimally (about 10%) to the effects of intravenous midazolam.

Elimination: In healthy test subjects, the midazolam elimination half-life ranges between 1.5 and 2.5 hours. Plasma clearance is 300 to 500 ml/min. Midazolam is mostly eliminated through the kidneys (60–80% of the dose injected) and is recovered as glucuronide-conjugated 1'-hydroxymidazolam. Less than 1% of the dose is recovered as unmodified substance in the urine. The elimination half-life of 1'-hydroxy-midazolam is under one hour. The elimination kinetics of midazolam when given by intravenous infusion are similar to that of bolus injection. Repeated administration of midazolam does not induce drug-metabolising enzymes.

Pharmacokinetics in Special Populations – Elderly: In adults over 60 years of age, the elimination half-life may be prolonged up to four times.

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

Neonates: In neonates the elimination half-life is on average 6–12 hours, probably due to liver immaturity, and clearance is reduced. Neonates with asphyxia-related hepatic

and renal impairment are at risk of generating unexpectedly high serum midazolam concentrations due to 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), due to an increase of approximately 50% in the volume of distribution corrected for total body weight. 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 clearance smaller compared to 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 metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in patients with severe renal impairment, producing prolonged sedation. Midazolam should therefore be administered carefully and titrated to the desired effect (see section 4.4).

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

Patients with Cardiac Insufficiency: The elimination half-life in patients with congestive heart failure is longer than in healthy subjects (see section 4.4).

5.3 Preclinical Safety Data

There are no further relevant preclinical data for the prescribing doctor beyond the information set out in other sections of this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium Chloride, Edetate Disodium, Hydrochloric Acid, Sodium Hydroxide, Water for Injection.

6.2 Incompatibilities

For intravenous infusion: the content of midazolam vials may be diluted in 0.9% sodium chloride or 5% glucose solution, in a ratio of 15 mg midazolam per 100 to 1000 ml of infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature (or for 3 days at 5°C).

SEDALAM® solution must not be diluted in glucose solution with Macrodex 6%, nor mixed with alkaline solutions for injection. SEDALAM® precipitates in solutions containing sodium bicarbonate.

6.3 Shelf Life

2 years.

6.4 Special Precautions for Storage

Do not store above 30°C. Protect from light.

6.5 Nature and Contents of Container

SEDALAM® 15 mg/3 mL: Clear tubular glass vial, 3 ml, with rubber stopper 13 mm.

SEDALAM® 5 mg/5 mL: Clear tubular glass vial (6R), with rubber stopper 20 mm – grey.

6.6 Special Precautions for Disposal and Other Handling

- SEDALAM® must not be mixed with other medicinal products except those mentioned in section 6.6.
- Inspect the solution before use. Only use clear solutions devoid of particulate matter.
- Any unused product or waste material should be disposed of in accordance with local requirements.
- SEDALAM® vials are for single use only. Discard all unused residual product.

Rectal Administration: For rectal administration of the vial's solution, a plastic applicator (rectal applicator) is fitted onto the syringe tip. If the administration volume is too low, water can be added to a total volume of 10 ml.

7. MARKETING AUTHORISATION HOLDER

MS Pharma – Jordan
King Abdullah (II) Bin Al-Hussein Industrial Estate, Amman, Jordan.
Telephone: +962 6 40 20 680
Fax: +962 6 40 20 679

8. MARKETING AUTHORISATION NUMBER(S)

H2019/CTD6904/13392

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

In Kenya: 21 January 2019.

10. DATE OF REVISION OF THE TEXT

December 2025.