MIDASIZ™

ATOMISER

1. Midazolam Nasal Spray

2. Qualitative and Quantitative composition

MIDASIZ

Each metered dose of 0.1ml delivers:

Midazolam IP .....1.25 mg

Excipients..... q.s.

MIDASIZ 0.5

Each metered dose of 0.1ml delivers:

Midazolam IP ..... 0.5 mg

Excipients..... q.s.

3. Dosage form and strength

Intranasal spray containing 1.25 mg Midazolam per dose.

Intranasal spray containing 0.5 mg Midazolam per dose.

4. Clinical particulars

4.1 Therapeutic indication

• Midazolam is indicated for sedation in minor surgical or investigative procedures, for premedication and induction of general anaesthesia.

• Intranasal midazolam has been used for over a decade now for sedating children before anaesthesia, due to its sedative and anxiolytic properties.

• Midazolam can be used instead of rectal and intravenous drugs for the emergency treatment of seizures, both in and out of hospital., Midazolam may be prescribed for a child with epilepsy who:

> Often has seizures lasting longer than 5 minutes.

> Has a pattern of seizures that recur closer together.

> Lives a long way from emergency services.

4.2 Posology and method of administration

For adults, dose is 5 mg, if weight <50 kg; and 10 mg, if weight >50 kg. The dose should be equally divided and administered into each nostril.

For children, the recommended dose of midazolam nasal spray is 0.2 mg/kg body weight. The dose should be equally divided and administered into each nostril.

4.3 Contraindication

• Hypersensitivity to benzodiazepines

• Uncontrolled pain

• Existing CNS depression

• Shock

• Acute narrow-angle glaucoma

• Acute alcohol intoxication

• Coma

4.4 Special warnings and precautions for use

• Midazolam must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. Prior to the administration of midazolam in any dose, the immediate available of oxygen, resuscitative drugs, age and size appropriate equipment for bag/valve/mask ventilation and intubation and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea, i.e., pulse oximetry. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because midazolam depresses respiration and because opioid agonists and other sedatives can add to this depression, midazolam should be administered as an induction agent only by a person trained in general anaesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway and supporting ventilation.

• When used for sedation/anxiolysis /amnesia, midazolam should always be titrated slowly in adult or pediatric patients. The sedative endpoint appears to reach more abruptly with midazolam. Appropriate precautions should therefore be taken.

• Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premeditation also depresses the ventilator response to carbon dioxide stimulation.

• Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of midazolam hydrochloride. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction.

PRECAUTIONS

General: Midazolam should be decreased for elderly and for debilitated patients. These patients will also probably take longer to recover completely after midazolam administration for the induction of anaesthesia.

Use with other CNS Depressants: The efficacy and safety of Midazolam in clinical use are functions of the dose administered, the clinical status of the individual patient and the use of concomitant medications capable of depressing the CNS. Anticipated effects range from mild sedation to deep levels of sedation virtually equivalent to a state of general anaesthesia where the patient may require external support of vital functions. Care must be taken to individualize and carefully titrate the dose of midazolam to the patient's underlying medical/surgical conditions, administer to the desired effect being certain to wait an adequate time for peak CNS effects of both midazolam hydrochloride and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention. Practitioners administering midazolam must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management.

Drug Abuse and Dependence

Midazolam is subject to Schedule IV control the Controlled Substances Act of 1970. Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam. There is no consensus in the medical literature regarding tapering schedules; therefore, practitioners are advised to individualize therapy to meet patient's needs.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs), Midazolam, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts, or behaviour, and/or any unusual changes in mood or behaviour.

4.5 Drug interactions

The sedative effect of midazolam is accentuated by any concomitantly administered medication, which depresses the CNS, particularly narcotics (e.g., morphine, meperidine and fentanyl) and secobarbital and droperidol. Consequently, the dosage of midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response. Caution is advised when midazolam is administered concomitantly with drug that are known to inhibit the P450-3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

No significant adverse interactions with commonly used premedication or drugs used during anaesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and other nondepolarizing muscle relaxants) or topical local anaesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl.

Drug/Laboratory Test Interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

4.6 Use in special population

• Pediatric: Generally safe in pediatric patients.

• Geriatric: Because geriatrics may have altered drug distribution and diminished hepatic and/ or renal function, reduced doses of midazolam are recommended. These patients will also probably take longer to recover completely after midazolam administration for the induction of anaesthesia.

• Liver impairment: The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared with those in healthy volunteers.

• Renal failure: Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites, which may result in slower recovery. The elimination half-life of midazolam is prolonged up to six times in the critically ill.

• Pregnancy and lactation: Category D: An increased risk of congenital malformations associated with the use of benzodiazepine drug (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the foetus.

The American Academy of Pediatrics considers that, although the effect of midazolam on breast-feeding infants is unknown its use by mothers during breast feeding may be concern since psychotropic drugs to appear in breast milk thus could conceivably alter CNS function in the infant both in the short and long term.

4.7 Effects on ability to drive and use machine

No patient should operate hazardous machinery or a motor vehicle until the side effects of the drug have subsided or until the day after anaesthesia and surgery, whichever is longer.

4.8 Undesirable effects

The most common side effects are mild to moderate, transient irritation of nasal and pharyngeal mucosa, watering of eyes or nose lasting for a few minutes, bad taste, split vision and dizziness. There are reports of hypertension, bradycardia & hypoxia in adults & children after intranasal midazolam administration, but these changes were always mild & transient & no patient required intubation or mechanical ventilation. In very rare cases, allergic reactions, urticaria & rashes are also observed. Nausea, vomiting, dizziness and drowsiness may occur.

4.9 Overdose

The manifestations of midazolam overdosage reported are like those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination,

diminished reflexes, coma, and untoward effects on vital signs. No evidence of specific organ toxicity from midazolam hydrochloride, overdosage has been reported. Treatment of Over dosage: Treatment of midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored, and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situation when an overdose with a benzodiazepine is known or suspected. Flumazenil is intended as an adjust to not as a substitute for, proper management of benzodiazepine overdose. Patients treated with Flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment.

5. Pharmacological properties

5.1 Mechanism of action

The exact mechanism of action for midazolam is not fully understood, but it is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABA-A receptor.

5.2 Pharmacodynamic properties

Pharmacodynamic properties of midazolam and its metabolites, which are similar to those of other benzodiazepines, include sedative, anxiolytic, amnesic and hypnotic activities. Benzodiazepine pharmacology effects appear to result from reversible interactions with the (gamma)-amino butyric acid (GABA) benzodiazepine receptor in the CNS, the major inhibitory neurotransmitter in the central nervous system. Recovery from anaesthesia or sedation for procedures in pediatric patients depends on the dose of midazolam administered, co-administration of other medications causing CNS depression and duration of the procedure.

5.3 Pharmacokinetic properties

Absorption: Absorption of midazolam is rapid, peak plasma concentrations being achieved within 20 to 60 minutes of administration depending on the route.

Midazolam usually has a short elimination half-life of about 2 hours although half-lives longer than 7 hours have been reported in some patients. The half-lives of midazolam is also prolonged in neonates, in the elderly, and in patients with liver disorders.

Intranasal administration of midazolam results in bioavailability of 50% to 83% when compared to the IV form. the variation in bioavailability depends on the method of administration, with atomization demonstrating higher levels than dropper application. In addition, CSF levels are higher than plasma levels presumably due to a “nose-brain” pathway. At 45 minutes, medication plasma curves are identical for intranasal and IV midazolam. Nasal midazolam has a slightly slower onset of action and peak affect compared to IV midazolam, but twice as fast of onset and 1 to 3 times higher peak plasma levels than rectal and oral midazolam.

In a study conducted to determine plasma concentration of midazolam over the first 2 h after 5-mg IV, IM, and IN midazolam administration it was found that midazolam was rapidly absorbed after IN administration, with concentrations reaching peak in 2 individuals at 5 min and in 75% of the individuals in < 10 min (median T_{max}=10min). C_{max} values after the IN-dose were higher than

those after the IM dose. A significantly shorter T_{max} was observed for the IN formulation (P = 0.0001).

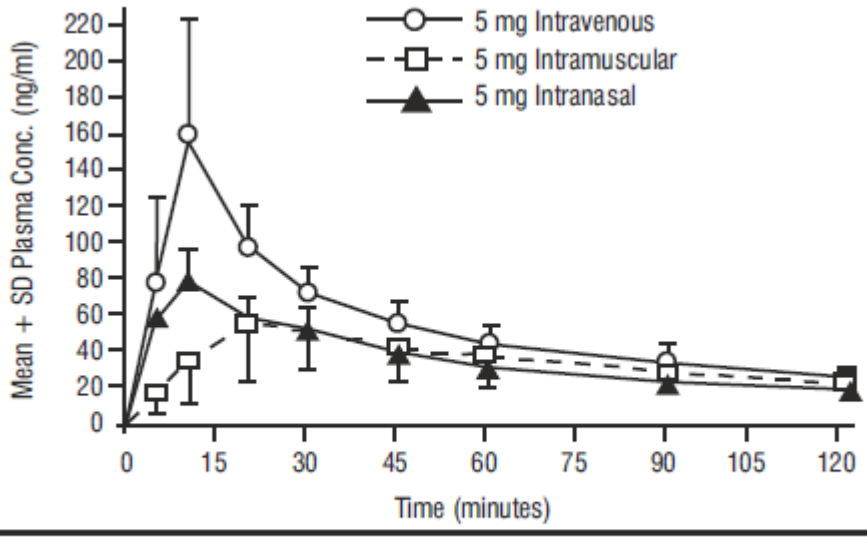


Fig. 1. Plasma concentrations of midazolam after 5-mg IV, IM, & IN midazolam administration. Values are mean (±sd) for 12 subjects for each dose.

On all measures, the order of magnitude of effect were identical with IV producing larger effects with faster onset of action than IN, which in turn produced larger effects with a faster onset than IM.

Children: Midazolam is absorbed rapidly when given by the intranasal route to children with mean maximum plasma concentrations being achieved within about 12 minutes, 2-4 values of 30% and 55% have been reported for the bioavailability 3-4 but methods to optimise nasal delivery have results in higher bioavailability in studies in adults. A study comparing intranasal, intravenous, and rectal administration of midazolam of children found that plasma concentrations from 45 minutes after intranasal and intravenous administration were similar; those following rectal administration were consistently less than after these other 2 routes.2 Possible reasons suggested for this included the effect that the wide inter individual variations in rectal pH may have had on the absorption of midazolam.

Plasma concentration of midazolam sufficient to induce conscious sedation are rapidly attained following intranasal administration. Although bioavailability of up to 55% had previously been obtained in children following intranasal administration, slow administration, and other methods to optimise nasal delivery had bioavailability of 83% in adults.

Distribution: Midazolam is lipophilic at physiological pH & is about 96% bound to plasma proteins.

Metabolism: Midazolam appears to be metabolised by at least 3 different cytochrome P450 isoenzymes which are found in the liver and in the kidney. Variation in the activity of these

enzymes might account for some of the interindividual differences in pharmacokinetics and pharmacodynamics seen with midazolam.

Elimination: The mean elimination half-life was 3.6 hours (SD 0.8), 3.8 hours (SD 1.0), 3.6 hours (SD 0.9), 4.0 hours (SD 1.6) and 3.6 hours (0.7) for intranasal midazolam 2.5 mg, intranasal midazolam 5.0 mg, intranasal midazolam 7.5 mg, intravenous midazolam 2.5 mg and intravenous midazolam solution administered intranasally, respectively in 25 healthy adults aged 18-42 years of age. The mean elimination half-life of midazolam ranged from 2.2 to 6.8 hours following single oral doses of 0.25, 0.5, and 1 mg/kg of midazolam (midazolam HCl syrup). Similar results (ranged from 2.9 to 4.5 hours) for the mean elimination half-life were observed following IV administration of 0.15 mg/kg of midazolam to pediatric patients (6 months to <16 years old). In the same group of patients receiving the 0.15 mg/kg IV dose, the mean total clearance ranged from 9.3 to 11 mL/min/kg.

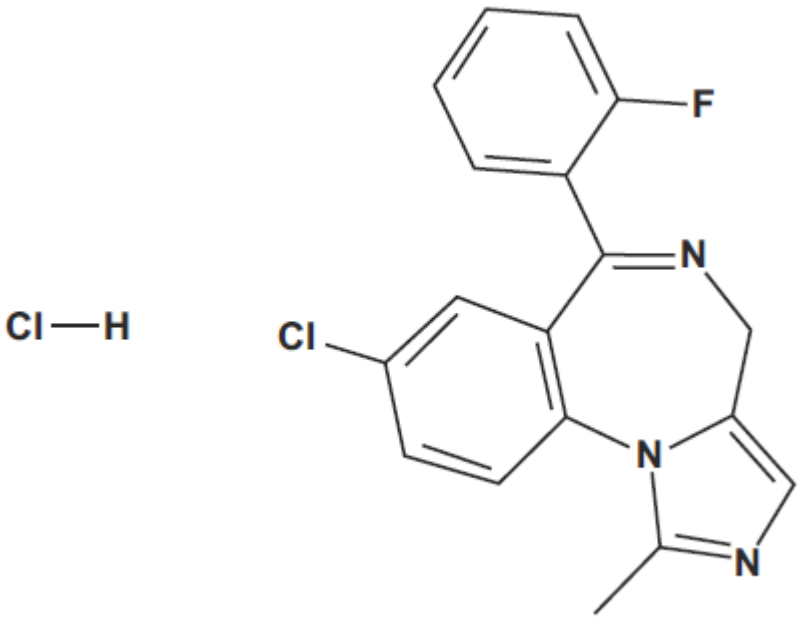
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Not required.

7. Description

Midazolam is a short acting benzodiazepine available as white or yellowish crystalline powder, practically insoluble in water but freely soluble in alcohol and in acetone; soluble in methyl alcohol. Chemically, midazolam is 8-chloro- 6-(2-flurophenyl)-1- methyl-4H- imidazo [1,5-a] [1,4] benzodiazepine. Midazolam has the molecular formula of $C_{18}H_{13}ClFN_3$ and a calculated molecular weight of 325.8.



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Midazolam is available as metered dose containing 25 and 50 metered doses.

Each metered Midazolam 1.25 Atomiser delivers 1.25 mg midazolam per dose.

Each metered Midazolam 0.5 Atomiser delivers 0.5 mg midazolam per dose.

8.4 Storage and handling instructions

Store in a cool place protected from light.

Keep away from children.

9. Patient Counselling Information

9.1 Adverse reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.8

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Details of manufacturer: Savi Health Science

11. M/779/2017

12. Date of revision: March 2024