PROFESSIONAL INFORMATION FOR

MIRANOST

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

MIRANOST (5 mg/0,1 mL nasal spray)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose nasal spray unit contains midazolam 5 mg/0,1 mL.

Contains ethanol (alcohol) 7,60 % *w/v.*

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Nasal spray.

MIRANOST is a clear, colourless to yellowish coloured solution, free from visible particles.

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death (see section 4.4 and 4.5).

- **Reserve concomitant prescribing of these medicines for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MIRANOST is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.

4.2 Posology and method of administration

Posology

Instructions prior to dosing

MIRANOST prescribers should consider the following prior to initiation of treatment: For patients at increased risk of respiratory depression from benzodiazepines, administration of MIRANOST under healthcare professional supervision should be considered prior to treatment with MIRANOST; this administration may be performed in the absence of a seizure episode (see **section 4.4**).

Prior to treatment, the healthcare professional should instruct the individual administering MIRANOST on how to identify seizure clusters and use the product appropriately. Patients and caregivers should be counselled to carefully read the **"Instructions for use"** for complete directions on how to properly administer MIRANOST.

Dosage information

Initial dose

Administer one spray (5 mg dose) into one nostril.

Second dose (if needed)

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One additional spray (5 mg dose) into the opposite nostril may be administered after 10 minutes if the patient has not responded to the initial dose.

A second dose of MIRANOST 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 cluster episode (see **section 4.4**).

Maximum dosage and treatment frequency

Do not use more than 2 doses of MIRANOST to treat a single episode.

It is recommended that MIRANOST be used to treat no more than one episode every three days and no more than 5 episodes per month (see **section 4.4**).

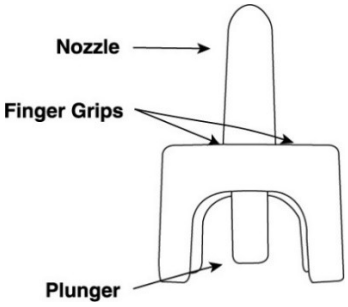
Method of administration

Administer MIRANOST by the nasal route only.

Instructions for use

The patient, family members or caregivers should read the **"Instructions for use"** before using MIRANOST and each time a repeat prescription is provided. There may be new information.

This information does not replace consulting the healthcare provider about the medical condition or treatment.



Important: MIRANOST is for use in the nose only.

- **There is only 1 dose of MIRANOST in the nasal spray unit**.
- **Do not** try to test or prime the nasal spray unit before use. You will lose the dose.
- **Do not** open the blister packaging until ready to use.
- **Do not** use if the nasal spray unit appears damaged.
- **Do not** use past the expiration date printed on the blister packaging.
- Throw away (dispose of) the nasal spray unit after use.

How to use MIRANOST:

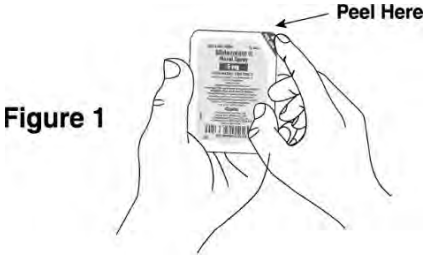


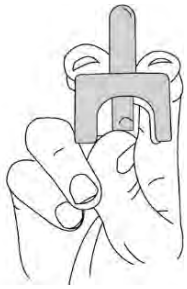
Figure 1

Step 1: Peel open the blister packaging

- When ready to use, open the blister packaging.
- Hold blister packaging in the palm of your hand.
- On the foil backing, find the "**Peel Here**" tab and pull down (see **Figure 1**).
- Remove the nasal spray unit carefully.

Step 2: Hold the nasal spray unit

Figure 2



- Hold the nasal spray unit with your thumb on the plunger and your middle and index fingers on each side of the nozzle (see **Figure 2**).
- **Do not press the plunger yet. If you press the plunger now you will lose the dose.**

Step 3: Place the tip into 1 nostril

Figure 3



- Place the tip of the nozzle into 1 nostril until your fingers on either side of the nozzle touches the bottom of the nose (see **Figure 3**).

Step 4: Press the plunger

Figure 4



- Press the plunger firmly to deliver the dose of MIRANOST (see **Figure 4**).
- Make sure to firmly press the plunger using 1 motion.

The patient does not need to breathe deeply when you give them the medicine.

What to do after the MIRANOST has been used:

Remove the nozzle from the nostril after giving the dose.

Note: The plunger will remain inside the nasal spray unit

after the dose is given.

Throw away (dispose of) the nasal spray unit and blister packaging in the trash.

What to do if a second dose is needed:

Important: If the seizure cluster is continuing **10 minutes** after the first dose of MIRANOST, a second dose of MIRANOST **may be used if you have been told to do so by your healthcare provider**.

If you need to give a second dose of MIRANOST, follow the instructions in this **"Instructions for use"** using a new nasal spray unit **in the other nostril**. (Repeat Step 1 through Step 4.)

4.3 Contraindications

MIRANOST is contraindicated in:

- Patients with known hypersensitivity to midazolam or to any of the excipients used in the formulation of MIRANOST (see **section 6.1**)**.**
- Acute narrow-angle glaucoma (see **section 4.4**).

4.4 Special warnings and precautions for use

Risks from concomitant use with opioids

Concomitant use of benzodiazepines, including MIRANOST, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioids alone. If a decision is made to prescribe MIRANOST concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when MIRANOST is used with opioids (see **section 4.5**).

Risks of cardiorespiratory adverse reactions

Serious cardiorespiratory adverse reactions have occurred after administration of midazolam, as in MIRANOST. These have included respiratory depression, airway obstruction, oxygen desaturation, apnoea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations, particularly in patients with haemodynamic instability. Hypotension occurs more frequently in patients premedicated with a narcotic. The danger of hypoventilation, airway obstruction, or apnoea is greater in elderly patients and those with chronic disease states or decreased pulmonary reserve; patients with chronic obstructive pulmonary disease are highly sensitive to the respiratory depressant effect of midazolam.

Respiratory depression can be observed with the administration of MIRANOST (see **section 4.8**).

Central nervous system depression from concomitant use with other central nervous system depressants, or moderate or strong CYP3A4 inhibitors

Medicines containing midazolam, including MIRANOST, have a central nervous system (CNS) depressant effect.

Risks from concomitant use with other CNS depressants

The potential for an increased CNS-depressant effect from concomitant use with alcohol or other CNS depressants (e.g., opioids) must be considered by the prescribing medical practitioner, and appropriate recommendations made to the patient and/or caregiver.

Concomitant use of barbiturates, alcohol, or other CNS depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnoea and may contribute to profound and/or prolonged medicine effect (see **section 4.5**).

Risks from concomitant use with moderate or strong CYP3A4 inhibitors

There is a potential for prolonged sedation from concomitant use with moderate or strong CYP3A4 enzyme inhibitors because of much higher midazolam exposures (see **section 4.5**).

Suicidal behaviour and ideation

Antiepileptic medicines (AEDs), including MIRANOST, increase the risk of suicidal thoughts or behaviour in patients taking these medicines 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.

Anyone considering prescribing midazolam, as in MIRANOST, or any other AED must balance the risk of suicidal thoughts or behaviours with the risk of untreated illness. Epilepsy and many

other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Impaired cognitive function

Midazolam, including MIRANOST, is associated with a high incidence of partial or complete impairment of recall for several hours following an administered dose. Gross tests of recovery from the effects of midazolam cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the medicine, such as drowsiness, have subsided, and as their medical condition permits (see **section 4.7**). For paediatric patients, particular care should be taken to ensure safe ambulation.

Glaucoma

Benzodiazepines, including MIRANOST, can increase intraocular pressure in patients with glaucoma. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam, as in MIRANOST. MIRANOST may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Patients with open-angle glaucoma may need to have their ophthalmologic status evaluated following treatment with MIRANOST. MIRANOST is contraindicated in patients with narrow-angle glaucoma (see **section 4.3**).

Other adverse reactions

When midazolam, as in MIRANOST, was used for sedation, reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, and combativeness have been reported. These reactions may be caused by inadequate or excessive

dosing or improper administration of midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions.

Medicine abuse and dependence

Abuse

Benzodiazepines, such as midazolam, may be subject to abuse. Abuse is the intentional non-therapeutic use of a medicine, even once, to achieve a desired psychological or physiological effect. Available data concerning the medicine abuse and dependence potential of midazolam, as in MIRANOST, suggest that its abuse potential is at least equivalent to that of diazepam.

The pharmacological profile of MIRANOST is similar to that of other benzodiazepines, particularly in its potentiation of GABA-ergic transmission through its action on $GABA_A$ receptors, which leads to sedation and somnolence.

Dependence

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the medicine, and/or administration of an antagonist.

Benzodiazepines can cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the medicine. Withdrawal symptoms (i.e., convulsions, hallucinations, tremors, abdominal and muscle cramps, vomiting, and sweating), similar in characteristics to those noted with barbiturates and alcohol, have occurred following abrupt discontinuation of midazolam, as in MIRANOST, following chronic administration.

Chronic use

MIRANOST is not recommended for chronic, daily use as an anticonvulsant because of the potential for development of tolerance to midazolam.

Chronic daily use of benzodiazepines may increase the frequency and/or severity of tonic clonic seizures, requiring an increase in the dosage of standard anticonvulsant medication. In such cases, abrupt withdrawal of chronic benzodiazepines may also be associated with a temporary increase in the frequency and/or severity of seizures.

Paediatric population

Safety and effectiveness of MIRANOST have been evaluated in the age group 12 to 17 years. Use of MIRANOST in this age group is supported by evidence from an adequate and well-controlled study of MIRANOST in adults and adolescents with seizure clusters and pharmacokinetic and safety data from adult and paediatric patients.

Safety and effectiveness in paediatric patients below the age of 12 years have not been established (see **section 4.1**).

Use in the elderly

Elderly patients have longer elimination half-lives for midazolam, as in MIRANOST, and its metabolites, which may result in prolonged medicine exposure. Elderly patients may have altered medicine distribution; diminished hepatic and/or renal function; and subjects over 70 years of age may be particularly sensitive. Administration of intramuscular (IM) midazolam to elderly patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression (see **"Risks of cardiorespiratory adverse reactions"**). In most of these cases, the patients also received other CNS depressants capable of depressing respiration, especially narcotics (see **"Risks from concomitant use with opioids"**, **"Central nervous system depression from concomitant use with other central nervous system depressants,**

or moderate or strong CYP3A4 inhibitors”). Close monitoring of elderly patients is recommended.

Renal impairment

Midazolam, as in MIRANOST, and 1-OH midazolam pharmacokinetics are expected to be similar in subjects with mild renal impairment when compared to normal subjects. Patients with moderate and severe renal impairment may have slower elimination of midazolam and its metabolites, which may result in prolonged medicine exposure (see **section 5.2**).

Congestive heart failure

Patients with congestive heart failure eliminate midazolam, as in MIRANOST, more slowly, which may result in prolonged medicine exposure (see **section 5.2**).

Ethanol (alcohol)

This medicine contains 7,60 mg alcohol (ethanol) in each single dose unit which is equivalent to 7,60 mg/0,1 mL (7,60 % *w/v*).

It may cause burning sensation on damaged skin.

4.5 Interaction with other medicines and other forms of interaction

CYP3A4 inhibitors

Concomitant use of CYP3A4 inhibitors, such as moderate CYP3A4 inhibitors erythromycin, diltiazem, or verapamil and strong CYP3A4 inhibitors ketoconazole, itraconazole, or clarithromycin may result in prolonged sedation because of a decrease in plasma clearance of midazolam. Avoid co-administration of MIRANOST with moderate or strong CYP3A4 inhibitors. MIRANOST should be used with caution when co-administered with mild CYP3A4 inhibitors.

Opioids

The concomitant use of benzodiazepines and opioids, such as morphine, hydrocodone, oxymorphone, codeine, or fentanyl increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Reserve concomitant prescribing of these medicines for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required (see **section 4.4**).

Other central nervous system (CNS) depressants

Concomitant use of barbiturates, alcohol, or other CNS depressants, such as other benzodiazepines and sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, antipsychotics, opioids, or alcohol may increase the risk of hypoventilation, airway obstruction, desaturation, or apnoea and may contribute to profound and/or prolonged medicine effect. Reserve concomitant prescribing of these medicines for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required (see **section 4.4**).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy has not been established.

There are no adequate and well-controlled studies of MIRANOST in pregnant women.

Available data suggest that the class of benzodiazepines is not associated with marked increases in risk for congenital anomalies. Although some early epidemiological studies suggested a

relationship between benzodiazepine medicine use in pregnancy and congenital anomalies such as cleft lip and or palate, these studies had considerable limitations. More recently completed studies of benzodiazepine use in pregnancy have not consistently documented elevated risks for specific congenital anomalies. There is insufficient evidence to assess the effect of exposure to benzodiazepines during pregnancy on neurodevelopment.

It has also been suggested that there is an increased risk of miscarriage (spontaneous abortion, early pregnancy loss) when used in pregnancy.

There are clinical considerations regarding exposure to benzodiazepines during the second and third trimesters of pregnancy or immediately prior to or during childbirth. These risks include decreased foetal movement and/or foetal heart rate variability, “floppy infant syndrome,” dependence, and withdrawal.

Published data for midazolam and other benzodiazepines suggest the possibility of neuronal cell death and long-term effects on neurobehavioral and immunological function in animals following prenatal or early postnatal exposure at clinically relevant doses. Advise a pregnant woman and women of childbearing age of the potential risk to a foetus.

Foetal/neonatal adverse reactions

Infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period. Clinical manifestations of withdrawal or neonatal abstinence syndrome may include hypertonia, hyperreflexia, hypoventilation, irritability, tremors, diarrhoea, and vomiting. These complications can appear shortly after delivery to 3 weeks after birth and persist from hours to several months depending on the degree of dependence and the pharmacokinetic profile of the benzodiazepine.

Symptoms may be mild and transient or severe. Standard management for neonatal withdrawal syndrome has not yet been defined. Observe newborns who are exposed to MIRANOST *in utero* during the later stages of pregnancy for symptoms of withdrawal and manage accordingly.

Labour and delivery

Administration of benzodiazepines immediately prior to or during childbirth can result in a floppy infant syndrome, which is characterised by lethargy, hypothermia, hypotonia, respiratory depression, and difficulty feeding. Floppy infant syndrome occurs mainly within the first hours after birth and may last up to 14 days. Observe exposed newborns for these symptoms and manage accordingly.

Congenital anomalies

Although there are no adequate and well-controlled studies of MIRANOST in pregnant women, there is information about benzodiazepines as a class. The effects of benzodiazepine, mainly chlordiazepoxide and diazepam, exposure during the first trimester of pregnancy were examined. An association between benzodiazepines and major malformations and oral cleft was suggested.

Neonatal withdrawal and floppy infant syndrome

Neonatal withdrawal syndrome and symptoms suggestive of floppy infant syndrome associated with administration of benzodiazepines during the later stages of pregnancy and peripartum period have been reported. Findings in published scientific literature suggest that the major neonatal side effects of benzodiazepines include sedation and dependence with withdrawal signs. Data from observational studies suggest that foetal exposure to benzodiazepines is associated with the neonatal adverse events of hypotonia, respiratory problems, hypoventilation, low Apgar score, and neonatal withdrawal syndrome.

Breastfeeding

Midazolam, as in MIRANOST, is excreted in human milk. Studies assessing the effects of midazolam in the breastfed infant or on milk production/excretion have not been performed. Post-marketing experience suggests that breastfed infants of mothers taking benzodiazepines, such as MIRANOST, may have effects of lethargy, somnolence, and poor sucking.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MIRANOST and any potential adverse effects on the breastfed infant from midazolam or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the medicine, such as drowsiness, have subsided, and as their medical condition permits (see **section 4.4**).

4.8 Undesirable effects

MedDRA system organ Class	**Frequency**	**Side effects**
Psychiatric disorders	Frequency unknown	Increase in risk of suicidal thoughts or behaviour, worsening of depression and/or any unusual changes in mood or behaviour.
Nervous system disorders	Frequent	Somnolence, headache, dysarthria.
	Frequency unknown	Sedation, respiratory depression, coma, and death (especially when used with opioids).

		Central nervous system (CNS) depression. Profound and/or prolonged medicine effect (when used with barbiturates, alcohol, or other CNS depressants). Partial or complete impairment of recall for several hours following an administered dose. Agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, and combativeness have been reported, possibly due to cerebral hypoxia or true paradoxical reactions.
Eye disorders	Frequent	Lacrimation increased.
	Frequency unknown	Increase in intraocular pressure in patients with glaucoma.
Cardiac disorders	Frequency unknown	Cardiac arrest, hypotension.
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal discomfort, throat irritation, rhinorrhoea, product taste abnormal.
	Frequency unknown	Respiratory depression, airway obstruction, oxygen desaturation, apnoea, respiratory arrest, sometimes resulting in death or permanent neurologic injury, hypoventilation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Symptoms

The manifestations of midazolam, as in MIRANOST, overdosage reported are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, and untoward effects on vital signs.

Treatment

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. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis, or haemodialysis are of any value in the treatment of midazolam overdosage.

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 situations when an overdose with MIRANOST is known or suspected. There are anecdotal reports of adverse

haemodynamic responses associated with midazolam following administration of flumazenil to paediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users. The administration of flumazenil in cases of benzodiazepine overdose can lead to withdrawal and adverse reactions, including increased seizures. Its use in patients with epilepsy is typically not recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 2.5 Anticonvulsants, including anti-epileptics

ATC code: N05CD08

Mechanism of action

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

Pharmacodynamic effects

The pharmacodynamic properties of midazolam and its metabolites, are similar to those of other benzodiazepines, including sedative, anxiolytic, amnestic, and hypnotic activities. The effects of midazolam on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications.

Treatment with MIRANOST was associated with effects on measures of sedation and measures of psychomotor performance (see **section 4.4**). Sedation and psychomotor impairment effects generally began to occur within 10 minutes post-dose with peak effects observed within 30 minutes to 2 hours post-dose. The pharmacodynamic effects generally returned to near baseline levels by 4 hours post-dose.

5.2 Pharmacokinetic properties

Based on a population pharmacokinetic analysis, plasma exposures (C_{max} and AUC) of midazolam in epilepsy patients increase approximately proportional to dose from 5,0 mg to 15 mg, 0,5 and 1,5 times the recommended maximum total dose (5 mg initial dose + 5 mg second dose), respectively.

Absorption

Following nasal administration of a single 5 mg midazolam dose to healthy adults, midazolam was absorbed with median T_{max} (range) of 17,3 (7,8 to 28,2) minutes; midazolam mean (±SD) C_{max} and $AUC_{0-\infty}$ were 54,7 (± 30,4) ng/mL and 126,2 (± 59) ng·hr/mL, respectively. The mean absolute bioavailability is approximately 44 %.

Distribution

In adults and paediatric patients, midazolam is approximately 97 % bound to plasma protein, principally albumin. In healthy volunteers, 1-hydroxymidazolam is bound to the extent of 89 %.

The estimated total volume of distribution of midazolam is 226,5 L.

In humans, midazolam has been shown to cross the placenta and enter into foetal circulation and has been detected in human milk and CSF.

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Biotransformation

Midazolam is primarily metabolised by liver and intestinal cytochrome P450 3A4 (CYP3A4) to its pharmacologic active metabolite, 1-hydroxymidazolam (also termed α-hydroxymidazolam). Midazolam is also metabolised to two other minor metabolites: 4-hydroxy metabolite and 1,4-dihydroxy metabolite. The principal urinary excretion products are glucuronide conjugates of the hydroxylated derivatives.

Studies of the intravenous administration of 1-hydroxymidazolam in humans suggest that 1-hydroxymidazolam is at least as potent as the parent compound and may contribute to the net pharmacologic activity of midazolam.

Since MIRANOST is metabolised by CYP3A4, interactions with medicines that inhibit or induce CYP3A4 are likely.

Concomitant use of CYP3A4 inhibitors may result in prolonged sedation because of a decrease in plasma clearance of midazolam.

Exposures (e.g., combined C_{max} or AUC of midazolam and the 1-OH-midazolam active metabolite) are decreased 16 to 26 % when MIRANOST is co-administered with anti-epileptic medicines that are strong CYP3A4 inducers (e.g., phenytoin, phenobarbital, primidone, carbamazepine). Exposures are decreased 8 to 15 % when MIRANOST is co-administered with anti-epileptic medicines that are weak to moderate CYP3A4 inducers (e.g., clobazam, eslicarbazepine, felbamate, oxcarbazepine, rufinamide, topiramate). These changes in exposures are not expected to be clinically significant.

Elimination

Following administration of MIRANOST, median midazolam and 1-hydroxymidazolam elimination half-lives ranged from 2,1 to 6,2 hours and 2,7 to 7,2 hours, respectively, independent of dose.

The principal urinary excretion product is 1-OH midazolam in the form of a glucuronide conjugate. Smaller amounts of the glucuronide conjugates of 4-hydroxy- and dihydroxymidazolam are detected as well.

Specific populations

Elderly patients

Mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of midazolam were 21 to 45 % higher in elderly subjects (> 65 years old) as compared to younger subjects. The terminal half-life was increased by approximately 2 hours in the elderly subjects because of a decrease in clearance.

Obesity

The mean half-life of midazolam administered by parenteral route was greater in obese patients (5,9 versus 2,3 hours). This was because of an increase of approximately 50 % in the volume of distribution (Vd) corrected for total body weight. The clearance was not significantly different between groups.

Patients with renal impairment

Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites.

Midazolam and 1-hydroxymidazolam pharmacokinetics in patients who developed acute renal failure (ARF) were compared with patients with normal renal function. Midazolam was

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administered as an infusion (5 to 15 mg/hr). Midazolam clearance was reduced (1,9 vs 2,8 mL/min/kg) and the half-life was prolonged (7,6 vs 13 hours) in the ARF patients. The renal clearance of the 1-hydroxymidazolam glucuronide was prolonged in the ARF group (4 vs 136 mL/min) and the half-life was prolonged (12 vs > 25 hours). Plasma levels accumulated in all ARF patients to about ten times that of the parent medicine. The relationship between accumulating metabolite levels and prolonged sedation is unclear.

In chronic renal failure patients receiving a single intravenous dose of midazolam, there was a 2-fold increase in the clearance and volume of distribution, but the half-life remained unchanged.

Patients with hepatic impairment

Midazolam pharmacokinetics were studied after an intravenous single dose (0,075 mg/kg) was administered to patients with biopsy proven alcoholic cirrhosis. The mean half-life of midazolam increased 2,5-fold in the patients with cirrhosis. Clearance was reduced by 50 % and the Vd increased by 20 %. In male patients with cirrhosis without ascites and with normal kidney function as determined by creatinine clearance, no changes in the pharmacokinetics of midazolam or 1-hydroxymidazolam were observed when compared to healthy individuals. The clinical significance of these findings is unknown.

Patients with congestive heart failure

In patients suffering from congestive heart failure, a 2-fold increase in the elimination half-life, a 25 % decrease in the plasma clearance, and a 40 % increase in the volume of distribution of midazolam were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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Ethanol (alcohol) 7,60 % *w/v*

Methoxy polyethylene glycol 350 (polyethylene glycol monomethyl ether 350)

Polyethylene glycol 400

Propylene glycol

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container.

6.5 Nature and contents of container

MIRANOST is packed in a Type I clear glass vial with rubber stopper and a white unit dose nasal spray device supplied in boxes of 2 nasal spray units, each contained within an individual blister pack.

6.6 Special precautions for disposal and other handling

- Do not open the blister packaging until ready to use. Do not test or prime before use.
- Do not use if the nasal spray unit appears damaged.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

58/2.5/0059

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 20 February 2024.

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

27 March 2026