MIDACIP 1.25 Nasal Spray (Midazolam)

## Composition

Midazolam IP .................. 1.25% w/v  
Benzalkonium Chloride IP (as preservative) .......... 0.01% w/v  
Each spray delivers:  
Midazolam, IP .................. 1.25 mg

## Dosage Form

Aqueous intranasal spray

## Pharmacology

### Pharmacodynamics

Midazolam is a short-acting, benzodiazepine, central nervous system (CNS) depressant. It has anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and anterograde amnestic effects, which are characteristic of benzodiazepines.  
The mechanism of action of the benzodiazepines is under continuous investigation. Benzodiazepines appear to intensify the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the brain.  
Midazolam acts as an agonist at the benzodiazepine receptors by forming a component of the midazolam-GABA receptor-chloride ionophore complex. This binding increases the permeability of the central pore of the receptor to chloride ion into the neuron. Increased chloride influx leads to hyperpolarization of neurons, which results in an inhibitory effect.  
Midazolam is a small molecular weight of 325.8 Da allows for easy permeation of nasal mucosa. Midazolam dissolves in water at a low pH, but at physiologic pH it becomes lipophilic, allowing the medication to cross the blood-brain-barrier.  
The pharmacodynamics effects of intranasal midazolam was assessed in a single dose (2.5 mg and 5 mg), phase-1, randomized, double-blind, 2-way crossover study (≥4 day washout period) in generally healthy geriatric (≥65 years; n=18) and non-geriatric (18-40 years; n=12) participants. Following a single 2.5 or 5 mg dose of intranasal midazolam, pharmacodynamic effects were observed shortly after administration and returned to baseline generally within 4 hours.  
Pharmacodynamics assessments included Standardford Sleepiness Scale (SSS) and Observer’s Assessment of Alertness/Sedation Scale sum score to assess sedation, and Digit-Symbol Substitution Test (DSST) percent correct and trial completion rate to assess psychomotor performance. Pharmacodynamics effects were observed shortly after administration and returned to baseline generally within 4 hours. Pharmacodynamics effects were more pronounced with 5 mg versus 2.5 mg. There were no significant differences in sedation and psychomotor impairment between the two age groups.

### Pharmacokinetics (trial)
Absorption
A recent phase I, five cross-over, open label study compared the pharmacokinetics, pharmacodynamics, and tolerability of 2.5, 5.0 and 7.5 mg midazolam formulation optimized for nasal delivery (MDZ-IN) versus midazolam intravenous (IV) solution administered intranasally (5.0 MDZ-Inj IN) or midazolam 2.5 mg administered intravenously (2.5 MDZ-Inj IV) in 25 healthy adults aged 18-42 years.

Increasing midazolam dose corresponded with increases in midazolam area under the concentration time curve (AUC) and maximum observed plasma concentration (Cmax), with all doses demonstrating rapid median time to Cmax (Tmax; 10–12 min). Midazolam nasal spray also demonstrated increased absorption, with a 134% relative bioavailability, compared with the same MDZ-inj IN dose. The pharmacokinetics of midazolam and its major metabolite, alpha-hydroxymidazolam is summarized in the table below.

Table 1: Pharmacokinetics of midazolam formulations (N = 25)

<table>
<thead>
<tr>
<th>Midazolam</th>
<th>MDZ-IN</th>
<th>MDZ-inj IV</th>
<th>MDZ-inj IN 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg IN</td>
<td>59(18)</td>
<td>73(20)</td>
<td>93(28)</td>
</tr>
<tr>
<td>5 mg IN</td>
<td>93(26)</td>
<td>170(54)</td>
<td>238(78)</td>
</tr>
<tr>
<td>7.5 mg IN</td>
<td>10(5-30)</td>
<td>10(5-30)</td>
<td>12(5-45)</td>
</tr>
<tr>
<td>2.5 mg IV</td>
<td>10(5-30)</td>
<td>12(5-45)</td>
<td>15(5-46)</td>
</tr>
<tr>
<td>5 mg IV</td>
<td>15(5-60)</td>
<td>15(5-60)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Midazolam</th>
<th>MDZ-IN</th>
<th>MDZ-inj IV</th>
<th>MDZ-inj IN 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg IN</td>
<td>3.6(0.8)</td>
<td>3.8(1.0)</td>
<td>3.6(0.9)</td>
</tr>
<tr>
<td>5 mg IN</td>
<td>3.6(0.9)</td>
<td>4.0(1.6)</td>
<td>3.6(0.7)</td>
</tr>
<tr>
<td>7.5 mg IN</td>
<td>10(5-30)</td>
<td>10(5-30)</td>
<td>12(5-45)</td>
</tr>
<tr>
<td>2.5 mg IV</td>
<td>10(5-30)</td>
<td>12(5-45)</td>
<td>15(5-46)</td>
</tr>
<tr>
<td>5 mg IV</td>
<td>15(5-60)</td>
<td>15(5-60)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alpha-hydroxymidazolam</th>
<th>MDZ-IN</th>
<th>MDZ-inj IV</th>
<th>MDZ-inj IN 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg IN</td>
<td>13 (4.6)</td>
<td>29 (9.6)</td>
<td>44 (13)</td>
</tr>
<tr>
<td>5 mg IN</td>
<td>4.2 (2.0)</td>
<td>8.9(5.2)</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>7.5 mg IN</td>
<td>14 (4.7)</td>
<td>14 (4.7)</td>
<td>27 (8.9)</td>
</tr>
<tr>
<td>2.5 mg IV</td>
<td>13 (7.8)</td>
<td>3.9 (1.7)</td>
<td>11 (7.1)</td>
</tr>
</tbody>
</table>

Distribution
The extent of plasma protein binding of midazolam is moderately high and concentration independent. In adults and pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin. In healthy volunteers, α-hydroxymidazolam is bound to the extent of 89%. In pediatric patients (6 months to <16 years)
receiving 0.15 mg/kg IV midazolam, the mean steady-state volume of distribution ranged from 1.24 to 2.02 L/kg.

**Metabolism**

Midazolam is primarily metabolized in the liver and gut by human cytochrome P450 IIIA4 (CYP3A4) to its pharmacologic active metabolite, α-hydroxymidazolam, followed by glucuronidation of the α−hydroxyl metabolite which is present in unconjugated and conjugated forms in human plasma. The α-hydroxymidazolam glucuronide is then excreted in urine. In a study in which adult volunteers were administered intravenous midazolam (0.1 mg/kg) and α−hydroxymidazolam (0.15 mg/kg), the pharmacodynamic parameter values of the maximum effect (Emax) and concentration eliciting half-maximal effect (EC50) were similar for both compounds. The results indicate that α−hydroxymidazolam is equipotent and equally effective as unchanged midazolam on a total plasma concentration basis. After oral or intravenous administration, 63% to 80% of midazolam is recovered in urine as α−hydroxymidazolam glucuronide. No significant amount of parent drug or metabolites is extractable from urine before beta-glucuronidase and sulfatase deconjugation, indicating that the urinary metabolites are excreted mainly as conjugates.

Midazolam is also metabolized to two other minor metabolites: 4-hydroxy metabolite (about 3% of the dose) and 1,4-dihydroxy metabolite (about 1% of the dose) are excreted in small amounts in the urine as conjugates.

**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.

**Pharmacokinetics in Special Populations**

**Geriatric**

Following a single 2.5 or 5 mg dose of intranasal midazolam, overall and maximum plasma midazolam exposure were slightly higher in geriatric versus non-geriatric participants. Mean half-life values were also longer in geriatric subjects, suggesting that the slightly higher plasma exposure is likely due to a decrease in clearance than an increase in fractional absorption. There was no significant differences in sedation and psychomotor impairment between the two age groups.

**Obese**

The mean half-life is greater in obese than in non-obese patients. This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

**Hepatic Impairment**

Chronic hepatic disease alters the pharmacokinetics of midazolam. Following oral administration of 15 mg of midazolam, C_{max} and bioavailability values were 43% and 100% higher, respectively, in adult patients with hepatic cirrhosis than adult subjects with normal liver function. In the same patients with hepatic cirrhosis, following IV administration of 7.5 mg of midazolam, the clearance of midazolam was reduced by about 40% and the elimination half-life was increased by about 90% compared with subjects with normal liver function. Midazolam should be titrated for the desired effect in patients with chronic hepatic disease.

**Critically Ill Patients**

The elimination half-life of midazolam is prolonged in the critically ill.

**Patients with Cardiac Insufficiency**
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects.

### Indications

Emergency treatment of intermittent bouts of increased seizure activity in adults and adolescence. MIDACIP 1.25 Nasal Spray must be used only where the patient has been diagnosed to have epilepsy.

### Dosage And Administration

#### Dosage

Adults: The recommended dose of MIDACIP 1.25 Nasal Spray is as below:
- Weight <50 kg: 5 mg
- Weight >50 kg: 10 mg

Adolescence: The recommended dose of MIDACIP 1.25 Nasal Spray should be individualized at 0.2 mg/kg body weight.

#### Administration

Each dosage unit (bottle) contains 16 metered doses (20 mg/unit). Each spray of MIDACIP 1.25 Nasal spray contains 1.25 mg of midazolam.

Prime the bottle when using for the first time by spraying 6 sprays in air with the nozzle pointing away from you. For any subsequent use, reprime the bottle by spraying 2-3 times in air with the nozzle pointing away from you. In case if the bottle has to be stored after usage, the nozzle and the protective dust cap has to be washed, as instructed in the patient information leaflet.

The dose should be equally divided and administered into each nostril. For administration methodology, kindly refer the patient information leaflet.

### Contraindications

Hypersensitivity to the active substance, benzodiazepines or to any of the excipients.
- Myasthenia gravis
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Severe hepatic impairment

Benzodiazepines may be used in patients with open-angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow-angle glaucoma.

### Warnings And Precautions

Serious respiratory adverse events have occurred after administration of oral midazolam, most often when midazolam was used in combination with other central nervous system depressants. These adverse events have included respiratory depression, airway obstruction, oxygen desaturation, apnea, and rarely, respiratory and/or cardiac arrest. Prior to the administration of midazolam in any dose, the immediate availability 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. Oral midazolam must never be used without individualization of dosage, particularly when used with other medications capable of producing central nervous system
depression.

Midazolam should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices that are equipped to provide continuous monitoring of respiratory and cardiac function. Oral midazolam must only be administered to patients if they will be monitored by direct visual observation by a health care professional. If oral midazolam will be administered in combination with other anesthetic drugs or drugs which depress the central nervous system, patients must be monitored by persons specifically trained in the use of these drugs and, in particular, in the management of respiratory effects of these drugs, including respiratory and cardiac resuscitation of patients in the age group being treated.

For deeply sedated patients, a dedicated individual whose sole responsibility is to observe the patient, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Patients should be continuously monitored for early signs of hypoventilation, airway obstruction, or apnea with means for detection readily available (e.g., pulse oximetry). Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective counter measures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because midazolam can depress respiration, especially when used concomitantly with opioid agonists and other sedatives, it 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.

Episodes of oxygen desaturation, respiratory depression, apnea, and airway obstruction have been occasionally reported following premedication (sedation prior to induction of anesthesia) with oral midazolam; such events are markedly increased when oral midazolam is combined with other central nervous system depressing agents and in patients with abnormal airway anatomy, patients with cyanotic congenital heart disease, or patients with sepsis or severe pulmonary disease.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported in both adult and pediatric patients. Consideration should be given to the possibility of paradoxical reaction. Should such reactions occur, the response to each dose of midazolam and all other drugs, including local anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric and adult patients.

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 premedication also depresses the ventilator response to carbon dioxide stimulation.

Coadministration of oral midazolam in patients who are taking ketoconazole, intraconazole and saquinavir has been shown to result in large increases in C and AUC of midazolam due to decrease in plasma clearance of midazolam. Due to potential for intense and prolonged sedation and respiratory depression, oral midazolam should only be coadministered with these medications if absolutely necessary and with appropriate equipment and personnel available to respond to respiratory insufficiency.

The decision as to when patients who have received oral midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of oral 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 drug, such as drowsiness, have subsided or until one full day after anesthesia and surgery, whichever is longer. Particular care should be taken to assure safe ambulation.

Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal failure or impaired hepatic function whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam.
Debilitated patients are more prone to the central nervous system effects of benzodiazepines, and, therefore, lower doses may be required. Midazolam should be avoided in patients with a medical history of alcohol or drug abuse. Midazolam may cause anterograde amnesia.

Drug Interactions

Midazolam is metabolized by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to oromucosal or parenteral midazolam as CYP3A4 enzymes are also present in the upper gastro-intestinal tract. After oromucosal administration, only systemic clearance will be affected. After a single dose of oromucosal midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. Hence, a careful monitoring of the clinical effects and vital signs is recommended during the use of midazolam with a CYP3A4 inhibitor even after a single dose.

Anaesthetics and narcotic analgesics: Fentanyl may reduce midazolam clearance.

Antiepileptics: Co-administration with midazolam may cause enhanced sedation or respiratory or cardiovascular depression. Midazolam may interact with other hepatically metabolised medicinal products, e.g. phenytoin, causing potentiation.

Calcium-channel Blockers: Diltiazem and verapamil have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Muscle Relaxants: e.g. baclofen. Midazolam may cause potentiation of muscle relaxants, with increased CNS depressant effects.

Nabulone: Co-administration with midazolam may cause enhanced sedation or respiratory and cardiovascular depression.

Ulcer-healing Medicinal Products: Cimetidine, ranitidine and omeprazole have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Xanthines: Metabolism of midazolam and other benzodiazepines is accelerated by xanthines.

Food

Grapefruit juice: reduces the clearance of midazolam and potentiates its action.

Azole Antifungals

Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold. Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold. Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 to 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole. Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

Macrolide Antibiotics

Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 to 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 to 1.8-fold. Clarithromycin increased the plasma concentrations of intravenous midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 to 2-fold.

HIV Protease Inhibitors

Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life.
Calcium-channel Blockers

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

Various Medicinal Products

*Atorvastatin* showed a 1.4-fold increase in plasma concentrations of intravenous midazolam compared to control group.

*Rifampicin* (7 days of 600 mg once daily) decreased the plasma concentrations of intravenous midazolam by about 60%. The terminal half-life decreased by about 50-60%.

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

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression. Examples include opiate derivatives (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non-recent H1-antihistamines and centrally acting antihypertensive medicinal products. Alcohol (including alcohol-containing medicinal products may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration. Midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics.

Renal Impairment

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.

Hepatic Impairment

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

Pregnancy

*Pregnancy Category C*

Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy. The administration of high doses of midazolam in the last trimester of pregnancy or during labour has been reported to produce maternal or foetal adverse reactions (risk of aspiration of fluids and stomach contents during labour in the mother, irregularities in the foetal heart rate, hypotonia, poor suckling, hypothermia and respiratory depression in the new-born infant). Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

Lactation

Midazolam passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast feeding following a single dose of midazolam.

Pediatric Use

*MIDACIP 1.25* is not meant to be used in the pediatric population.

Geriatric Use

Because geriatric patients 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.

Use in Patients with Heart Disease

Following oral administration of 7.5 mg to midazolam to adult patients with congestive heart failure, the half-life of midazolam was 43% higher in control subjects. One study suggests that hypercarbia or hypoxia following premedication with oral midazolam might pose a risk to children with congenital heart disease and pulmonary hypertension, although there are no known reports of pulmonary hypertensive crises that had been triggered by premedication.

Drug Abuse and Dependence

Midazolam is a benzodiazepine and is a Schedule IV controlled substance that can produce drug dependence of the diazepam-type. Therefore, midazolam may be subject to misuse, abuse and addiction. Benzodiazepines can cause physical dependence. Physical dependence results in 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 following chronic administration. Abdominal distention, nausea, vomiting and tachycardia are prominent symptoms of withdrawal in infants.

Undesirable Effects

The most common adverse events reported with intranasal midazolam in the adult patients include headache, bradycardia, hypotension, dizziness, blurred vision, euphoria, somnolence, pharyngitis, rhinitis, amblyopia, diplopia, conjunctivitis, lacrimation, taste perversion, cough and eye irritation. The most common adverse events reported with oromucosal midazolam in children included; sedation, somnolence, depressed levels of consciousness, respiratory depression, nausea, vomiting, pruritis, rash and urticaria. The adverse events which have been reported to occur when midazolam is injected in children and or adults are aggression, agitation, anger, state of confusion, euphoric mood, hallucination, hostility, movement disorder, physical assault, anterograde amnesia, ataxia, dizziness, headache, seizures, paradoxical reactions, bradycardia, cardiac arrest, hypotension, vasodilation, apnoea, dyspnoea, laryngospasm, respiratory arrest, constipation, dry mouth, fatigue and hiccups. An increase risk for falls and fractures has been recorded in elderly benzodiazepine users. Life-threatening incidents are more likely to occur in those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when a high dosage is administered.

“If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.”

Overdosage

Midazolam overdose should not present a threat to life unless the patient has pre-existing respiratory or cardiac insufficiency, or when combined with other CNS depressants (including alcohol). In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken. Following overdose with oral midazolam, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental
confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. Flumazenil may be useful as an antidote.

**Incompatibility**

Not applicable

**SHELF LIFE**

18 Months

**Storage And Handling Instructions**

Store in a cool place. Protect from light.

**Packaging Information**

Midacip 1.25 mg Nasal Spray contains 16 metered doses

*Last Updated: August 2017*

*Last Reviewed: August 2017*

**Parts Of Midacip Nasal Spray**

![Diagram of Midacip Nasal Spray parts]

**How To Use Midacip Nasal Spray**

1. Shake the bottle gently and then remove the protective dust cap. Hold the bottle with your forefinger and middle finger on either side of the nozzle and your thumb underneath the bottle, as shown in the figure.
If using for the first time, prime the pump by spraying it six times in the air, with the nozzle pointing away from you and the patient.

If the patient is in the supine position, the head should be lifted slightly upwards, as shown in the figure. The device should be tilted slightly forward and placed near the patient’s nose, as shown in the figure.

Now insert the nozzle into the nostril. Depress the pump with a firm even stroke. The patient need not inhale. Do not tilt the patient’s head backward while spraying – this will avoid swallowing of the solution. Administer one spray at a time into each nostril (continue according to the prescribed dose).

**For Subsequent Use**

For subsequent use of the device, prime the pump by spraying 2-3 times in air with the nozzle pointing away from you.
After Use

If all 16 metered doses have been used, then the device should be discarded safely. If the device has to be used the second time (as per prescribing instructions), then the nozzle and dusting cap must be washed before storage.

How To Clean Midacip Nasal Spray

1. Pull the nozzle upwards to detach from the bottle.

2. Soak the nozzle and the dust cap in warm water for a few minutes.

3. Rinse the nozzle and the dust cap under clean running water. Shake off the excess water and allow nozzle and cap to dry at room temperature before refitting into the bottle.

Important Information

Use the nasal spray as directed by the physician. Do not exceed the recommended dose.
This medicine has been recommended by the doctor for a specific patient. Do not use it in any other patient. Keep the nasal spray out of the reach of children. Do not use a pin or sharp object to unblock the nozzle as this will damage the spray mechanism.

**MIDACIP 1.25 Nasal Spray**

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