MIDACIP Nasal Spray (Midazolam)

Composition

MIDACIP Nasal Spray
Each spray delivers:
Midazolam, BP ............... 0.5 mg (0.5% w/v)
Benzalkonium Chloride, IP ...... 0.01% w/v
(as preservative)

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 anetrograde 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 has a relatively high affinity (about twice that of diazepam) for the benzodiazepine receptor.

Pharmacokinetics

Absorption
Under optimal conditions, absorption of midazolam via the nasal mucosa is quick and virtually complete. Mean peak plasma concentrations are reached within 10.2–12.6 minutes. The bioavailability is between 55% and 57%.

Distribution
Midazolam is lipophilic at physiological pH. It is extensively bound to plasma proteins (94–98%), with only 4% being unbound. The major fraction of plasma protein binding is due to albumin. Midazolam has a short distribution half-life of several minutes as a result of fast tissue uptake. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid.

In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

Metabolism
Midazolam is extensively metabolized by the cytochrome P450 3A4 to its primary metabolite, alpha-hydroxy-midazolam, and minimally to inactive metabolites. These metabolites are then excreted in the urine as glucuronide conjugates. Alpha-hydroxy-midazolam is pharmacologically active and has sedative properties equivalent to midazolam. Plasma concentrations of alpha-hydroxy-midazolam are 12% those of the parent compound.

**Elimination**

Midazolam is mainly eliminated by the renal route; 60–80% of the dose is excreted in urine as glucuroconjugated alpha-hydroxy-midazolam. The elimination half-life of this metabolite is <1 hour. Less than 1% of the dose is recovered in urine as the unchanged substance.

Compounds that inhibit or induce cytochrome P450 3A4 (CYP3A) may alter a patient’s elimination of midazolam clearance and the dose may need to be adjusted accordingly.

**Pharmacokinetics in Special Populations**

**Geriatric**

In adults over 60 years of age, the elimination half-life may be prolonged up to four times.

**Paediatric**

A trial conducted in children compared the pharmacokinetics of midazolam after intranasal and intravenous administration. Accordingly, 12 children (1–5 years old) were assigned to receive midazolam 0.2 mg/kg either by the intranasal or intravenous routes. The individual data after intranasal dosing showed rapid absorption, as the maximum concentration (104 mcg/l) was observed 12 minutes after administration. Bioavailability was estimated to be around 55% after intranasal administration. It is higher than the oral (19%) and rectal (18%) routes in children. The half-life ($t_{1/2}$ 2.22 hours) and mean residence time (MRT 2.71 hours) were found to be similar to the values obtained for the intravenous route ($t_{1/2}$ 2.4 hours, MRT 2.7 hours). The apparent plasma clearance (1.44 /hr/kg) and volume of distribution (4.12 l/kg) were about twice as high as after intravenous administration. This suggests faster absorption and distribution phases in comparison to the elimination phase.

**Neonates**

In seriously ill neonates, the terminal elimination half-life of midazolam is substantially prolonged on average 6-12 hours, probably due to liver immaturity and the clearance is reduced.

**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

- Premedication before induction of anaesthesia
- Conscious sedation before diagnostic or surgical interventions carried out under local anaesthesia
- For the emergency treatment of seizures, both in and out of hospital (for patients who often have seizures lasting longer than 5 minutes, and/or have a pattern of seizures that recur close together)

### Dosage And Administration

**Adults**

The recommended dose of MIDACIP Nasal Spray is as below:

- Weight <50 kg: 5 mg
- Weight >50 kg: 10 mg
The dose should be equally divided and administered into each nostril.

### Children

The recommended dose of MIDACIP Nasal Spray is 0.2 mg/kg body weight. The dose should be equally divided and administered into each nostril. Placing half the medication in each nostril will reduce the volume while doubling the available surface area for absorption.

**Dosing Guidelines of MIDACIP Nasal Spray**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Dose (mg)</th>
<th>Metered Doses in Each Nostril</th>
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<tbody>
<tr>
<td>½ - 1</td>
<td>&lt;10</td>
<td>1.25 - 2</td>
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<td>1 - 4</td>
<td>10 - 16</td>
<td>2.5</td>
<td>2 - 3</td>
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<td>4 - 10</td>
<td>16 - 32</td>
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<tr>
<td>&gt;10</td>
<td>&gt; 32</td>
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**Contraindications**

MIDACIP Nasal Spray is contraindicated in patients with Myasthenia gravis, or those with hypersensitivity to the active substance, benzodiazepines or to any of the excipients. It should also not be used in patients with existing CNS depression, shock, acute alcohol intoxication, coma, and uncontrolled pain. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy.

**Warnings And Precautions**

Midazolam must never be used without individualization of dosage, particularly when used with other medications capable of producing CNS depression. 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 ventilation should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airways obstruction, or apnoea, i.e. pulse oximetry. Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures 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 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 the 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 paediatric patients. The sedative endpoint appears to reach more abruptly with midazolam. Appropriate precautions should therefore be taken. Serious cardiorespiratory adverse events have occurred after administration of midazolam. 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 adult or paediatric patients with haemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with a narcotic.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported in both adult and paediatric patients. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of midazolam and all other drugs, including local anaesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in paediatric patients.

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 drug effect. Narcotic premeditation also depresses the ventilator response to carbon dioxide stimulation.

Higher risk adult and paediatric surgical patients, elderly patients and debilitated adult and paediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or paediatric patients with chronic obstructive pulmonary disease (COPD) are unusually sensitive to the respiratory depressant effect of midazolam hydrochloride. Paediatric 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. Due to an increased risk of apnoea, extreme caution is advised when sedating preterm and former preterm non-intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required. Special caution should be exercised when administering midazolam to paediatric patients especially those with cardiovascular instability.

Midazolam should be used with caution in patients with chronic renal failure, and 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. No patient should operate hazardous machinery or a motor vehicle until the side effects of the drug such as drowsiness have subsided or until the day after anaesthesia and surgery, whichever is longer. For paediatric patients, particular care should be taken to assure safe ambulation.

Midazolam dosage 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. Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light, general 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.
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 also 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.

**CYP3A4 Inhibitors**

The metabolism of midazolam is predominantly mediated by cytochrome P450 3A4 (CYP3A4) isozyme. Approximately 25% of the total cytochrome P450 system in the adult liver is from the CYP3A4 subfamily. Inhibitors and inducers of this isozyme may lead to interaction with midazolam.

Azole Antifungals like ketoconazole increased the plasma concentration of midazolam by 5-fold while the terminal half-life increased by about 3-fold. If midazolam is co-administered with the strong CYP3A inhibitor, ketoconazole, it should be done in an intensive care unit (ICU) or similar setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single dose of midazolam is administered.

Fluconazole and itraconazole both increased the plasma concentrations of midazolam by 2- to 3-fold, along with an increase in the terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively. Posaconazole increased the plasma concentrations of midazolam by about 2-fold.

**Erythromycin**

Co-administration of midazolam and erythromycin prolonged the elimination half-life of midazolam from 3.5 to 6.2 hours. Although only relatively minor pharmacodynamic changes were observed, it is advised to adjust doses of intravenous midazolam, especially if high doses are being administered.

**Clarithromycin**

Co-administration of midazolam and clarithromycin increased the AUC of intravenous midazolam by approximately 2.5-fold and was associated with a 2.7-fold increase in the terminal half-life.

**Roxithromycin**

Co-administration of midazolam and roxithromycin has less of an effect on the pharmacokinetics of midazolam than erythromycin or clarithromycin. Maximum plasma concentration ($C_{\text{max}}$) of midazolam increased approximately 40% compared with increases of 2.7-fold caused by erythromycin and 2.8-fold with clarithromycin, while the 40% increase in AUC $0-\text{infinity}$ is matched by 4.4-fold and 7-fold increases, respectively. The mild effect on the terminal half-life of midazolam (~ 30%) indicates that the effects of roxithromycin on midazolam may be minor.

**Cimetidine and Ranitidine**

Cimetidine increased the steady-state plasma concentration of midazolam by 26%, whereas ranitidine had no effect. Co-administration of midazolam and cimetidine or ranitidine had no clinically significant effect on the pharmacokinetics and pharmacodynamics of midazolam. These data indicate that intravenous midazolam can be used in usual doses with cimetidine and ranitidine and dosage adjustment is not required.

**Cyclosporin**

There is no pharmacokinetic and pharmacodynamic interaction between cyclosporin and midazolam. Therefore, the dosage of midazolam needs no adjustment when given concomitantly with cyclosporin.

**Nitrendipine**

Nitrendipine did not affect the pharmacokinetics and pharmacodynamics of midazolam. Both medicines can be given concomitantly and no dosage adjustment of midazolam is required.

**Other Interactions**

**HIV Protease Inhibitors**
Saquinavir and other HIV protease inhibitors: Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of midazolam increased by 5.4-fold, and were associated with a similar increase in terminal half-life. If midazolam is co-administered with HIV protease inhibitors, the treatment setting should follow the description in the section above for ketoconazole within azole antifungals.

**Oral Contraceptives**
The pharmacokinetics of midazolam was not affected by the use of oral contraceptives. Both medicines can be given concomitantly and no dosage adjustment of midazolam is required.

**Sodium Valproate**
Displacement of midazolam from its plasma protein-binding sites by sodium valproate may increase the response to midazolam and, therefore, care should be taken to adjust the midazolam dosage in patients with epilepsy.

**Lidocaine**
Midazolam had no effect on the plasma protein-binding of lidocaine in patients undergoing anti-arrhythmic therapy or regional anaesthesia with lidocaine.

**Diltiazem**
After pre-treatment with lorazepam and a single dose of diltiazem, on cessation of midazolam, the AUC from cessation for 23 hours increased approximately by 25% and the terminal half-life was prolonged approximately by 43%.

**Verampil**
Increased the \( C_{\text{max}} \) of midazolam 2-fold, while \( \text{AUC}_{\text{0–\infty}} \) increased 3- and 4-fold, respectively. The terminal-half-life of midazolam increased 41% and 49%, respectively.

**Atorvastatin**
A 1.4-fold increase in plasma concentrations of midazolam was seen with atorvastatin compared to control group. Aprepitant dose dependently increased the plasma concentrations of midazolam therefore increasing the risk of prolonged sedation. Rifampicin decreased the plasma concentrations of midazolam by about 60% after 7 days of rifampicin 600mg o.d. The terminal half-life decreased by about 50-60%. Carbamazepine / phenytoin: Repeat dosages of carbamezepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 90% and a shortening of the terminal half-life by 60%.

**Efavirenz**
The 5-fold increase in the ratio of the CYP3A4 generated metabolite \( \alpha \)-hydroxymidazolam to midazolam confirms its CYP3A4-inducing effect.

**St John's Wort**
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.

**Opioids**
The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA 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. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Alcohol may enhance the sedative effect of midazolam.

No significant adverse interactions with commonly used premedications 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 benzocaine) have been observed in adults or paediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl.
Renal Impairment

Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites, which may result in slower recovery.

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 D*

There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Lactation

There is evidence that midazolam is excreted in breast milk and its effects on the newborn are not known. Therefore, midazolam is not recommended for use in nursing mothers.

Paediatric Use

The safety and efficacy of midazolam have been established in the paediatric patients. Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation. The use in children less than 6 months of age is not recommended, as there is limited available data in this population.

*Clinical Studies*

A study conducted in paediatric patients assessed the effect of midazolam through the nasal route. A total of 45 children (2–5 years of age) scheduled for minor elective surgery were eligible. Patients were divided to receive normal saline (Group I) and 0.2 mg/kg midazolam (Group II) intranasally. Vital parameters and level of sedation (using a sedation scale) were assessed before administering the drug and at 5 minutes interval up to the induction of anaesthesia. A statistically significant change in the level of sedation was found at 5 min in the midazolam group as compared to the control group. Also, parental separation was significantly easier in the midazolam group (80%). Mask acceptance rate was also found to be significantly higher in the midazolam group. At 30 minutes, there was no statistical difference in recovery parameters in the two groups. The study concluded that 0.2 mg/kg intranasal midazolam is an effective method of producing anxiolysis and sedation in paediatric patients without side effects.

Another study conducted in children assessed the efficacy of intranasal midazolam in the treatment of acute childhood seizures. Accordingly, 70 children (aged 2 months - 15 years) with acute seizures (febrile or afebrile) admitted to the paediatric emergency department of a general hospital during a 14-month period were eligible. They were randomized to receive intranasal midazolam 0.2 mg/kg and intravenous diazepam 0.2 mg/kg. In 60% of children receiving intranasal midazolam, seizure control was achieved in 3.58 minutes and within 10 minutes in the others. The study showed that intranasal midazolam was effective in the management of acute seizures in children.

In a study, a total of 358 paediatric patients with epilepsy and who visited a paediatric neurology clinic were prescribed a home rescue medication for their next seizure. Caretakers were randomized to use either 0.2 mg/kg of intranasal midazolam (maximum, 10 mg) or 0.3 to 0.5 mg/kg of rectal diazepam (maximum, 20 mg) at home for their child’s next seizure if it lasted more than 5 minutes. The median time from medication administration to seizure cessation was found to be 1.3 minutes less for intranasal midazolam (3.0 minutes) compared with rectal diazepam (4.3 minutes) ($p = 0.09$). Ease of administration and overall satisfaction was higher with intranasal midazolam compared with rectal diazepam.
In most of the studies, the recovery time was found to be approximately 30 minutes after intranasal midazolam administration. However, recovery from anaesthesia or sedation for procedures in paediatric patients depends on the dose of midazolam administered, co-administration of other medications causing CNS depression, and duration of the procedure.

### 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.

### 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 have been reports of hypertension, bradycardia and hypoxia in adults and children after intranasal administration, but these changes were always mild and transient and no patient required intubation or mechanical ventilation. In very rare cases, allergic reactions, urticaria and rashes are also observed. Nausea and vomiting, dizziness and drowsiness may occur.

A number of studies conducted in paediatric patients have shown no alteration in the heart rate, respiratory rate and oxygen saturation rate or any other complication after administration of intranasal midazolam.

In adults, fluctuations in vital signs have been noted following administration of midazolam and include respiratory depression (22.9% following intravenous administration and 10.8% of patients following intramuscular administration and apnoea (19% following intravenous administration), as well as variations in blood pressure and pulse rate. These common occurrences during anaesthesia and surgery are affected by the lightening or deepening of anaesthesia, instrumentation, intubation and use of concomitant drugs.

Administration of midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other CNS depressants capable of depressing respiration, especially narcotics.

The following additional adverse reactions were reported after intramuscular administration: headache (1.3%); local effects at the intramuscular injection site, including pain (3.7%), induration (0.5%), redness (0.5%), and muscle stiffness (0.3%).

The following additional adverse effects were reported subsequent to intravenous administration of midazolam in adults and paediatric patients.

### Respiratory

Laryngospasm, bronchospasm, dyspnoea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnoea.

### Immune System

Generalized hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylactic shock.

### CNS/Neuromuscular

Confusional state, euphoric mood, hallucinations, dysphoria, paradoxical reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, argumentativeness, nervousness, anxiety, irritability, tension, emergency delirium or agitation, dysphoria, dysphonia, paresthesia, mood changes, restlessness, paroxysmal excitement and assault, have been
Use of midazolam, even in therapeutic doses, may lead to the development of physical dependence. After prolonged intravenous administration, discontinuation of the product may be accompanied by withdrawal symptoms, including withdrawal convulsions.

### Nervous System Disorder

Prolonged sedation, decreased alertness, headache, dizziness, ataxia, dreaming during sleep, sleep disturbance, insomnia, athetoid movements, slurred speech, dysphonia, paraesthesia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported. Convulsions have been reported in premature infants and neonates.

### Cardiovascular

Severe cardio-respiratory adverse effects have occurred on rare occasions. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects, bigeminy, premature ventricular contractions, tachycardia, nodal rhythm, cardiovascular collapse, and vasovagal episode. Life-threatening incidents are more likely to occur in adult over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered. Coughing and hiccoughs have also been reported.

### Gastrointestinal

Nausea, vomiting, constipation, dry mouth, acid taste, retching, excessive salivation.

### Skin and Appendages

Skin rash, urticaria, pruritus.

### General and Effects at the Site of Application

Nasal irritation, watering of eyes, erythema and pain at the application site, redness, tenderness, induration.

### Ophthalmic

Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, difficulty in focusing.

### Miscellaneous

Yawning, lethargy, chills, weakness, continued phonation, ears blocked, loss of balance, light-headedness, toothache, faint feeling, haematoma.

### Injury, Poisoning and Procedural Complications

There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

### Drug Abuse and Dependence

Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970. Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs. Midazolam produced physical dependence of a mild-to-moderate intensity in cynomolgus monkeys after 5–10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse
Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, hallucinations, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuation of benzodiazepines, including midazolam. Abdominal distention, nausea, vomiting, and tachycardia are prominent symptoms of withdrawal in infants. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally, milder withdrawal symptoms (e.g. dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. There is no consensus in the medical literature regarding tapering schedules; therefore, practitioners are advised to individualize therapy to meet the needs of the patients. In some case reports, patients who have had severe withdrawal reactions due to abrupt discontinuation of high-dose long-term midazolam have been successfully weaned off midazolam over a period of several days.

**Overdosage**

The manifestations of midazolam 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. No evidence of specific organ toxicity from midazolam overdosage has been reported.

**Treatment of Overdosage**

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. 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 a benzodiazepine is known or suspected. There are anecdotal reports of reversal 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. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for reedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. Flumazenil will only reverse benzodiazepine-induced effects but will not reverse the effects of other concomitant medications. 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 and in cyclic antidepressant overdose.

**Incompatibility**

Not applicable.
Storage And Handling Instructions

Store in a cool place. Protect from light.

Packaging Information

MIDACIP Nasal Spray is available in vial of 5 ml
Last Updated: Aug 2017
Last Reviewed: Aug 2017

Parts Of Midacip Nasal Spray

How To Use Midacip Nasal Spray

1. Shake the bottle gently and then remove the protective dust cap. Hold the bottle as shown with your forefinger and middle finger on either side of the nozzle and your thumb underneath the bottle.

2. If using for the first time or if you have not used it for a week or more, prime the pump by spraying once in air with the nozzle pointing away from you.
With the patient’s head upright, insert nozzle into the nostril. Depress pump with a firm even stroke. Patient does not have to sniff. Do not tilt head backward while spraying to avoid swallowing of the solution. Administer one spray at a time into each nostril (continue according to the prescribed dose).

**After Use**

Wipe the nozzle with a clean handkerchief/tissue and replace the protective dust cap.

**How To Clean Midacip Nasal Spray**

1. Pull the nozzle upwards to detach it from the bottle.
2. Soak the nozzle and the dust cap in warm water for a few minutes.
Rinse the nozzle and the dust cap under clean running water. Shake off the excess water and allow the nozzle and cap to dry at room temperature before refitting onto the bottle.

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.

MIDACIP Nasal Spray

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