SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

MEZOLAM

Midazolam Injection B.P.

Strength:

5 mg/ml – 1 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION :

Sr. No.	Particulars	Grade	Qty./ml	Function
1.	Midazolam	B.P.	5 mg	Active

For the full List of Excipients See section 6.1

3. PHARMACEUTICAL FORM :

Solution for Injection

A clear colourless solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Midazolam Injection is indicated:

•Intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia;

•Intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;

•Intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia).

4.2 Dosage and method of administration:

Route of administration : For I.M. / I.V. Use

The 1 ml and 2 ml Midazolam Injection vials include a cautionary label that extends above the main label and highlights the drug name and strength per total volume. The purpose of the extended label is to prevent medication errors due to the different strengths of Midazolam Injection.

Clinical experience has shown midazolam to be 3 to 4 times as potent per mg as diazepam.

BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTSHAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTIONOF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAMINJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS.

Midazolam Injection should only be administered IM or IV. Care should be taken to avoid intra-arterial injection or extravasation.

Midazolam Injection may be mixed in the same syringe with the following frequently used premedications : morphine sulfate, meperidine, atropine sulfate or scopolamine. Midazolam, at a concentration of 0.5 mg/mL, is compatible with 5% w/v dextrose in water and 0.9% w/v sodium chloride for up to 24 hours and with lactated Ringer's solution for up to 4 hours. Both the 1 mg/mL and 5 mg/mL formulations of midazolam may be diluted with 0.9% w/v sodium chloride or 5% w/v dextrose in water.

Pediatrics - For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure. Intravenous access is not thought to be necessary for all pediatric patients sedated fora diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose of sedating the child; rather, emphasis should be placed upon having the intravenous equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

Usual Adult Dose –

Intramuscularly

For preoperative sedation/anxiolysis/ amnesia (induction of sleepiness or drowsiness and relief of apprehension and to impair memory of perioperative events). For intramuscular use, midazolam should be injected deep in a large muscle mass. The recommended premedication dose of midazolam for good risk (ASA Physical Status I & II) adult patients below the age of 60 years is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM) administered up to 1 hour before surgery. For intramuscular use, midazolam should be injected deep in a large muscle mass. The dose must be individualized and reduced when IM midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant narcotics or other CNS depressants. In a study of patients 60 years or older, who did not receive concomitant administration of narcotics, 2 to 3 mg (0.02 to 0.05 mg/ kg) of midazolam produced adequate sedation during the preoperative period. The dose of 1 mg IM midazolam may suffice for some older patients if the anticipated intensity and duration of sedation is less critical. As with any potential respiratory depressant, these patients require observation for signs of cardiorespiratory depression after receiving IM midazolam. Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concomitantly with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

Intravenously

Sedation/ anxiolysis /amnesia for Procedures: Narcotic premedication results in less variability in patient response and a reduction in dosage of midazolam. For per oral procedures, the use of an appropriate topical anestheticis recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended. Midazolam 1 mg/mL formulation is recommended for sedation/anxiolysis/amnesia for procedures to facilitate slower injection. Both the 1 mg/mL and the 5 mg/mL formulations may be diluted with 0.9% w/v sodium chloride or 5% w/v dextrose in water.

When used for sedation/anxiolysis/amnesia for a procedure, dosage must be individualized and titrated. Midazolam should always be titrated slowly; administer over at least 2minutes and allow an additional 2 or more minutes to fully evaluate

the sedative effect. Individual response will vary with age, physical status and concomitant medications, but may also vary independent of these factors

1.Healthy Adults Below the Age of 60: Titrate slowly to the desired effect, e.g., the initiation of slurred speech. Some patients may respond to as little as 1 mg. No more than 2.5 mg should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, continue to titrate, using small increments, to the appropriate level of sedation. Wait an additional 2 or more minutes after each increment to fully evaluate the sedative effect. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint.

If narcotic premedication or other CNS depressants are used, patients will require approximately 30% less midazolam than unpremedicated patients.

2. Patients Age 60 or Older, and Debilitated or Chronically Ill Patients: Because the danger of hypoventilation, airway obstruction, or apnea is greater in elderly patients and those with chronic disease states or decreased pulmonary reserve, and because the peak effect may take longer in these patients, increments should be smaller and the rate of injection slower.

Titrate slowly to the desired effect, e.g., the initiation of slurred speech. Some patients may respond to as little as 1 mg. No more than 1.5 mg should be given over a period of no less than 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of no more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary. If concomitant CNS depressant premedications are used in these patients, they will require at least 50% less midazolam than healthy young unpremedicated patients.

3. Maintenance Dose: Additional doses to maintain the desired level of sedation may be given in increments of 25% of the dose used to first reach the sedative endpoint, but again only by slow titration, especially in the elderly and chronically ill or debilitated patient. These additional doses should be given only after a thorough clinical evaluation clearly indicates the need for additional sedation. Induction of Anesthesia: For induction of general anesthesia, before administration of other anesthetic agents. Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status. When midazolam is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25%of the usual initial dose of the individual agents.

Unpremedicated Patients - In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 0.35 mg/kg for induction, administered over 20 to 30seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used; induction may instead be completed with inhalational anesthetics. In resistant cases, up to 0.6 mg/ kg total dose may be used for induction, but such larger doses may prolong recovery.

Premedicated Patients - When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15 to 0.35 mg/kg. In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice. The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years.

Except for intravenous fentanyl, administered 5 minutes before induction, all other premedications should be administered approximately 1 hour prior to the time anticipated for midazolam induction.
Injectable midazolam can also be used during maintenance of anesthesia, for surgical procedures, as a component of balanced anesthesia. Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.
Effective narcotic premedication is especially recommended in such cases.
Continuous Infusion - For continuous infusion, midazolam 5 mg/mL formulation is recommended diluted to a concentration of 0.5 mg/mL with 0.9% w/v sodium chloride or 5% w/v dextrose in water.
Usual Adult Dose - If a loading dose is necessary to rapidly initiate sedation, 0.01 to 0.05 mg/kg (approximately0.5 to 4 mg for a typical adult) may be given slowly or infused over several minutes.This dose may be repeated at 10 to 15 minute intervals until adequate sedation is achieved. For maintenance of sedation, the usual initial infusion rate is 0.02 to 0.10 mg/kg/hr (1 to7 mg/hr).

4.3 Contraindications:

Injectable midazolam is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Midazolam Injection is not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form.

4.4 Special warnings and precautions for use:

WARNING
Midazolam must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. Prior to the intravenous 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.
Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea, i.e., pulse oximetry. Because intravenous 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 anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway and supporting ventilation.
Injectable midazolam should not be administered to adult or pediatric patients in shock or coma, or in acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of intravenous midazolam in adult or pediatric patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.
Usage in Pregnancy
An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus. Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines

Usage in Preterm Infants and Neonates
Rapid IV injection (less than 2 minutes) has been associated with severe hypotension should be avoided in the neonatal population, particularly when the patient has also received Seizures have been reported in several neonates following rapid intravenous administration

PRECAUTIONS
General
Intravenous doses of midazolam should be decreased for elderly and for debilitated patients. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia. 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 anesthesia.
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 anesthesia 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 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. For information regarding withdrawal.
Information for Patients
To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate. Any alcohol consumption and medicine you are now taking, especially blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment. If you are pregnant or are planning to become pregnant and if you are nursing mother. Effects of midazolam, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients who have received injectable 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. If receiving continuous infusion of midazolam in critical care settings over an extended period of time may experience symptoms of withdrawal following abrupt discontinuation.

4.5 Interaction with other medicinal products and other forms of interaction:

The sedative effect of intravenous midazolam is accentuated by any concomitantly administered medication which depresses the central nervous system, 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.

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450-3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

Caution is advised when midazolam is administered to patients receiving erythromycin since this may result in a decrease in the plasma clearance of midazolam.

Carcinogenesis: The tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis, Impairment of Fertility: No human studies are done.

Nonteratogenic Effects: Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.

Pregnancy Category D: Teratogenic Effects

Nursing Mothers: Midazolam is excreted in human milk. Caution should be exercised when midazolam is administered to a nursing woman.

4.6 Fertility, pregnancy and lactation:

Pregnancy

Midazolam should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean.

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, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or foetal adverse effects (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).

Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the post-natal period.

The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

Breast-feeding

Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of midazolam.

4.7 Effects on ability to drive and use machines:

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines.

Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.

4.8 Undesirable effects:

The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam is administered with other medications capable of depressing the central nervous system. The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube, e.g., upper endoscopy and dental procedures.

Adults

Local effects at IM Injection site: pain, induration redness, muscle stiffness. hiccoughs, nausea, vomiting, coughing, "oversedation", headache, drowsiness. Local effects at the IV site: tenderness, pain during injection, redness, induration, phlebitis.

Pediatric Patients

desaturation, apnea, hypotension, paradoxical reactions, hiccough, seizure-like activity and nystagmus.

Neonates

For information concerning hypotensive episodes and seizures following the administration of midazolam to neonates,

Special Sense

Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness.

Integumentary

Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site.

Hypersensitivity

Allergic reactions including anaphylactoid reactions, hives, rash, pruritus.

4.9 Overdose:

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.

Treatment of Overdosage

Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. 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

5. PHARMACOLOGICAL PROPERTIES :

5.1 Pharmacodynamic properties :

Pharmacotherapeutic group:

Hypnotics and sedatives (benzodiazepine derivatives), ATC code: N05CD08.

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water.

The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of midazolam to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

Mechanism of action

The pharmacological action of midazolam is characterised by short duration because of rapid metabolic transformation. Midazolam has a sedative and sleep-inducing effect of

pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect.

After i.m. or i.v. administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).

5.2 Pharmacokinetic properties :

Absorption after i.m. injection

Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after i.m. injection is over 90%.

Distribution

When midazolam is injected i.v., the plasma concentration-time curve shows one or two distinct phases of distribution. The volume of distribution at steady state is 0.7 - 1.2 l/kg. 96 - 98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. 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.

Biotransformation

Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30 - 60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxymidazolam. Plasma concentrations of alpha-hydroxymidazolam are 12% of those of the parent compound. Alpha-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

Elimination

In healthy volunteers, the elimination half-life of midazolam is between 1.5 - 2.5 hours. Plasma clearance is in the range of 300 - 500ml/min. Midazolam is excreted mainly by renal route (60 - 80% of the injected dose) and recovered as glucuroconjugated alpha-hydroxymidazolam. Less than 1% of the dose is recovered in urine as unchanged drug. The elimination half-life of alpha-hydroxy-midazolam is shorter than 1 hour. When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection.

5.3 Pre-clinical Safety Data:

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Sodium chloride BP
Disodium Edetate BP
Hydrochloric acid BP
Water for injections (bulk) BP

6.2 Incompatibilities:

Midazolam Injection is stable, both physically and chemically, for up to 1 hour at room temperature when mixed in the same syringe with Atropine Sulphate Injection BP or Hyoscine Hydrobromide Injection 0.4mg/ml. There is no evidence of the adsorption of midazolam onto the plastic of infusion apparatus or syringes.

Midazolam Injection when mixed with 500ml infusion fluids containing dextrose 4% with sodium chloride 0.18%, dextrose 5% or sodium chloride 0.9% is chemically and physically stable for up to 24 hours at 25°C and up to 72 hours at 2 to 8°C. However, for pharmaceutical microbiological reasons, the product should be used immediately after dilution. When aseptically prepared, the diluted solution may be kept for not more than 24 hours if stored under refrigeration at a temperature between 2-8°C.

Admixture with Hartmann's solution is not recommended, as the potency of midazolam decreases.

6.3 Shelf – life:
24 Months

6.4 Special precautions for storage:
Store below 30°C, Protected from light.
Do Not Freeze.

6.5 Nature and contents of container:
2 blisters of 5 ampoules of 1 ml each, packed in a unit carton along with direction slip. Such 10 unit cartons are packed in a parcel pack and 12 such parcel packs are packed in a shipper.

6.6 Special Precautions for Handling and Disposal:
Use as directed by a physician.

7. MARKETING AUTHORIZATION HOLDER:
M/s. NEON LABORATORIES LIMITED
140, Damji Shamji Industrial Complex,
28, Mahal Indl. Estate, Mahakali Caves Road,
Andheri (East), Mumbai - 400 093

8. MARKETING AUTHORIZATION NUMBER :

07271/09071/NMR/2021

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORISATION:

Date of first authorisation: 12-04-2022

10. DATE OF REVISION OF THE TEXT: JULY 2023

11. REFERENCE

- Midazolam 5 mg in 1 ml Injection - Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/6419/smpc#gref
- Midazolam Injection - https://dailymed.nlm.nih.gov/dailymed/