Press Release

Hikma launches Midazolam Injection, USP, in a prefilled syringe in the US

London, 8 May 2024 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Midazolam Injection, USP, in 2mg/2mL and 10mg/2mL doses. The product has been launched in the US in a prefilled syringe form and is indicated for:

- 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);
- continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

According to IQVIA, US sales of Midazolam Injection, USP, 2mg/2mL and 10mg/2mL were approximately $20 million in the 12 months ending February 2024.

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 150 products. We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care.

- ENDS –

This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

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[1] Source: IQVIA MAT February 2024, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

hikma.

About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/positive Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 45 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across the North America, the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 9,100 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

Important Safety Information for Midazolam Injection, USP, 2mg/2mL and 10mg/2mL:

BOXED WARNING

WARNINGS

Personnel and Equipment for Monitoring and Resuscitation
Adults and Pediatrics: **Intravenous midazolam has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous monitoring of respiratory and cardiac function, e.g., pulse oximetry. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured. (See WARNINGS.) For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.**

Risks From Concomitant Use With Opioids
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Monitor patients for respiratory depression and sedation (see WARNINGS, PRECAUTIONS; Drug Interactions).

Individualization of Dosage
Midazolam must never be used without individualization of dosage. The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS) depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Doses of sedative medications in pediatric patients must be calculated on a mg/kg basis, and initial doses and all subsequent doses should always be titrated slowly. The initial pediatric dose of midazolam for sedation/anxiolysis/amnesia is age, procedure and route dependent (see DOSAGE AND ADMINISTRATION for complete dosing information).

Neonates: **Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl (see DOSAGE AND ADMINISTRATION for complete information).**

CONTRAINDICATIONS

Injectable midazolam is contraindicated in patients with a known hypersensitivity to the drug. 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. Measurements of intraocular pressure in

patients without eye disease show a moderate lowering following induction with midazolam; patients with glaucoma have not been studied.

WARNINGS & PRECAUTIONS

- **Personnel and Equipment for Monitoring and Resuscitation –** 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.
- **Risks From Concomitant Use With Opioids –** Concomitant use of benzodiazepines, including midazolam, and opioids may result in profound sedation, respiratory depression, coma, and death.
- **Risk of Respiratory Adverse Events** – Serious cardiorespiratory adverse events have occurred after administration of midazolam.
- **Individualization of Dosage –** Midazolam must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression.
- **Other Adverse Events –** 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.
- **Concomitant Use of Central Nervous System Depressants –** 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 ventilatory response to carbon dioxide stimulation.
- **Debilitation and Comorbid Considerations –** Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of midazolam. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Adult and pediatric patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduced initial dosage of midazolam is recommended, and the possibility of profound and/or prolonged effect should be considered. 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.
- **Risk of Intra-arterial Injection –** There have been limited reports of intra-arterial injection of midazolam. Extravasation should also be avoided. The safety and efficacy of midazolam following nonintravenous and nonintramuscular routes of administration have not been established. Midazolam should only be administered intramuscularly or intravenously.
- **Return to Full Cognitive Function –** Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours. 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. For pediatric patients, particular care should be taken to assure safe ambulation.
- **Neonatal Sedation and Withdrawal Syndrome** – Use of Midazolam Injection late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate.
- **Usage in Preterm Infants and Neonates –** Rapid injection should be avoided in the neonatal population. Midazolam administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration. The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of midazolam.
- **Pediatric Neurotoxicity –** Published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours. Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anesthetic agents early in life and may result in adverse cognitive or behavioral effects.
- **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.

- **Information for Patients –** To assure safe and effective use of benzodiazepines, information and instructions from the package insert should be communicated to the patient when appropriate.

ADVERSE REACTIONS

See **WARNINGS** concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following intravenous and 10.8% of patients following intramuscular administration) and apnea (15.4% of patients following intravenous administration), as well as variations in blood pressure and pulse rate. 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
See package insert for additional adverse reactions reported after intramuscular administration.

Administration of intramuscular 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 central nervous system depressants capable of depressing respiration, especially narcotics.

See package insert for additional adverse reactions reported subsequent to intravenous administration as a single sedative/anxiolytic/amnestic agent in adult patients.

Pediatric Patients
The following adverse events related to the use of intravenous midazolam in pediatric patients were reported in the medical literature: desaturation 4.6%, apnea 2.8%, hypotension 2.7%, paradoxical reactions 2.0%, hiccough 1.2%, seizure-like activity 1.1% and nystagmus 1.1%. The majority of airway-related events occurred in patients receiving other CNS depressing medications and in patients where midazolam was not used as a single sedating agent.

Neonates
For information concerning hypotensive episodes and seizures following the administration of midazolam to neonates, see **Boxed WARNING, CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS** sections.

Other adverse experiences, observed mainly following intravenous injection as a single sedative/anxiolytic/amnesia agent and occurring at an incidence of <1.0% in adult and pediatric patients, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea
Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm
Gastrointestinal: Acid taste, excessive salivation, retching
CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia
Special Senses: 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
Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma

DRUG INTERACTIONS

Effect of Concomitant Use of Benzodiazepines and 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 $GABA_A$ 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. Monitor patients closely for respiratory depression and sedation.

Other CNS Depressants
The sedative effect of intravenous midazolam is accentuated by any concomitantly administered medication which depresses the central nervous system, particularly opioids (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.

Other Drug Interactions
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.

The effects of diltiazem (60 mg three times a day) and verapamil (80 mg three times a day) on the pharmacokinetics and pharmacodynamics of oral midazolam were investigated in a three-way crossover study (n=9). The half-life of midazolam increased from 5 to 7 hours when midazolam was taken in conjunction with verapamil or diltiazem. No interaction was observed in healthy subjects between midazolam and nifedipine.

In a placebo-controlled study, where saquinavir or placebo was administered orally as a 1200 mg dose, three times a day, for 5 days (n=12), a 56% reduction in the clearance of midazolam following a single 0.05 mg/kg intravenous dose was observed. The half-life was approximately doubled.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular midazolam for premedication in adults.

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia.

Although the possibility of minor interactive effects has not been fully studied, midazolam and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine, and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

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

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal. Available data from published observational studies of pregnant women exposed to benzodiazepines do not report a clear association with benzodiazepines and major birth defects.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Benzodiazepines cross the placenta and may produce respiratory depression, hypotonia, and sedation in neonates.

Data
Human Data
Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects.

Nursing Mothers
Risk Summary
There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breast milk. Based on data from published studies, midazolam is present in human milk in low levels. There are no data on the effects of midazolam on milk production.

Pediatric Use
The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require closer monitoring. In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation. Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid intravenous administration, particularly with concomitant use of fentanyl.

Geriatric Use
Because geriatric patients may have altered drug distribution and diminished hepatic and/or renal function, reduced doses of midazolam are recommended. Intravenous and intramuscular doses of midazolam should be decreased for elderly and for debilitated patients and subjects over 70 years of age may be particularly sensitive. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia. Administration of intramuscular and intravenous midazolam to elderly and/or high-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 central nervous system depressants capable of depressing respiration, especially narcotics.

DOSAGE AND ADMINISTRATION

Midazolam is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown midazolam to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAM INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excessive single doses or rapid intravenous administration may result in respiratory depression, airway obstruction and/or arrest. The potential for these latter effects is increased in debilitated patients, those receiving concomitant medications capable of depressing the CNS, and patients without an endotracheal tube but undergoing a procedure involving the upper airway such as endoscopy or dental.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported in adult and pediatric patients. Should such reactions occur, caution should be exercised before continuing administration of midazolam.

Midazolam Injection should only be administered intramuscular or intravenous. 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% dextrose in water and 0.9% 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% sodium chloride or 5% dextrose in water.

Monitoring
Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients. Sedative doses should be individually titrated, taking into account patient age, clinical status and concomitant use of other CNS depressants. Continuous monitoring of respiratory and cardiac function is required (i.e., pulse oximetry).

Adults and Pediatrics
Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to sedation/analgesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

Titration to effect with multiple small doses is essential for safe administration. It should be noted that adequate time to achieve peak central nervous system effect (3 to 5 minutes) for midazolam should be allowed between doses to minimize the potential for oversedation. Sufficient time must elapse between doses of concomitant sedative medications to allow the effect of each dose to be assessed before subsequent drug administration. This is an important consideration for all patients who receive intravenous midazolam.

Immediate availability of resuscitative drugs and *age*- and *size-appropriate* equipment and personnel trained in their use and skilled in airway management should be assured.

See package insert for usual adult dose information.

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 for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining intravenous 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.

See package insert for usual pediatric and neonatal dose information.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DRUG ABUSE AND DEPENDENCE

Midazolam injection contains midazolam, a Schedule IV controlled substance. 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 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

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 patient's needs. 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 of midazolam over a period of several days.

OVERDOSAGE

Clinical Presentation

Overdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include drowsiness, confusion, dysarthria, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) may occur. In severe overdosage cases, patients may develop respiratory depression and coma. Overdosage of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal (see **WARNINGS: Abuse, Misuse, and Addiction**). Markedly abnormal (lowered or elevated) blood pressure, heart rate, or respiratory rate raise the concern that additional drugs and/or alcohol are involved in the overdosage.

Management of Overdose

In managing benzodiazepine overdosage, employ general supportive measures, including intravenous fluids and airway maintenance. Flumazenil a specific benzodiazepine receptor antagonist indicated for the complete or partial reversal of the sedative effects of benzodiazepines in the management of benzodiazepine overdosage, can lead to withdrawal and adverse reactions, including seizures, particularly in the context of mixed overdosage with drugs that increase seizure risk (e.g., tricyclic and tetracyclic antidepressants) and in patients with long-term benzodiazepine use and physical dependency. The risk of withdrawal seizures with flumazenil use may be increased in patients with epilepsy. Flumazenil is contraindicated in patients who have received a benzodiazepine for control of a potentially life-threatening condition (e.g., status epilepticus). If the decision is made to use flumazenil, it should be used as an adjunct to, not as a substitute for, supportive management of benzodiazepine overdosage. See the flumazenil injection Prescribing Information.

Consider contacting a poison center (1-800-222-1222), poisoncontrol.org or a medical toxicologist for additional overdosage management recommendations.

INDICATIONS AND USAGE

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);
- continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

HOW SUPPLIED/STORAGE AND HANDLING

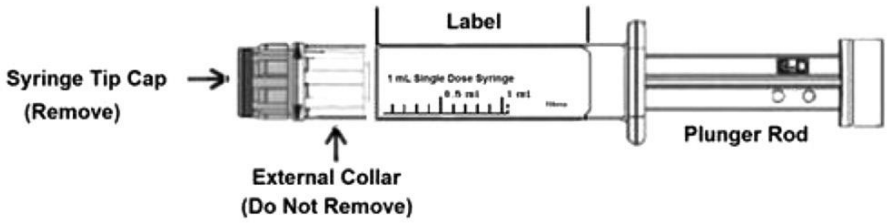
Midazolam Injection, USP, as a clear, colorless liquid, is available in the following:

1 mg/mL midazolam hydrochloride equivalent to 1 mg midazolam/mL
2 mL Syringe packaged in 10s (NDC 0641-6220-10)

5 mg/mL midazolam hydrochloride equivalent to 5 mg midazolam/mL
1 mL Syringe packaged in 10s (NDC 0641-6218-10)
2 mL Syringe packaged in 10s (NDC 0641-6219-10)

Store at 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

INSTRUCTIONS FOR USE
CAUTION: Certain glass syringes may malfunction, break or clog when connected to some Needleless Luer Access Devices (NLADs) and needles. This syringe has a larger internal syringe tip and an external collar (luer collar). The external collar must remain attached to the syringe. However, spontaneous disconnection of this glass syringe from needles and NLADs with leakage of drug product may occur. Assure that the needle or NLAD is securely attached before beginning the injection. Visually inspect the glass syringe-needle or glass syringe-NLAD connection before and during drug administration. (See Figure 1)
Figure 1



1. Inspect the outer packaging (plastic tube) by verifying:
   - plastic tube integrity
   - drug name
   - drug strength
   - dose volume
   - route of administration
   - expiration date to be sure that the drug has not expired
   - sterile field applicability

Do not use if package has been damaged.
2. Remove the plastic tube cap of the outer packaging that displays the product information to access the syringe.
3. Remove the syringe from the plastic tube.
4. Perform visual inspection on the syringe by verifying:
   - absence of syringe damage
   - absence of external particles
   - absence of internal particles
   - proper drug color
   - expiration date to be sure that the drug has not expired
   - drug name
   - drug strength
   - dose volume
   - route of administration
   - sterile field applicability
5. Push plunger rod slightly to break the stopper loose while tip cap is still on.
6. Remove tip cap by twisting it off. (See Figure 2)

Figure 2

7. Discard the tip cap.
8. Expel air bubble.

9. Adjust dose by expelling extra volume (where applicable) from the syringe into sterile material prior to administration.
10. Connect the syringe to appropriate injection connection depending on route of administration. Before injection, ensure that the syringe is securely attached to the needle or needleless luer access device (NLAD).
11. Depress plunger rod to deliver medication. Ensure that pressure is maintained on the plunger rod during the entire administration.
12. Remove syringe from NLAD (if applicable) and discard into appropriate receptacle. To prevent needle-stick injuries, needles should not be recapped.

NOTES:

- All steps must be done sequentially
- **Do not autoclave syringe**
- **Do not use this product on a sterile field**
- Do not introduce any other fluid into the syringe at any time
- This product is for single dose only.

ENDING INFORMATION

For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or the FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.
For Product Inquiry call 1-877-845-0689.

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