Press Release

Hikma launches Midazolam in 0.9% Sodium Chloride Injection in the US

London, 30 June 2023 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Midazolam in 0.9% Sodium Chloride (NaCl) Injection bags, in 50mg/50mL and 100mg/100mL doses. The product has been launched in the US and is indicated for continuous intravenous infusion for sedation of intubated and mechanically ventilated adult, pediatric, and neonatal patients as a component of anesthesia or during treatment in a critical care setting.

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 -

Enquiries

Hikma Pharmaceuticals PLC

Susan Ringdal
EVP, Strategic Planning and Global Affairs
+44 (0)20 7399 2760/ +44 7776 477050
uk-investors@hikma.uk.com

Steve Weiss
David Belian
US Communications and Public Affairs
+1 732 720 2830/ +1 732 788 8279
+1 732 720 2814/+1 848 254 4875
uscommunications@hikma.com

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

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 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 8,800 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

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.

[1] Source: IQVIA MAT April 2023, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

hikma.

Important Safety Information for Midazolam in 0.9% Sodium Chloride (NaCl) Injection, 50mg/50mL and 100mg/100mL:

Please see package insert for referenced section numbering, where appropriate.

BOXED WARNING

WARNING: PERSONNEL AND EQUIPMENT FOR MONITORING AND RESUSCITATION AND RISKS FROM CONCOMITANT USE WITH OPIOID ANALGESICS AND OTHER SEDATIVE HYPNOTICS

Personnel and Equipment for Monitoring and Resuscitation

- **Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer midazolam in sodium chloride injection *[see Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)]*.**
- **Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation *[see Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)]*.**
- **Resuscitative drugs, and age- and size-appropriate equipment for bag/valve/mask assisted ventilation must be immediately available during administration of midazolam in sodium chloride injection *[see Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)].***
- **Continuously monitor vital signs during sedation and during the recovery period *[see Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)]*.**

Risks from Concomitant Use with Opioid Analgesics and Other Sedative Hypnotics

Concomitant use of benzodiazepines, including midazolam in sodium chloride injection, and opioids may result in profound sedation, respiratory depression, coma, and death. Continuously monitor patients for respiratory depression and depth of sedation *[see Warnings and Precautions (5.2) and Drug Interaction (7.1)]*.

CONTRAINDICATIONS

Midazolam in sodium chloride injection is contraindicated in patients with:

- Known hypersensitivity to midazolam
- Acute narrow-angle glaucoma

WARNINGS & PRECAUTIONS

Personnel and Equipment for Monitoring and Resuscitation

- Prior to the intravenous administration of midazolam in any dose, ensure 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.
- Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer midazolam in sodium chloride injection.
- Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation.
- Continuously monitor patients for early signs of hypoventilation, airway obstruction, or apnea, with means readily available (e.g., pulse oximetry). Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately.
- A benzodiazepine reversal agent (i.e., flumazenil) should be immediately available during administration of midazolam in sodium chloride injection.
- Continuously monitor vital signs during the recovery period. Because intravenous midazolam can depress respiration [see *Clinical Pharmacology (12)*], especially when used concomitantly with opioid agonists and other sedatives [see *Dosage and Administration (2)*], it should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway, and supporting ventilation.

Risks from Concomitant Use with Opioids, Other Sedative Hypnotics, or Other Central Nervous System Depressants

- 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 and Precautions (5.2)* and *Drug Interactions (7.1)*].

- Titrate the dose of midazolam in sodium chloride injection when administered with opioid analgesics and sedative-hypnotics to the desired clinical response.
- Continuously monitor sedated patients for hypotension, airway obstruction, hypoventilation, apnea, and oxygen desaturation. These cardiorespiratory effects may be more likely to occur in patients with obstructive sleep apnea, the elderly, and ASA-PS III or IV patients.
- Concomitant use of barbiturates, alcohol, or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Risk of Cardiorespiratory Adverse Reactions

- Serious cardiorespiratory adverse reactions have occurred after administration of midazolam. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, 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 pediatric patients with hemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with an opioid.
- Excessive single doses or rapid intravenous administration may result in respiratory depression, airway obstruction and/or arrest. When used for sedation/anxiolysis/amnesia, midazolam should always be titrated slowly in adult or pediatric patients. Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should also be avoided in this population. Continuously monitor patients for early signs of hypoventilation, airway obstruction, and apnea using capnography, pulse oximetry, and clinical assessment [see *Dosage and Administration (2.2)*].

Risk of Paradoxical Behavior

- 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. 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 anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric patients.

Risk of Dependence and Withdrawal with Long-Term Use of Midazolam in Sodium Chloride Injection

- The continued use of benzodiazepines for several days to weeks may lead to clinically significant physical dependence. If used for long-term use (i.e., for several days to weeks), abrupt discontinuation or rapid dosage reduction of midazolam, or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening.
- Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use.
- After extended therapy, do not abruptly discontinue midazolam in sodium chloride injection. When discontinuing midazolam in a physically-dependent patient, gradually taper the dosage using a tapering schedule that is individualized to the patient [see *Dosage and Administration (2.3)*, *Dependence (9.3)*].

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 [see *Clinical Pharmacology (12.3)*]. 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.
- Do not administer midazolam in sodium chloride injection 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. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.
- The safety and efficacy of midazolam in sodium chloride injection following nonintravenous routes of administration have not been established. Midazolam in sodium chloride injection should only be administered intravenously.

Impaired Cognitive Function

- Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours. 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. Gross tests of recovery from the effects of midazolam [see *Clinical Pharmacology (12.3)]* cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until one full day after anesthesia and surgery, whichever is longer. For pediatric patients, particular care should be taken to assure safe ambulation.

Risk of Hypotension and Seizure in Preterm Infants and Neonates

- Rapid injection should be avoided in the neonatal population. Midazolam administered rapidly as an intravenous injection (i.e., 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.

Neonatal Sedation and Withdrawal Syndrome

- Receiving midazolam in sodium chloride 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. Monitor neonates exposed to midazolam in sodium chloride injection during pregnancy or labor for signs of sedation and manage these neonates accordingly [see *Use in Specific Populations (8.1)*].

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. The clinical significance of these findings is not clear. However, based on the available data, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans [see *Nonclinical Pharmacology (13.2)*].
- 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. These studies have substantial limitations, and it is not clear if the observed effects are due to the anesthetic/sedation drug administration or other factors such as the surgery or underlying illness.
- Anesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Risk of Increased Intraocular Pressure in Patients with Glaucoma

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

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections:

- Cardiorespiratory Adverse Reactions [see *Warnings and Precautions (5.3)*]
- Paradoxical Behavior [see *Warnings and Precautions (5.4)*]
- Dependence and Withdrawal [see *Warnings and Precautions (5.5)*]
- Impaired Cognitive Function [see *Warnings and Precautions (5.8)*]
- Hypotension and Seizure in Preterm Infants and Neonates [see *Warnings and Precautions (5.9)*]
- Neonatal Sedation and Withdrawal Syndrome [see *Warnings and Precautions (5.10)*, *Use in Specific Populations (8.1)*]
- Pediatric Neurotoxicity [see *Warnings and Precautions (5.11)*]

The following adverse reactions have been identified from literature or postmarketing reports of midazolam. Because some of these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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 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 reactions, 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

Table 2: Additional Adverse Reactions Reported Subsequent to Intravenous Administration as a Single Sedative/anxiolytic/amnestic Agent in Adult Patients:

hiccoughs (3.9%)	**Local effects at the intravenous site**
nausea (2.8%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5%)
coughing (1.3%)	redness (2.6%)
“oversedation” (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

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%, 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

There have been reports of hypotensive episodes and seizures following the administration of midazolam to neonates, *[see Warnings and Precautions (5.9)].*

Other Adverse Reactions Occurring at an Incidence of <1% Following Intravenous Injection as a Single Sedative/Anxiolytic/Amnesia Agent

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 anaphylactic reactions, hives, rash, pruritus
Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma

DRUG INTERACTIONS

Opioid Analgesics and Other Sedative Hypnotics
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.

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 [see *Dosage and Administration (2)*].

Cytochrome P450-3A4 Inhibitors
Concomitant administration with drugs that are known to inhibit the P450-3A4 enzyme system, such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole, may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

The effect of single oral doses of 800 mg cimetidine and 300 mg ranitidine on steady-state concentrations of midazolam was examined in a randomized crossover study (n=8). Cimetidine increased the mean midazolam steady-state concentration from 57 to 71 ng/mL. Ranitidine increased the mean steady-state concentration to 62 ng/mL. No change in choice reaction time or sedation index was detected after dosing with the H2 receptor antagonists.

In a placebo-controlled study, erythromycin administered as a 500 mg dose, three times a day, for 1 week (n=6), reduced the clearance of midazolam following a single 0.5 mg/kg intravenous dose. The half-life was approximately doubled.

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.

Saquinavir
In a placebo-controlled study, saquinavir administered as a 1200 mg dose, tid, 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.

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

Halothane
The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of midazolam administered; 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.

Pancuronium
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.

Other Drugs Used in the Surgical Setting
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, including midazolam, late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal [see *Warnings and Precautions (5.10)*, and *Clinical Considerations*]. Available data from published observational studies of pregnant women exposed to benzodiazepines do not report a clear association with benzodiazepines and major birth defects (see *Data*).

Available data from randomized controlled trials, cohort studies and case reports over several decades with midazolam use in pregnant women for anesthesia have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Most of the reported exposures to midazolam occurred at the time of cesarean delivery. Rare case reports of the prolonged use of midazolam in pregnant women for sedation in a critical care setting are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes (see *Data*).

In pregnant rats and rabbits, midazolam did not cause adverse effects to the fetus at doses of up to 1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparisons.

Published studies in pregnant primates demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see Data).

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 background risk of major birth defects and 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. Monitor neonates exposed to midazolam during pregnancy or labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to midazolam during pregnancy for signs of withdrawal. Manage these neonates accordingly [see *Warnings and Precautions (5.2)*].

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. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of more recent case-control and cohort studies of benzodiazepine use during pregnancy, which were adjusted for confounding exposures to alcohol, tobacco and other medications, have not confirmed these findings.

Lactation
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 (see *Data*). There are no data on the effects of midazolam on milk production.

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

Clinical Considerations
Infants exposed to midazolam through breast milk should be monitored for sedation, poor feeding, and poor weight gain. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment for a range of at least 4 to 8 hours after midazolam administration in order to minimize drug exposure to a breastfed infant.

Data
Published clinical lactation studies describe the presence of midazolam in human milk at low levels 4 to 8 hours after midazolam administration. These lactation studies have limitations including poor methodology and lack of validated analytical methods. Published study guidelines recommend pumping and discarding breast milk for a range of at least 4 to 8 hours after treatment with midazolam. No safety signals have been identified in breastfed infants exposed to midazolam.

Pediatric Use
The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following 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. Doses of midazolam in sodium chloride injection should be decreased for elderly and for debilitated patients [see *Warnings and Precautions (5.6)* and *Dosage and Administration (2)*] 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 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 opioids [see *Dosage and Administration (2)*].

Midazolam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions
- Midazolam in sodium chloride injection should only be administered intravenously. Avoid intra-arterial injection or extravasation [see *Warnings and Precautions (5.7)*].
- Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer Midazolam in Sodium Chloride Injection.
- Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation.
- Supplemental oxygen, resuscitative drugs, and age- and size-appropriate equipment for bag/valve/mask

assisted ventilation must be immediately available during administration of midazolam in sodium chloride injection. A benzodiazepine reversal agent should be immediately available.
- Continuously monitor vital signs during sedation and through the recovery period [*see Warnings and Precautions (5.1)*].

Midazolam must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression [*Warnings and Precautions (5.2)*].

Midazolam in sodium chloride injection can cause respiratory depression. It is a potent sedative agent that requires slow administration and individualization of dosage. Excessive single doses or rapid intravenous administration may result in respiratory depression, airway obstruction and/or arrest. Continuously monitor patients for early signs of hypoventilation, airway obstruction, and apnea using capnography, pulse oximetry, and clinical assessment [see *Warnings and Precautions (5.3)*].

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported in adult and pediatric patients. Should such reactions occur, the response to each dose of midazolam and all other drugs, including local anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric patients [see *Warnings and Precautions (5.4)*].

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. If solution is discolored or particulate matter is present, do not use.

General Dosing Information
Individualize dosing and titrate to desired clinical response, taking into account patient age, clinical status, and concomitant use of other CNS depressants. Titrate to effect with multiple small doses while continuously monitoring respiratory and cardiac function (i.e., pulse oximetry). To minimize the potential for oversedation, allow adequate time between doses to achieve peak central nervous system effect (3 to 5 minutes).

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.

Pediatrics:
Pediatric patients generally require higher dosages of midazolam (mg/kg) than adults. For deeply sedated pediatric patients a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Elderly and Debilitated Patients:
Intravenous doses of midazolam should be decreased for elderly and for debilitated patients [see *Warnings and Precautions (5.6)*]. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia [see *Warnings and Precautions (5.8)*].

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. Continuously monitor vital signs during sedation and through the recovery period [see *Warnings and Precautions (5.1)*].

Dosing Recommendations
Table 1 provides dosing recommendations for adult, pediatric, and neonatal patients.

Table 1. Dosing Recommendations for Continuous Intravenous Infusion in Adult, Pediatric, and Neonatal Patients

ADULT PATIENTS	If a loading dose is necessary to rapidly initiate sedation, 0.01 mg/kg to 0.05 mg/kg (approximately 0.5 mg 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 mg/kg/hr to 0.10 mg/kg/hr (1 mg/hr to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some patients. Use the lowest recommended doses in patients with residual effects from anesthetic drugs, or in those concurrently receiving other sedatives or opioids. Individual response to midazolam is variable. Titrate the infusion rate to the desired level of sedation, taking into account the patient's age, clinical status and current medications. In general, midazolam should be infused at the lowest rate that produces the desired level of sedation. Assess sedation at regular intervals and adjust the midazolam infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of midazolam and provides for the most rapid recovery once the infusion is terminated.
PEDIATRIC 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 adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients. In obese pediatric patients, calculate the dose based on ideal body weight. Titrate the dose to the desired level of sedation. Assess for desired level of sedation and vital signs at regular intervals.
PRETERM AND TERM NEONATAL PATIENTS	Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates WHOSE TRACHEA WAS INTUBATED, initiate continuous intravenous infusions of midazolam in sodium chloride injection at a rate of 0.03 mg/kg/hr (0.5 mcg/kg/min) in neonates <32 weeks and 0.06 mg/kg/hr (1 mcg/kg/min) in neonates >32 weeks. Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. Frequently assess the rate of infusion, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. When sedating preterm and former preterm neonates WHOSE TRACHEA WAS NOT INTUBATED, monitor respiratory parameters due to an increased risk of apnea.

Safe Discontinuation of Midazolam in Sodium Chloride Injection After Long-Term Use
If midazolam in sodium chloride injection is administered long-term (for several days to weeks), do not abruptly discontinue. Gradually taper the dosage in physically-dependent patients using a tapering schedule that is individualized to the patient. (see *Warnings and Precautions (5.5)*).

DRUG ABUSE AND DEPENDENCE

Controlled Substance
Midazolam in sodium chloride injection contains midazolam, a Schedule IV controlled substance.

Abuse
Midazolam in sodium chloride injection contains the benzodiazepine, midazolam. Benzodiazepines are a class of sedative drugs with a known potential for abuse. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Both abuse and misuse may lead to addiction. 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.

Dependence
Midazolam may produce physical dependence after long-term use. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. If midazolam in sodium chloride injection is administered long-term (i.e., for several days to weeks), abrupt discontinuation or rapid dosage reduction, or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use [see Warnings and Precautions (5.5)].

To reduce the risk of withdrawal reactions, after extended therapy, do not abruptly discontinue midazolam in sodium chloride injection. Gradually taper the dosage using a tapering schedule that is individualized to the patient.

Acute Withdrawal Signs and Symptoms
Acute withdrawal signs and symptoms have included abnormal involuntary movements, anxiety, blurred vision, cognitive disorder, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, homicidal thoughts, mania, psychosis, and suicidality.

Protracted Withdrawal Syndrome
Protracted withdrawal syndrome is characterized by anxiety, cognitive impairment, depression, insomnia, formication, motor symptoms (e.g., weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months.

Tolerance
Midazolam may produce tolerance after long-term use. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance may develop within days or weeks of the therapeutic effects of Midazolam; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

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 and Precautions (5.2)*]. 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. No evidence of specific organ toxicity from midazolam overdosage has been reported.

Management of Overdosage
In managing benzodiazepine overdosage, employ general supportive measures, including intravenous fluids and airway management. 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 the Poison Help Line (1-800-222-1222) or medical toxicologist for additional overdosage management for recommendations.

INDICATIONS AND USAGE

Midazolam in sodium chloride injection is indicated:

- Continuous intravenous infusion for sedation of intubated and mechanically ventilated adult, pediatric, and neonatal patients as a component of anesthesia or during treatment in a critical care setting.

HOW SUPPLIED/STORAGE AND HANDLING

Midazolam in Sodium Chloride Injection is a clear, colorless solution supplied in single-dose bags with an aluminum overwrap available as:

Total Strength per Total Volume	Strength per mL	10 single-dose bags NDC	Bag and Overwrap NDC
50 mg per 50 mL	1 mg/mL	0143-9379-10	0143-9379-01
100 mg per 100 mL	1 mg/mL	0143-9380-10	0143-9380-01

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from Freezing. Individual containers may be used up to 48 hours after initial penetration. Discard unused portion.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
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 FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured by:
HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Estrada do Rio da Mó, 8, 8A e 8B – Fervença – 2705-906 Terrugem SNT, PORTUGAL

Distributed by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922 USA

Document Identification Number: HK-2226-v1