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Press Release

Hikma launches Diazepam Injection, USP in single-dose prefilled syringe

Company expands prefilled syringe offerings to help treat patients faster and with reduced risk

London, 21 January 2022 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces it launched Diazepam Injection, USP, through its US affiliate, Hikma Pharmaceuticals USA Inc. The company has launched 5mg/mL in 2mL dose. This is the second medicine Hikma has launched in prefilled syringe form.

Diazepam, which has been in short supply until recently, is indicated for the management of anxiety, convulsive seizures and alcohol withdrawals.

“We are excited to announce the launch of Diazepam Injection, our second product in prefilled syringe form which may help treat patients faster, more easily and with reduced risk, particularly in time-sensitive situations,” said Riad Mishlawi, President of Hikma Injectables. “We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care. This launch leverages the investments we have made to expand our Injectables manufacturing capacity and capabilities and we look forward to bringing more medicines in this form to patients and healthcare professionals in the US.”

According to IQVIA, US sales of Diazepam Injection, USP, 5mg/ml in 2mL were approximately $31 million in the 12 months ending November 2021.

Hikma is the second largest US supplier of generic injectable medicines by volume, with a growing portfolio of over 120 products. Today one in every six injectable generic medicines used in US hospitals is a Hikma product.

- ENDS -

Enquiries

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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 United States (US), 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 8,600 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 Diazepam Injection, USP, 5mg/ml in 2mL:

BOXED WARNING

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death (see WARNINGS).**
- **Reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation (see WARNINGS and PRECAUTIONS).**
- **The use of benzodiazepines, including diazepam, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing diazepam and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see WARNINGS).**
- **The continued use of benzodiazepines may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Although diazepam is indicated only for intermittent use (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION), if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of diazepam may precipitate acute withdrawal reactions, which can be life-threatening. For patients using diazepam more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue diazepam (see WARNINGS).**

CONTRAINDICATIONS

Diazepam is contraindicated in patients with a known hypersensitivity to this drug; acute narrow angle glaucoma; and open angle glaucoma unless patients are receiving appropriate therapy.

WARNINGS & PRECAUTIONS

- Concomitant use of benzodiazepines, including diazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe diazepam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when diazepam is used with opioids.
- The use of benzodiazepines, including diazepam, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death.
- Before prescribing diazepam and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. Use of diazepam, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of diazepam along with monitoring for signs and symptoms of abuse, misuse, and addiction. Do not exceed the recommended dosing frequency; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and

advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

- For patients using diazepam more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue diazepam (a patient-specific plan should be used to taper the dose). Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages, and those who have had longer durations of use.
- The continued use of benzodiazepines may lead to clinically significant physical dependence. Although diazepam is indicated only for intermittent use, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of diazepam or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures).
- In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.
- When used intravenously, the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment; the solution should be injected slowly, taking one minute for administration; do not use small veins, such as those on the dorsum of the hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation.
- Do not mix or dilute diazepam with other solutions or drugs in syringe or infusion container. If it is not feasible to administer diazepam directly intravenous, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.
- Extreme care must be used in administering diazepam injection, particularly by the intravenous route, to the elderly, to very ill patients and to those with limited pulmonary reserve because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates, alcohol or other central nervous system depressants increases depression with increased risk of apnea. Resuscitative equipment including that necessary to support respiration should be readily available.
- When diazepam is used with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one-third and administered in small increments. In some cases the use of a narcotic may not be necessary.
- Diazepam injection should not be administered to patients in shock, coma, or in acute alcoholic intoxication with depression of vital signs. As is true of most CNS-acting drugs, patients receiving diazepam should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.
- Tonic status epilepticus has been precipitated in patients treated with intravenous diazepam for petit mal status or petit mal variant status.
- Although seizures may be brought under control promptly, a significant proportion of patients experience a return to seizure activity, presumably due to the short-lived effect of diazepam after intravenous administration. The physician should be prepared to re-administer the drug. However, diazepam is not recommended for maintenance, and once seizures are brought under control, consideration should be given to the administration of agents useful in longer term control of seizures.
- The usual precautions in treating patients with impaired hepatic function should be observed. Metabolites of diazepam are excreted by the kidney; to avoid their excess accumulation, caution should be exercised in the administration to patients with compromised kidney function.
- Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended.
- Propylene glycol toxicity has been reported in patients treated with diazepam injection at doses significantly greater than recommended. In these cases, diazepam was being used to treat alcohol withdrawal symptoms at doses greater than 900 mg/day. Propylene glycol toxicity is associated with an anion gap metabolic acidosis, serum hyperosmolality, and increased lactate. Propylene glycol toxicity can cause acute tubular necrosis (which can progress to multi-organ failure), mental status changes, hypotension, seizures, and cardiac arrhythmias. Patients at high risk for propylene glycol toxicity include those with renal dysfunction, hepatic dysfunction, impaired alcohol dehydrogenase enzymes, or other comorbidities (such as a history of alcoholism).
- Until additional information is available, diazepam injection is not recommended for obstetrical use.
- Lower doses (usually 2 mg to 5 mg) should be used for elderly and debilitated patients.

Patient Counseling

- Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when diazepam is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined.
- Inform patients that the use of diazepam more frequently than recommended, even at recommended dosages,

exposes users to risks of abuse, misuse, and addiction, which can lead to overdose and death, especially when used in combination with other medications (e.g., opioid analgesics), alcohol, and/or illicit substances. Inform patients about the signs and symptoms of benzodiazepine abuse, misuse, and addiction; to seek medical help if they develop these signs and/or symptoms; and on the proper disposal of unused drug.

- Inform patients that use of diazepam more frequently than recommended may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of diazepam may precipitate acute withdrawal reactions, which can be life-threatening. Inform patients that in some cases, patients taking benzodiazepines have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.

ADVERSE REACTIONS

Side effects most commonly reported were drowsiness, fatigue, and ataxia; venous thrombosis and phlebitis at the site of injection. Other adverse reactions less frequently reported include:

CNS: Confusion, depression, [including respiratory depression], dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo.

G.I: Constipation, nausea.

G.U: Incontinence, changes in libido, urinary retention.

Cardiovascular: Bradycardia, cardiovascular collapse, hypotension.

EENT: Blurred vision, diplopia, nystagmus.

Skin: Urticaria, skin rash.

Other: Hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after diazepam therapy and are of no known significance.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm, and pain in throat or chest have been reported.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy.

DRUG INTERACTIONS

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA sites and opioids interact primarily at mμ receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

If diazepam is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed—particularly with known compounds which may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors, and other antidepressants. In highly anxious patients with evidence of accompanying depression, particularly those who may have suicidal tendencies, protective measures may be necessary.

Diazepam injection has produced hypotension or muscular weakness in some patients particularly when used with narcotics, barbiturates, or alcohol.

The clearance of diazepam and certain other benzodiazepines can be delayed in association with cimetidine administration. The clinical significance of this is unclear.

USE IN SPECIFIC POPULATIONS

Usage in Pregnancy

An increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamate, and chlordiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

In humans, measurable amounts of diazepam were found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, diazepam injection is not recommended for obstetrical use.

Pediatric Use
Efficacy and safety of parenteral diazepam has not been established in the neonate (30 days or less of age).

Prolonged central nervous system depression has been observed in neonates, apparently due to inability to biotransform diazepam into inactive metabolites.

In pediatric use for the treatment of status epilepticus or severe recurrent convulsive seizures, in order to obtain maximal clinical effect with the minimum amount of drug and thus to reduce the risk of hazardous side effects, such as apnea or prolonged periods of somnolence, it is recommended that the drug be given as a slow IV push over 1 minute. The safety and tolerability of the recommended dosage regimen is supported by a randomized, double-blind study that included 162 pediatric patients ages 3 months to 17 years who received intravenous diazepam for the treatment of status epilepticus. In this study, 16% of pediatric patients who received diazepam experienced severe or life-threatening respiratory depression.

Benzyl alcohol has been reported to be associated with a fatal gasping syndrome in premature infants.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. The usual recommended dose in older children and adults ranges from 2 mg to 20 mg intramuscular or intravenous, depending on the indication and its severity. In some conditions, e.g., tetanus, larger doses may be required. (See dosage for specific indications.) In acute conditions the injection may be repeated within one hour although an interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 mg to 5 mg) and slow increase in dosage should be used for elderly or debilitated patients and when other sedative drugs are administered.

For dosage in infants above the age of 30 days and children, see the specific indications below. When intravenous use is indicated, facilities for respiratory assistance should be readily available.

Intramuscular: Diazepam Injection, USP should be injected deeply into the muscle.

Intravenous Use: The solution should be injected slowly, taking one minute for administration. Do not use small veins, such as those on the dorsum of the hand or wrist. Extreme care should be taken to avoid intra-arterial administration or extravasation.

Do not mix or dilute diazepam with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer diazepam directly intravenous, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Refer to table in the package insert for usual adult dosage and dosage range in children.

Once the acute symptomatology has been properly controlled with diazepam injection, the patient may be placed on oral therapy with diazepam if further treatment is required.

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Diazepam injection is a schedule IV controlled substance.

Abuse
Diazepam is a benzodiazepine and a CNS depressant with a potential for abuse and addiction. 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. Even taking benzodiazepines as prescribed may put patients at risk for abuse and misuse of their medication. Abuse and misuse of benzodiazepines may lead to addiction.

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders.

The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use (especially benzodiazepines with other CNS depressants such as opioids and alcohol).

Dependence
Physical Dependence After Use of Diazepam More Frequently Than Recommended
Diazepam may produce physical dependence if used more frequently than recommended. 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. Although diazepam is indicated only for intermittent use, if used more frequently than recommended, 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.

For patients using diazepam more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue diazepam.

Acute Withdrawal Signs and Symptoms
Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, 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, mania, psychosis, seizures, and suicidality.

Protracted Withdrawal Syndrome
Protracted withdrawal syndrome associated with benzodiazepines 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. As a result, there may be difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used.

Tolerance
Tolerance to diazepam may develop after use more frequently than recommended. 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 to the therapeutic effect of benzodiazepines may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

MANAGEMENT OF OVERDOSAGE

Manifestations of diazepam overdosage include somnolence, confusion, coma, and diminished reflexes. Respiration, pulse, and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained.

Hypotension may be combated by the use of norepinephrine bitartrate or metaraminol. Dialysis is of limited value.

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. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including **CONTRAINDICATIONS, WARNINGS**, and **PRECAUTIONS** should be consulted prior to use.

Discontinuation or Dosage Reduction of Diazepam
To reduce the risk of withdrawal reactions, use a gradual taper to discontinue diazepam or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly.

INDICATIONS AND USAGE

Diazepam is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

In acute alcohol withdrawal, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

As an adjunct prior to endoscopic procedures if apprehension, anxiety or acute stress reactions are present, and to diminish the patient's recall of the procedures.

Diazepam is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff-man syndrome; and tetanus.

Diazepam injection is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.

Diazepam is a useful premedication (the intramuscular route is preferred) for relief of anxiety and tension in patients who are to undergo surgical procedures. Intravenously, prior to cardioversion for the relief of anxiety and tension and to diminish the patient's recall of the procedure.

HOW SUPPLIED/STORAGE AND HANDLING

Diazepam Injection, USP is available as follows:

- 10 mg per 2 mL single-dose prefilled disposable syringe packaged in cartons of ten (NDC 0641-6244-10)

Do not use if solution is darker than slightly yellow or contains a precipitate.

Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]. **Protect from light.**

To prevent needle-stick injuries, needles should not be recapped, purposely bent, or broken by hand.

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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