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Press Release

Hikma launches Dexmedetomidine Hydrochloride in 0.9% Sodium Chloride Injection

London, 6 May 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Dexmedetomidine Hydrochloride in 0.9% Sodium Chloride Injection, 200mcg/50mL & 400mcg/100mL, in the US, through its US affiliate, Hikma Pharmaceuticals USA Inc.

Dexmedetomidine Hydrochloride in 0.9% Sodium Chloride Injection is indicated for the sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting and of non-intubated patients prior to and/or during surgical and other procedures.

According to IQVIA, US sales of Dexmedetomidine Hydrochloride in 0.9% Sodium Chloride Injection, 50mL and 100mL, were approximately $232 million in the 12 months ending March 2021.

Riad Mishlawi, President of Injectables said, “We are pleased to add Dexmedetomidine Hydrochloride Injection to our US portfolio. At Hikma, we are committed to putting better health within reach every day. This ready-to-administer bag, demonstrates our commitment to developing products that respond to the needs of our patients and the hospitals we support.”

Hikma is the third largest US supplier of generic injectable medicines by volume, with a growing portfolio of over 100 products. Today one in every six injectable generic medicines used in US hospitals is a Hikma product.

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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,

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are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

Important Safety Information for Dexmedetomidine Hydrochloride in 0.9% Sodium Chloride Injection 200mcg/50mL & 400mcg/100mL:

CONTRAINDICATIONS

None.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
Dexmedetomidine hydrochloride injection is not a controlled substance.

Dependence
The dependence potential of dexmedetomidine hydrochloride has not been studied in humans. However, since studies in rodents and primates have demonstrated that dexmedetomidine hydrochloride exhibits pharmacologic actions similar to those of clonidine, it is possible that dexmedetomidine hydrochloride may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation.

WARNINGS & PRECAUTIONS

- **Drug Administration:** dexmedetomidine hydrochloride should be administered only by persons skilled in the management of patients in the operating room setting. Due to the known pharmacological effects of dexmedetomidine hydrochloride, patients should be continuously monitored while receiving dexmedetomidine hydrochloride.
- **Hypotension, Bradycardia, and Sinus Arrest:** clinically significant episodes of bradycardia and sinus arrest have been reported with dexmedetomidine hydrochloride administration in young, healthy adult volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration.

  Reports of hypotension and bradycardia have been associated with dexmedetomidine hydrochloride infusion. Some of these cases have resulted in fatalities.

  Caution should be exercised when administering dexmedetomidine hydrochloride to patients with advanced heart block and/or severe ventricular dysfunction. Because dexmedetomidine hydrochloride decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension and in elderly patients.

  In clinical trials where other vasodilators or negative chronotropic agents were co-administered with Dexmedetomidine hydrochloride an additive pharmacodynamic effect was not observed. Nonetheless, caution should be used when such agents are administered concomitantly with dexmedetomidine hydrochloride.
- **Transient Hypertension:** transient hypertension has been observed primarily during the loading dose in association with the initial peripheral vasoconstrictive effects of dexmedetomidine hydrochloride.
- **Arousability:** some patients receiving dexmedetomidine hydrochloride have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.
- **Withdrawal:** in adult subjects, withdrawal symptoms were not seen after discontinuation of short-term infusions of dexmedetomidine hydrochloride (<6 hours).
- **Tolerance and Tachyphylaxis:** use of dexmedetomidine beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions.
- **Hepatic Impairment:** since dexmedetomidine hydrochloride clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.

ADVERSE REACTIONS

The most common adverse reactions (incidence greater than 2%) are hypotension, bradycardia, and dry mouth.

Adverse reactions associated with infusions greater than 24 hours in duration include ARDS (acute respiratory distress syndrome), respiratory failure, and agitation.

Use of dexmedetomidine hydrochloride has been associated with the following serious adverse reactions:
- Hypotension, bradycardia and sinus arrest
- Transient hypertension

Procedural Sedation
Adverse reaction information is derived from the two trials for procedural sedation in which 318 adult patients received dexmedetomidine hydrochloride. The following adverse reactions were reported: hypotension (54%), respiratory depression (37%), bradycardia (14%), hypertension (13%), tachycardia (5%), nausea (3%), dry mouth (3%), hypoxia (2%), and bradypnea (2%).

Postmarketing Experience
The following post approval adverse reactions have been reported:

Blood and Lymphatic System Disorders: Anemia

Cardiac Disorders: Aarrhythmia, atrial fibrillation, atrioventricular block, bradycardia, cardiac arrest, cardiac disorder, extrasystoles, myocardial infarction, supraventricular tachycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia, electrocardiogram T wave inversion, electrocardiogram QT prolonged

Eye Disorders: Photopsia, visual impairment, abnormal vision

Gastrointestinal Disorders: Abdominal pain, diarrhea, nausea, vomiting

General Disorders and Administration Site Conditions: Chills, hyperpyrexia, pain, pyrexia, thirst

Hepatobiliary Disorders: Hepatic function abnormal, hyperbilirubinemia,
alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, increased gamma-glutamyl transpepsidase)

Metabolism and Nutrition Disorders: Acidosis, hyperkalemia, hypoglycemia, hypovolemia, hypernatremia

Nervous System Disorders: Convulsion, dizziness, headache, neuralgia, neuritis, speech disorder

Psychiatric Disorders: Agitation, confusional state, delirium, hallucination, illusion

Renal and Urinary Disorders: Oliguria, polyuria

Respiratory, Thoracic and Mediastinal Disorders: Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation hypoxia, pulmonary congestion, respiratory acidosis

Skin and Subcutaneous Tissue Disorders: Hyperhidrosisor, increased/excessive sweating

Surgical and Medical Procedures: Light anesthesia

Vascular Disorders: Blood pressure fluctuation, hemorrhage, hypertension, hypotension

MONITORING

- Attenuation of heart rate and blood pressure increases in response to endotracheal intubation and a decrease in anesthetic/opioid requirements are indicative of a therapeutic response to dexmedetomidine when given as an anesthetic adjunct
- Patients may be arousable and alert when stimulated; this alone should not be considered as indicative of lack of efficacy
- Blood pressure, heart rate, respiratory rate, and oxygen levels; continuously during dexmedetomidine infusion and after discontinuation, as clinically necessary

DRUG INTERACTIONS

Anesthetics, Sedatives, Hypnotics, Opioids
Enhancement of pharmacodynamic effects. Reduction in dosage of dexmedetomidine hydrochloride or the concomitant medication may be required

Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine hydrochloride and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with dexmedetomidine hydrochloride, a reduction in dosage of dexmedetomidine hydrochloride or the concomitant anesthetic, sedative, hypnotic or opioid may be required.

Neuromuscular Blockers
In one study of 10 healthy adult volunteers, administration of dexmedetomidine hydrochloride for 45 minutes at a plasma concentration of 1 ng/mL resulted in no clinically meaningful increases in the magnitude of neuromuscular blockade associated with rocuronium administration.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm
There are no adequate and well-controlled studies of dexmedetomidine hydrochloride use in pregnant women. In an *in vitro* human placenta study, placental transfer of dexmedetomidine occurred. Thus, fetal exposure should be expected in humans, and dexmedetomidine hydrochloride should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Labor and Delivery
The safety of dexmedetomidine hydrochloride during labor and delivery has not been studied.

Nursing Mothers: Caution should be exercised when administered to a nursing woman
It is not known whether dexmedetomidine hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dexmedetomidine hydrochloride is administered to a nursing woman.

Pediatric Use
Safety and efficacy have not been established for Procedural Sedation in pediatric patients. The use of dexmedetomidine for procedural sedation in pediatric patients has not been evaluated.

Geriatric Use: Dose reduction should be considered.
Intensive Care Unit Sedation
A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200 patients were 75 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of dexmedetomidine hydrochloride.

Procedural Sedation
A total of 131 patients in the clinical studies were 65 years of age and over. A total of 47 patients were 75 years of age and over. Hypotension occurred in a higher incidence in dexmedetomidine hydrochloride-treated patients 65 years or older (72%) and 75 years or older (74%) as compared to patients <65 years (47%).

Hepatic Impairment
Since dexmedetomidine hydrochloride clearance decreases with increasing severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.

DOSAGE AND ADMINISTRATION

Dexmedetomidine hydrochloride should be administered only by persons skilled in the management of patients in the intensive care or operating room setting. Due to the known pharmacological effects of dexmedetomidine hydrochloride, patients should be continuously monitored while receiving dexmedetomidine hydrochloride.

Dosage Information

For Adult Intensive Care Unit Sedation: generally initiate at one mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hour.

For Adult Procedural Sedation: generally initiate at one mcg/kg over 10 minutes, followed by a maintenance infusion initiated at 0.6 mcg/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hour.

Alternative doses: recommended for patients over 65 years of age and awake fiberoptic intubation patients.

Refer to full package insert for further initiation dosage and maintenance dosage information

Dosing Guidelines

- Dexmedetomidine hydrochloride injection dosing should be individualized and titrated to desired clinical response.
- Dexmedetomidine hydrochloride injection is not indicated for infusions lasting longer than 24 hours.
- Dexmedetomidine hydrochloride injection should be administered using a controlled infusion device.

Dosage Adjustment

Due to possible pharmacodynamic interactions, a reduction in dosage of dexmedetomidine hydrochloride injection or other concomitant anesthetics, sedatives, hypnotics or opioids may be required when co-administered. Dosage reductions may need to be considered for **adult** patients with hepatic impairment, and geriatric patients.

Preparation of Solution

Strict aseptic technique must always be maintained during handling of Dexmedetomidine Hydrochloride Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Flexible Containers

Dexmedetomidine Hydrochloride in 0.9% Sodium Chloride Injection is supplied in flexible containers containing a premixed, ready to use Dexmedetomidine in Hydrochloride Solution in 0.9% Sodium Chloride in water. No further dilution of these preparations are necessary.

Check the container for minute leaks by squeezing it firmly. If leaks are found, or if the seal is not intact, discard the solution as the sterility may be compromised.

Do not use flexible containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Administration with Other Fluids

Dexmedetomidine hydrochloride injection infusion should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established.

Dexmedetomidine hydrochloride injection has been shown to be incompatible when administered with the following drugs: **Amphotericin B, diazepam.**

Dexmedetomidine hydrochloride injection has been shown to be compatible when administered with the following intravenous fluids:

- 0.9% sodium chloride in water
- 5% dextrose in water
- 20% mannitol
- Lactated Ringer's solution
- 100 mg/mL magnesium sulfate solution
- 0.3% potassium chloride solution

Compatibility with Natural Rubber

Compatibility studies have demonstrated the potential for absorption of dexmedetomidine hydrochloride injection to some types of natural rubber. Although dexmedetomidine hydrochloride injection is dosed to effect, it is advisable to use administration components made with synthetic or coated natural rubber gaskets.

OVERDOSAGE

The tolerability of dexmedetomidine hydrochloride was studied in one study in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hr. The maximum blood concentration achieved in this study was approximately 13 times the upper boundary of the therapeutic range. The most notable effects observed in two subjects who achieved the highest doses were first degree atrioventricular block and second-degree heart block. No hemodynamic compromise was noted with the atrioventricular block and the heart block resolved spontaneously within one minute.

One patient who received a loading bolus dose of undiluted dexmedetomidine hydrochloride (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

INDICATIONS AND USAGE

Intensive Care Unit Sedation
Dexmedetomidine Hydrochloride in 0.9% Sodium Chloride Injection is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Dexmedetomidine hydrochloride injection should be administered by continuous infusion not to exceed 24 hours.

Dexmedetomidine Hydrochloride in 0.9%Sodium Chloride Injection has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post extubation. It is not necessary to discontinue Dexmedetomidine hydrochloride injection prior to extubation.

Procedural Sedation
Dexmedetomidine Hydrochloride in 0.9% Sodium Chloride Injection is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

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 the FDA at 1-800-FDA-1088 or **http://www.fda.gov/medwatch**.

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