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Press Release

Hikma expands addiction therapy portfolio with the launch of Naloxone Hydrochloride Injection, USP, in prefilled syringe

London, 4 January 2023 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces it has launched Naloxone Hydrochloride Injection, USP, 2mg/2mL, in prefilled syringe (PFS) form. The drug, launched in the US, is used for the emergency treatment of a known or suspected opioid overdose and is the third PFS product launched.

According to IQVIA, US sales of Naloxone Hydrochloride Injection, 2mg/2mL, were approximately $23 million in the 12 months ending October 2022.

The launch of the Naloxone Hydrochloride Injection PFS expands Hikma's portfolio of addiction therapy treatments, which includes, among others, a naloxone vial and KLOXXADO®[1] (naloxone HCl) nasal spray 8mg, as well as buprenorphine and methadone medication options to meet the urgent needs of US patients and communities.

Hikma is a top three supplier of generic injectable medicines by volume in the US with a portfolio of over 130 products.[2]

"As an experienced provider of addiction therapy treatments we are pleased to be able to leverage our capabilities to deliver another important new tool in this fight," said Riad Mishlawi, President of Hikma Injectables. "Our Naloxone Hydrochloride Injection PFS is ready-to-administer and will help improve the speed, safety and accuracy of patient care, particularly in time sensitive situations such as an opioid overdose. We are continually investing in R&D to develop our pipeline of new products and we look forward to bringing more affordable treatment options to serve the growing needs of healthcare professionals and their patients around the world."

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[1] Kloxxado® is a registered trademark of Hikma Specialty USA Inc.
[2] IQVIA MAT through October 2022, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

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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 8,700 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 Naloxone Hydrochloride Injection, USP, 2mg/2mL:

CONTRAINDICATIONS

Naloxone hydrochloride injection is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients contained in the formulation.

WARNINGS & PRECAUTIONS

- **Drug Dependence –** Naloxone hydrochloride injection should be administered cautiously to persons, including newborns of mothers, who are known or suspected to be physically dependent on opioids. In such cases, an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.
- **Repeat Administration –** The patient who has satisfactorily responded to naloxone should be kept under continued surveillance and repeated doses of naloxone should be administered, as necessary, since the duration of action of some opioids may exceed that of naloxone.
- **Respiratory Depression Due to Other Drugs –** Naloxone is not effective against respiratory depression due to non-opioid drugs and in the management of acute toxicity caused by levopropoxyphene. Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete or require higher doses of naloxone. If an incomplete response occurs, respirations should be mechanically assisted as clinically indicated.
- **General –** In addition to naloxone, other resuscitative measures such as maintenance of free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute opioid poisoning.

ADVERSE REACTIONS

Postoperative
The following adverse events have been associated with the use of naloxone hydrochloride injection in postoperative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone in postoperative patients may result in significant reversal of analgesia and may cause agitation.

Opioid Depression
Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death.

Opioid Dependence
Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but are not limited to, the following signs and symptoms: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia. In the neonate, opioid withdrawal may also include: convulsions, excessive crying, and hyperactive reflexes.

Adverse events associated with the postoperative use of naloxone hydrochloride injection are listed by organ system and in decreasing order of frequency as follows:

Cardiac Disorders: pulmonary edema, cardiac arrest or failure, tachycardia, ventricular fibrillation, and ventricular tachycardia. Death, coma, and encephalopathy have been reported as sequelae of these events.
Gastrointestinal Disorders: vomiting, nausea
Nervous System Disorders: convulsions, paraesthesia, grand mal convulsion
Psychiatric Disorders: agitation, hallucination, tremulousness
Respiratory, Thoracic, and Mediastinal Disorders: dyspnea, respiratory depression, hypoxia
Skin and Subcutaneous Tissue Disorders: nonspecific injection site reactions, sweating
Vascular Disorders: hypertension, hypotension, hot flashes, or flushing

DRUG INTERACTIONS

Large doses of naloxone are required to antagonize buprenorphine since the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression. The barbiturate methohexital appears to block the acute onset of withdrawal symptoms induced by naloxone in opiate addicts.

USE IN SPECIFIC POPULATIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies in animals to assess the carcinogenic potential of naloxone have not been conducted.

Use in Pregnancy – *Teratogenic Effects:*
Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m2), demonstrated no embryotoxic or teratogenic effects due to naloxone. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed.

Use in Pregnancy – *Non-teratogenic Effects*:
Risk-benefit must be considered before naloxone is administered to a pregnant woman who is known or suspected to be opioid-dependent since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta and may precipitate withdrawal in the fetus as well as in the mother. Patients with mild to moderate hypertension who receive naloxone during labor should be carefully monitored as severe hypertension may occur.

Use in Labor and Delivery
It is not known if naloxone hydrochloride injection affects the duration of labor and/or delivery. However, published reports indicated that the administration of naloxone during labor did not adversely affect maternal or neonatal status.

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

Pediatric Use
Naloxone hydrochloride injection may be administered intravenously, intramuscularly, or subcutaneously in children and neonates to reverse the effects of opiates. The American Academy of Pediatrics, however, does not endorse subcutaneous or intramuscular administration in opiate intoxication since absorption may be erratic or delayed.

Pediatric Use – *Usage in Pediatric Patients and Neonates for Septic Shock*:
The safety and effectiveness of naloxone hydrochloride injection in the treatment of hypotension in pediatric patients and neonates with septic shock have not been established. One study of two neonates in septic shock reported a positive pressor response; however, one patient subsequently died after intractable seizures.

Geriatric Use
Clinical studies of naloxone hydrochloride injection did not include sufficient numbers of subjects aged 65 and over

to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Insufficiency/Failure
The safety and effectiveness of naloxone hydrochloride injection in patients with renal insufficiency/failure have not been established in well-controlled clinical trials. Caution should be exercised when naloxone is administered to this patient population.

Liver Disease
The safety and effectiveness of naloxone hydrochloride injection in patients with liver disease have not been established in well-controlled clinical trials. Caution should be exercised when naloxone is administered to patients with liver disease.

DOSAGE AND ADMINISTRATION

Naloxone Hydrochloride Injection, USP may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration, which is recommended in emergency situations.

Since the duration of action of some opioids may exceed that of naloxone, the patient should be kept under continued surveillance. Repeated doses of naloxone should be administered, as necessary.

Intravenous Infusion: Naloxone Hydrochloride Injection, USP may be diluted for intravenous infusion in 0.9% sodium chloride injection or 5% dextrose injection. The addition of 2 mg of naloxone hydrochloride in 500 mL of either solution provides a concentration of 0.004 mg/mL. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Naloxone Hydrochloride Injection, USP should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to Naloxone Hydrochloride Injection, USP unless its effect on the chemical and physical stability of the solution has first been established.

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

Usage in Adults
Opioid Overdose - Known or Suspected: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2- to 3-minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of opioid induced or partial opioid induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Opioid Depression: For the partial reversal of opioid depression following the use of opioids during surgery, smaller doses of naloxone hydrochloride are usually sufficient. The dose of naloxone should be titrated according to the patient's response. For the initial reversal of respiratory depression, naloxone hydrochloride should be injected in increments of 0.1 to 0.2 mg intravenously at two- to three-minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of naloxone may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of naloxone may be required within one- to two-hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of opioid. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

Septic Shock: The optimal dosage of naloxone or duration of therapy for the treatment of hypotension in septic shock patients has not been established.

Usage in Children
Opioid Overdose - Known or Suspected: The usual initial dose in pediatric patients is 0.01 mg/kg body weight given intravenously. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an intravenous route of administration is not available, naloxone hydrochloride may be administered intramuscularly or subcutaneously in divided doses. If necessary, Naloxone Hydrochloride Injection, USP can be diluted with sterile water for injection.

Postoperative Opioid Depression: Follow the recommendations and cautions under **Usage in Adults, Postoperative Opioid Depression**. For the initial reversal of respiratory depression, naloxone hydrochloride should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three minute intervals to the desired degree of reversal.

Usage in Neonates
Opioid-Induced Depression: The usual initial dose is 0.01 mg/kg body weight administered intravenously, intramuscularly, or subcutaneously. This dose may be repeated in accordance with adult administration guidelines for postoperative opioid depression.

Do not administer unless solution is clear and container is undamaged. Discard unused portion.

DRUG ABUSE AND DEPENDENCE
Naloxone hydrochloride injection is an opioid antagonist. Physical dependence associated with the use of naloxone hydrochloride injection has not been reported. Tolerance to the opioid antagonist effect of naloxone is not known to occur.

OVERDOSAGE

There is limited clinical experience with naloxone hydrochloride injection overdosage in humans.

Adult Patients
In one small study, volunteers who received 24 mg/70 kg did not demonstrate toxicity. In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m2/min) of naloxone hydrochloride injection followed immediately by 2 mg/kg/hr for 24 hours. Twenty-three patients experienced adverse events associated with naloxone use, and naloxone was discontinued in seven patients because of adverse effects. The most serious adverse events were: seizures (2 patients), severe hypertension (1), and hypotension and/or bradycardia (3). At doses of 2 mg/kg in normal subjects, cognitive impairment and behavioral symptoms, including irritability, anxiety, tension, suspiciousness, sadness, difficulty concentrating, and lack of appetite have been reported. In addition, somatic symptoms, including dizziness, heaviness, sweating, nausea, and stomachaches were also reported. Although complete information is not available, behavioral symptoms were reported to often persist for 2 to 3 days.

Pediatric Patients
Up to 11 doses of 0.2 mg naloxone (2.2 mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulfate. Pediatric reports include a 2½ year-old child who inadvertently received a dose of 20 mg naloxone for treatment of respiratory depression following overdose with diphenoxylate hydrochloride with atropine sulfate. The child responded well and recovered without adverse sequelae. There is also a report of a 4½ year-old child who received 11 doses during a 12-hour period, with no adverse sequelae.

Patient Management
Patients who experience a naloxone overdose should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date patient management information.

INDICATIONS AND USAGE

Naloxone hydrochloride injection is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol and cyclazocine. Naloxone hydrochloride is also indicated for the diagnosis of suspected or known acute opioid overdosage.

Naloxone may be useful as an adjunctive agent to increase blood pressure in the management of septic shock.

HOW SUPPLIED/STORAGE AND HANDLING

Naloxone Hydrochloride Injection, USP is available in the following package:

1 mg/mL, 2 mL single-dose prefilled syringes packaged in 10s (NDC 0641-6205-10)

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Store in carton until ready for use. **Protect from light.**

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 FDA at 1-800 FDA-1088 or www.fda.gov/medwatch. For Product Inquiry call 1-877-845-0689.

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