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Press Release

Hikma announces US launch of KLOXXADO™ (naloxone HCl) nasal spray 8mg

Important new option for reversing opioid overdoses

London, August 4, 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces the launch of KLOXXADO™ (naloxone HCl) nasal spray 8mg in the US. KLOXXADO™ was approved by the US Food and Drug Administration (FDA) in April 2021 for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients.

KLOXXADO™ contains twice as much naloxone per spray as Narcan® Nasal Spray 4mg in a ready-to-use nasal spray to reverse the effects of opioid overdose, providing an important new treatment option in addressing the opioid epidemic.

“Last year, fueled by the COVID-19 pandemic and the increasing prevalence of illicitly manufactured synthetic opioids, the number of Americans who died from a drug overdose rose by nearly 30% to more than 93,000, with approximately 75% of those deaths involving opioids,[1]” said Desiree Crevecoeur-MacPhail, Ph.D., Assistant Professor of Psychology, Chapman University and former Director of Quality Assurance and Utilization Management for the Los Angeles Centers for Alcohol and Drug Abuse. “There is an urgent need for additional resources to combat this epidemic, and KLOXXADO™ will provide an important new tool for those on the front lines of this fight.”

“Naloxone has long been recognized as an important, safe and effective treatment in the fight against opioid overdose,[2] but with the increasing prevalence of illicitly manufactured synthetic opioids, organizations including the CDC,[3] the American Medical Association[4] and others have noted that a higher dose of naloxone may be required to revive a patient due to their high potency,” said Daniel Buffington, PharmD, MBA, FAPhA, a clinical pharmacology specialist, President and Practice Director at Clinical Pharmacology Service and faculty member at the University of South Florida Colleges of Medicine and Pharmacy. “As a ready-to-use nasal spray that contains twice as much naloxone per spray than the current standard of care, KLOXXADO™ provides an important new treatment for those suffering from an opioid overdose.”

In a survey of community organizations to which Narcan® (naloxone HCl) nasal spray 4mg had been distributed, 34% of attempted reversals used two or more doses.[5] Additionally, a separate study published in 2019 found that the percent of overdose-related EMS calls in the US requiring multiple doses of naloxone during 2013-2016 had increased to 21%, representing a 43% increase over those four years.[6]

“We are committed to ensuring KLOXXADO™ is widely accessible to all who can benefit from it, including patients, friends, family members and the public health community,” said Brian Hoffmann, President, Hikma Generics. “As an experienced provider of addiction therapy treatments and a leading

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[1] https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
[2] https://emergency.cdc.gov/han/2020/han00438.asp
[3] https://emergency.cdc.gov/han/2020/han00438.asp
[4] https://apnews.com/article/opioids-business-health-government-and-politics-8263d4b147b3c6b104346b4ca31c28a3
[5] *2016 FDA Advisory Committee on the Most Appropriate Dose or Doses of Naloxone to Reverse the Effects of Life-threatening Opioid Overdose in the Community Settings, Page 149: https://www.fda.gov/media/100409/download*
[6] *2019 Geiger et. al., Substance Abuse: https://www.tandfonline.com/doi/abs/10.1080/08897077.2019.1640832*

producer of nasal sprays in the US, we are pleased to leverage our capabilities to deliver an important new tool in the fight against opioid overdose."

About Naloxone
Naloxone hydrochloride is an opioid antagonist that antagonises opioid effects by competing for the same receptor sites. Administration of naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation and hypotension. Naloxone has a long history of safe use as the standard of care for reversing opioid overdoses.[7]

KLOXXADO™ is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients. KLOXXADO™ is not a substitute for emergency medical care. KLOXXADO™ is intended for immediate administration as emergency therapy in settings where opioids may be present.

KLOXXADO™ is a trademark of Hikma Pharmaceuticals USA Inc.
NARCAN® is a registered trademark of ADAPT Pharma Operations Limited.

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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

[7] https://www.fda.gov/consumers/consumer-updates/having-naloxone-hand-can-save-life-during-opioid-overdose

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KLOXXADO™ (naloxone hydrochloride) Nasal Spray Important Safety Information

CONTRAINDICATIONS

- Hypersensitivity to naloxone hydrochloride or to any of the other ingredients in KLOXXADO™

WARNINGS AND PRECAUTIONS

- **Risk of Recurrent Respiratory and Central Nervous System Depression**

Seek emergency assistance immediately after administration of the first dose and keep the patient under continued surveillance. The duration of action of most opioids may exceed that of KLOXXADO, resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Administer additional doses as necessary if the patient is not adequately responding or responds and then relapses back into respiratory depression.

- **Risk of Limited Efficacy With Partial Agonists or Mixed Agonist/Antagonists**

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists may be incomplete. Larger or repeat doses of naloxone hydrochloride may be required.

- **Precipitation of Severe Opioid Withdrawal**

Use in patients who are opioid-dependent may precipitate opioid withdrawal characterized by body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness and increased blood pressure. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include convulsion, excessive crying and hyperactive reflexes. Monitor the patient for the development of the signs and symptoms of opioid withdrawal. For more information about management of opioid withdrawal, see the full Prescribing Information.

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated an acute withdrawal syndrome. In some patients, there was aggressive behavior upon abrupt reversal of an opioid overdose.

Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema and cardiac arrest. Death, coma and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. Monitor these patients closely in an appropriate healthcare setting.

ADVERSE REACTIONS

In two pharmacokinetic studies, a total of 47 healthy adult volunteers were exposed to a single dose of KLOXXADO, one spray in one nostril.

- The following adverse reactions were reported in two subjects each: abdominal pain, asthenia, dizziness, headache, nasal discomfort, and presyncope.

- Signs of nasal inflammation and nasal congestion were observed

- Serious adverse reactions reported: none

The following most frequently reported events (in decreasing frequency) have been identified primarily during post-approval use of naloxone hydrochloride: withdrawal syndrome, vomiting, nonresponsiveness to stimuli, drug ineffective, agitation, somnolence, and loss of consciousness.

USE IN SPECIFIC POPULATIONS

- **Pregnancy**

Naloxone may precipitate opioid withdrawal in the pregnant woman and fetus. Careful monitoring is needed until the fetus and mother are stabilized.

- **Infants**

In situations where the primary concern is for infants at risk for opioid overdose, consider the availability of alternate naloxone-containing products.

For more information, please see the full Prescribing Information and Patient Information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit https://www.fda.gov/medwatch or call 1-800-FDA-1088.

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