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Press Release

# Hikma launches Buprenorphine Hydrochloride Injection

**London, 4 May, 2020** – Hikma Pharmaceuticals PLC (Hikma, Group), the multinational generic pharmaceutical company, has launched Buprenorphine Hydrochloride Injection, 0.3mg/mL, the generic version of Buprenex®[1] in the United States through its US affiliate, Hikma Pharmaceuticals USA Inc.

According to IQVIA, US sales of Buprenorphine Hydrochloride Injection, 0.3mg/mL, were approximately $16 million in the 12 months ending February 2020.

Buprenorphine HCl Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses reserve Buprenorphine HCl Injection for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

Riad Mishlawi, President of Injectables said, “We are committed to providing doctors and patients with the medicines they need and are pleased to launch Buprenorphine HCl vials, an important medicine used for pain management.”

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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**About Hikma**
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1/stable Moody's and BB+/positive S&P)

[1] Buprenex® is a registered trademark of Reckitt Benckiser Healthcare (UK) Limited

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Hikma helps put better health within reach every day for millions of people in more than 50 countries 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 Buprenorphine Hydrochloride Injection, 0.3mg/mL:**

**BOXED WARNING**

**WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

**Addiction, Abuse, and Misuse**
**Buprenorphine HCl exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing buprenorphine HCl, and monitor all patients regularly for the development of these behaviors and conditions.**

**Life-Threatening Respiratory Depression**
**Serious, life-threatening, or fatal respiratory depression may occur with use of buprenorphine HCl. Monitor for respiratory depression, especially during initiation of buprenorphine HCl or following a dose increase**.

**Neonatal Opioid Withdrawal Syndrome**
**Prolonged use of buprenorphine HCl during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.**

**Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**
**Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death**.

- **Reserve concomitant prescribing of buprenorphine HCl and benzodiazepines or other CNS depressants for use 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.**

**CONTRAINDICATIONS**

Buprenorphine HCl Injection is contraindicated in patients with:

- Significant respiratory depression.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment.
- Known or suspected gastrointestinal obstruction, including paralytic ileus.
- Hypersensitivity to buprenorphine (e.g. anaphylaxis) or any other ingredient in Buprenorphine HCl Injection.

**WARNINGS & PRECAUTIONS**

- Buprenorphine HCl contains buprenorphine, a Schedule III controlled substance. As an opioid, buprenorphine HCl exposes users to the risks of addiction, abuse, and misuse.
- Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed buprenorphine HCl. Addiction can occur at recommended doses and if the drug is misused or abused. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression).
- Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing buprenorphine HCl. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug.
- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory depression and death. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of buprenorphine HCl, the risk is greatest during the initiation of therapy or following a dosage increase.
- Overestimating the buprenorphine HCl dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.
- Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion.
- Prolonged use of buprenorphine HCl during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts.
- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of buprenorphine HCl with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol).
- The use of buprenorphine HCl in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.
- Buprenorphine HCl-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of buprenorphine HCl.
- Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.
- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- Buprenorphine has been observed to prolong the QTc interval in some subjects participating in clinical trials. Avoid the use of buprenorphine HCl in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval.
- Buprenorphine HCl may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has

already been compromised by a reduced blood volume, or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics).

- In patients with circulatory shock, buprenorphine HCl may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of buprenorphine HCl in patients with circulatory shock.
- In patients who may be susceptible to the intracranial effects of $CO_2$ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), buprenorphine HCl may reduce respiratory drive, and the resultant $CO_2$ retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of buprenorphine HCl in patients with impaired consciousness or coma.
- Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in post-marketing experience. Buprenorphine HCl is contraindicated in patients with a history of hypersensitivity to buprenorphine.
- Buprenorphine HCl is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The buprenorphine in buprenorphine HCl injection may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase.
- The buprenorphine in buprenorphine HCl injection may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures in other clinical settings associated with seizures.
- Buprenorphine HCl may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
- Buprenorphine HCl should be administered with caution in the elderly, debilitated patients, in children and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism; adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.
- Because buprenorphine HCl is metabolized by the liver, the activity of buprenorphine HCl may be increased and/or extended in those individuals with impaired hepatic function or those receiving other agents known to decrease hepatic clearance.
- Buprenorphine HCl has been shown to increase intracholedochal pressure to a similar degree as other opioid analgesics, and thus should be administered with caution to patients with dysfunction of the biliary tract.

**Information for Patients**

- Inform patients that the use of buprenorphine HCl, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death. Instruct patients not to share buprenorphine HCl with others and to take steps to protect buprenorphine HCl from theft or misuse.
- Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting buprenorphine HCl or when the dosage is increased, and that it can occur even at recommended dosages. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.
- Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications.
- Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

**ADVERSE REACTIONS**

The following adverse reactions have been reported: sedation, nausea, dizziness/vertigo, sweating, hypotension, vomiting, miosis, headache, hypoventilation. The following adverse reactions were reported to have occurred in less than 1% of the patients: CNS effect (confusion, blurred vision, euphoria, weakness/fatigue, dry mouth, nervousness, depression, slurred speech paresthesia), cardiovascular

(hypertension, tachycardia, bradycardia), gastrointestinal (constipation), respiratory (dyspnea, cyanosis), dermatological (pruritus), ophthalmological (diplopia, visual abnormalities), miscellaneous (injection site reaction, urinary retention, dreaming, flushing/warmth, chills/cold, tinnitus, conjunctivitis, Wenckebach block, and psychosis) infrequent (malaise, hallucinations, depersonalization, coma, dyspepsia, flatulence, apnea, rash, amblyopia, tremor, and pallor), rare (loss of appetite, dysphoria/agitation, diarrhea, urticaria, and convulsions/lack of muscle coordination), and allergic reactions (acute and chronic hypersensitivity including rashes, hives, pruritus, bronchospasm, angioneurotic edema, and anaphylactic shock).

The following postmarketing adverse reactions have been reported: cases of serotonin syndrome (during concomitant use of opioids with serotonergic drugs), cases of adrenal insufficiency (more often following greater than one month of use), and cases of androgen deficiency (with chronic use of opioids).

## DRUG INTERACTIONS

**Benzodiazepines and Other Central Nervous System (CNS) Depressants**
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

**Inhibitors of CYP3A4**
The concomitant use of buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of buprenorphine HCl is achieved.

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the buprenorphine plasma concentration will decrease, potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine.

**CYP3A4 Inducers**
The concomitant use of buprenorphine and CYP3A4 inducers can decrease the plasma concentration of buprenorphine, potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to buprenorphine.

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase, which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression.

**Serotonergic Drugs**
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

**Monoamine Oxidase Inhibitors (MAOIs)**
MAOI interactions with opioids may manifest as serotonin syndrome opioid toxicity (e.g., respiratory depression, coma).

**Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics**
May reduce the analgesic effect of buprenorphine HCl and/or precipitate withdrawal symptoms.

**Muscle Relaxants**
Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

**Diuretics**

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

**Anticholinergic Drugs**
The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

**Antiretrovirals: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**
Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.

**Antiretrovirals: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delaviridine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.

**Antiretrovirals: Protease Inhibitors (PIs)**
Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**
**Risk Summary**
Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with buprenorphine HCl in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

**Clinical Considerations**
***Fetal/neonatal adverse reactions***
Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with buprenorphine HCl. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary.

***Labor and Delivery***
The safety of buprenorphine HCl given during labor and delivery has not been established. As with all opioids, use of buprenorphine prior to delivery may result in respiratory depression in the newborn. Closely monitor neonates for signs of respiratory depression. An opioid antagonist such as naloxone should be available for reversal of opioid induced respiratory depression in the neonate.

**Lactation**
Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in nursing mothers treated with buprenorphine HCl.

**Females and Males of Reproductive Potential**
**Infertility**
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

**Pediatric Use**
The safety and effectiveness of buprenorphine HCl have been established for children between 2 and 12 years of age. The available information provides reasonable evidence that buprenorphine HCl may be used safely in children ranging from 2 to 12 years of age, and that it is of similar effectiveness in children as in adults.

**Geriatric Use**
Elderly patients (aged 65 years or older) may have increased sensitivity to buprenorphine. In general, use caution when selecting a dosage for an elderly patient, 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.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid tolerant or when opioids were co-administered with other agents that depress respiration.

Buprenorphine 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**

Use the lowest effective dosage for the shortest duration consistent with individual patients treatment goals. Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with buprenorphine HCl and adjust the dosage accordingly.

Extra caution should be exercised with the intravenous route of administration, particularly with the initial dose. Occasionally, it may be necessary to administer single doses of up to 0.6 mg to adults depending on the severity of the pain and the response of the patient. This dose should only be given I.M. and only to adult patients who are not in a high-risk category. At this time, there are insufficient data to recommend single doses greater than 0.6 mg for long-term use.

**Safety and Handling**
Buprenorphine HCl is supplied in sealed vials and poses no known environmental risk to health care providers. Accidental dermal exposure should be treated by removal of any contaminated clothing and rinsing the affected area with water.

Buprenorphine HCl is a potent opioid, and like all drugs of this class has been associated with abuse and dependence among healthcare providers. To control the risk of diversion, it is recommended that measures appropriate to the health care setting be taken to provide rigid accounting, control of wastage, and restriction of access.

**Drug Abuse and Dependence**

**Abuse**
Buprenorphine HCl Injection contains buprenorphine, a Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. Buprenorphine HCl can be abused and is subject to misuse, addiction and criminal diversion. All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

**Risks Specific to Abuse of Buprenorphine HCl**
Abuse of buprenorphine HCl poses a risk of overdose and death. The risk is increased with concurrent abuse of buprenorphine HCl with alcohol and other central nervous system depressants. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

**Dependence**
Both tolerance and physical dependence can develop during chronic therapy. Buprenorphine HCl should not be abruptly discontinued. If buprenorphine HCl is abruptly discontinued in a physically dependent patient, an abstinence a withdrawal syndrome may occur. Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy.

**Overdosage**

**Clinical Presentation**
Acute overdose with buprenorphine HCl can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

**Treatment of Overdose**
In the case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated.

Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to buprenorphine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to buprenorphine overdose.

In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered.

**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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