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Press Release

Hikma launches Ropivacaine HCl Injection, USP for anaesthesia and acute pain management

London, 10 December, 2020 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Ropivacaine HCl Injection, USP 40mg/20mL in the US, through its US affiliate, Hikma Pharmaceuticals USA Inc.

Ropivacaine HCl Injection, USP is indicated for the production of local or regional anesthesia for surgery and for acute pain management. For surgical anesthesia it is used as part of the epidural during caesarean section, to induce major nerve block or is used in local infiltration. In acute pain management, it is used as part of continuous epidural infusion or can be provided intermittently, for example during postoperative or labor or local infiltration.

According to IQVIA, US sales of Ropivacaine HCl Injection, USP 40mg/20mL were approximately $4 million in the 12 months ending September 2020.

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.

- ENDS -

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1/stable Moody's and BBB-/stable S&P)

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,

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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 Ropivacaine HCl Injection, USP 40mg/20mL:

CONTRAINDICATIONS

Ropivacaine Hydrochloride Injection is contraindicated in patients with a known hypersensitivity to ropivacaine or to any local anesthetic agent of the amide type.

WARNINGS & PRECAUTIONS

- In performing Ropivacaine Hydrochloride Injection blocks, unintended intravenous injection is possible and may result in cardiac arrhythmia or cardiac arrest.
- Ropivacaine Hydrochloride Injection should be administered in incremental doses. It is not recommended for emergency situations, where a fast onset of surgical anesthesia is necessary.
- Prior to receiving major blocks the general condition of the patient should be optimized and the patient should have an IV line inserted. All necessary precautions should be taken to avoid intravascular injection.
- Solutions of Ropivacaine Hydrochloride Injection should not be used for the production of obstetrical paracervical block anesthesia, retrobulbar block, or spinal anesthesia (subarachnoid block) due to insufficient data to support such use. Intravenous regional anesthesia (bier block) should not be performed due to a lack of clinical experience and the risk of attaining toxic blood levels of ropivacaine.
- Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions.
- Ropivacaine Hydrochloride Injection should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.
- Patients treated with class III antiarrhythmic drugs (e.g., amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.
- Cases of methemoglobinemia have been reported in association with local anesthetic use.
- Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use. Injections should be made slowly and incrementally, with frequent aspirations before and during the injection to avoid intravascular injection.
- During epidural administration, Ropivacaine Hydrochloride Injection should be administered in incremental doses of 3 to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection.
- Ropivacaine plasma concentrations may approach the threshold for central nervous system toxicity after the administration of 300 mg of ropivacaine for brachial plexus block. Caution should be exercised when using the 300 mg dose.
- Major peripheral nerve blocks may result in the administration of a large volume of local anesthetic in highly vascularized areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations.
- Small doses of local anesthetics injected into the head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses.
- The use of Ropivacaine Hydrochloride Injection in retrobulbar blocks for ophthalmic surgery has not been studied. Until appropriate experience is gained, the use of Ropivacaine Hydrochloride Injection for such surgery is not recommended.

Information for Patients

- When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity in the anesthetized part of the body following proper administration of lumbar epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the Ropivacaine Hydrochloride Injection package insert.
- Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

ADVERSE REACTIONS

Reactions to ropivacaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs may be associated with excessive plasma levels, which may be due to overdosage, unintentional intravascular injection or slow metabolic degradation.

Incidence ≥ 5%
For the indications of epidural administration in surgery, cesarean section, postoperative pain management, peripheral nerve block, and local infiltration, the following treatment-emergent adverse events were reported with an incidence of ≥5% in all clinical studies (N=3988): hypotension (37%), nausea (24.8%), vomiting (11.6%), bradycardia (9.3%), fever (9.2%), pain (8%), postoperative complications (7.1%), anemia (6.1%), paresthesia (5.6%), headache (5.1%), pruritus (5.1%), and back pain (5%).

Incidence 1 to 5%
Urinary retention, dizziness, rigors, hypertension, tachycardia, anxiety, oliguria, hypoesthesia, chest pain, hypokalemia, dyspnea, cramps, and urinary tract infection.

Incidence in Controlled Clinical Trials
The reported adverse events are derived from controlled clinical studies with Ropivacaine Hydrochloride Injection (concentrations ranged from 0.125% to 1% for Ropivacaine Hydrochloride Injection and 0.25% to 0.75% for bupivacaine) in the U.S. and other countries involving 3,094 patients. Refer to the package insert for Table 3A and 3B which list adverse events (number and percentage) that occurred in at least 1% of Ropivacaine Hydrochloride Injection-treated patients in these studies. The majority of patients receiving concentrations higher than 5 mg/mL (0.5%) were treated with Ropivacaine Hydrochloride Injection.

Incidence < 1%
The following adverse events were reported during the Ropivacaine Hydrochloride Injection clinical program in more than one patient (N=3988), occurred at an overall incidence of <1%, and were considered relevant:

Application Site Reactions - injection site pain
Cardiovascular System - vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities
Female Reproductive - poor progression of labor, uterine atony
Gastrointestinal System - fecal incontinence, tenesmus, neonatal vomiting
General and Other Disorders - hypothermia, malaise, asthenia, accident and/or injury
Hearing and Vestibular - tinnitus, hearing abnormalities
Heart Rate and Rhythm - extrasystoles, non-specific arrhythmias, atrial fibrillation
Liver and Biliary System - jaundice
Metabolic Disorders - hypomagnesemia
Musculoskeletal System - myalgia
Myo/Endo/Pericardium - ST segment changes, myocardial infarction

Nervous System - tremor, Horner's syndrome, paresis, dyskinesia, neuropathy, vertigo, coma, convulsion, hypokinesia, hypotonia, ptosis, stupor
Psychiatric Disorders - agitation, confusion, somnolence, nervousness, amnesia, hallucination, emotional lability, insomnia, nightmares
Respiratory System - bronchospasm, coughing
Skin Disorders - rash, urticaria
Urinary System Disorders - urinary incontinence, micturition disorder
Vascular - deep vein thrombosis, phlebitis, pulmonary embolism
Vision - vision abnormalities

Refer to the package insert for the most common adverse events compared between different concentrations of Ropivacaine Hydrochloride Injection and bupivacaine, the number of patients experiencing hypotension is displayed by patient age, drug and concentration, and the common adverse events broken down by gender.

Also refer to the package insert for description of Systemic Reactions, Neurologic Reactions, Cardiovascular System Reactions, and Allergic Reactions.

DRUG INTERACTIONS

Specific trials studying the interaction between ropivacaine and class III antiarrhythmic drugs (e.g., amiodarone) have not been performed, but caution is advised.

Ropivacaine Hydrochloride Injection should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive. Cytochrome P4501A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. *In vivo*, the plasma clearance of ropivacaine was reduced by 70% during coadministration of fluvoxamine (25 mg bid for 2 days), a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of cytochrome P4501A2, such as fluvoxamine, given concomitantly during administration of Ropivacaine Hydrochloride Injection, can interact with Ropivacaine Hydrochloride Injection leading to increased ropivacaine plasma levels. Caution should be exercised when CYP1A2 inhibitors are coadministered. Possible interactions with drugs known to be metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur. Coadministration of a selective and potent inhibitor of CYP3A4, ketoconazole (100 mg bid for 2 days with ropivacaine infusion administered 1 hour after ketoconazole) caused a 15% reduction in *in vivo* plasma clearance of ropivacaine.

Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to other drugs, which could include other local anesthetics. Refer to the package insert for the table of examples of drugs associated with methemoglobinemia.

USE IN SPECIFIC POPULATIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals of most local anesthetics, including ropivacaine, to evaluate the carcinogenic potential have not been conducted.

Weak mutagenic activity was seen in the mouse lymphoma test. Mutagenicity was not noted in the other assays, demonstrating that the weak signs of *in vitro* activity in the mouse lymphoma test were not manifest under diverse *in vivo* conditions. Studies performed with ropivacaine in rats did not demonstrate an effect on fertility or general reproductive performance over 2 generations.

Pregnancy
Reproduction toxicity studies have been performed in pregnant New Zealand white rabbits and Sprague-Dawley rats. No teratogenic effects were observed in rats and rabbits at the highest doses tested. There

were no treatment-related effects on late fetal development, parturition, lactation, neonatal viability, or growth of the offspring.

In another study with rats, the males were dosed daily for 9 weeks before mating and during mating. The females were dosed daily for 2 weeks before mating and then during the mating, pregnancy, and lactation, up to day 42 post coitus. At 23 mg/kg/day, an increased loss of pups was observed during the first 3 days postpartum. The effect was considered secondary to impaired maternal care due to maternal toxicity.

There are no adequate or well-controlled studies in pregnant women of the effects of Ropivacaine Hydrochloride Injection on the developing fetus. Ropivacaine Hydrochloride Injection should only be used during pregnancy if the benefits outweigh the risk.

Teratogenicity studies in rats and rabbits did not show evidence of any adverse effects on organogenesis or early fetal development in rats (26 mg/kg sc) or rabbits (13 mg/kg). The doses used were approximately equal to total daily dose based on body surface area. There were no treatment-related effects on late fetal development, parturition, lactation, neonatal viability, or growth of the offspring in 2 perinatal and postnatal studies in rats, at dose levels equivalent to the maximum recommended human dose based on body surface area. In another study at 23 mg/kg, an increased pup loss was seen during the first 3 days postpartum, which was considered secondary to impaired maternal care due to maternal toxicity.

Labor and Delivery
Local anesthetics, including ropivacaine, rapidly cross the placenta, and when used for epidural block can cause varying degrees of maternal, fetal and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia with Ropivacaine Hydrochloride Injection for obstetrical pain relief. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable. Epidural anesthesia has been reported to prolong the second stage of labor by removing the patient's reflex urge to bear down or by interfering with motor function. Spontaneous vertex delivery occurred more frequently in patients receiving Ropivacaine Hydrochloride Injection than in those receiving bupivacaine.

Nursing Mothers
Some local anesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a nursing woman. The excretion of ropivacaine or its metabolites in human milk has not been studied. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration in humans is of the same order, the total Ropivacaine Hydrochloride Injection dose to which the baby is exposed by breast-feeding is far lower than by exposure *in utero* in pregnant women at term.

Pediatric Use
The safety and efficacy of Ropivacaine Hydrochloride Injection in pediatric patients have not been established.

Geriatric Use
Of the 2,978 subjects that were administered Ropivacaine Hydrochloride Injection in 71 controlled and uncontrolled clinical studies, 803 patients (27%) were 65 years of age or older which includes 127 patients (4%) 75 years of age and over. Ropivacaine Hydrochloride Injection was found to be safe and effective in the patients in these studies. Clinical data in one published article indicate that differences in

various pharmacodynamic measures were observed with increasing age. In one study, the upper level of analgesia increased with age, the maximum decrease of mean arterial pressure (MAP) declined with age during the first hour after epidural administration, and the intensity of motor blockade increased with age.

This drug and its metabolites are known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased hepatic, renal, or cardiac function, as well as concomitant disease. Therefore, care should be taken in dose selection, starting at the low end of the dosage range, and it may be useful to monitor renal function.

DOSAGE AND ADMINISTRATION

The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered.

There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. Ropivacaine Hydrochloride Injection is not approved for this use.

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anesthesia is frequently indicated in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

Refer to the package insert for dosage recommendations based on Surgical Anesthesia, Labor Pain Management, and Postoperative Pain Management.

Overdosage

Acute emergencies from local anesthetics are generally related to high plasma levels encountered, or large doses administered, during therapeutic use of local anesthetics or to unintended subarachnoid or intravascular injection of local anesthetic solution.

Therapy with Ropivacaine Hydrochloride Injection should be discontinued at the first sign of toxicity. No specific information is available for the treatment of toxicity with Ropivacaine Hydrochloride Injection; therefore, treatment should be symptomatic and supportive.

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.

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