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Press Release

Hikma launches Labetalol Hydrochloride Injection in ready-to-use bags

London, 1 June 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces it has launched Labetalol Hydrochloride Injection in ready-to-use bags through its US affiliate, Hikma Pharmaceuticals USA Inc. The company has launched Labetalol Hydrochloride (Labetalol HCl) 1mg/mL in 200mL Dextrose Injection and 100mL, 200mL and 300mL in Sodium Chloride Injection.

Labetalol HCl in Sodium Chloride Injection and Labetalol HCl in Dextrose Injection are indicated for severe hypertension, to lower blood pressure.

According to IQVIA, US sales of Labetalol HCl Injection, 100mg/20mL and 200mg/40mL vial were approximately $6 million in the 12 months ending March 2021.

“We are proud to introduce the first generic Labetalol HCl Injection in ready-to-use bags, a new therapeutic entity used to treat severe hypertension,” said Riad Mishlawi, President of Injectables. “Ready-to-use formulations improve the speed and safety of patient care and help hospitals, pharmacists, doctors and nurses treat patients more easily and with reduced risk of medication preparation error. This is another example of how Hikma is using its capabilities as a leading generic pharmaceutical company to expand its portfolio of essential medicines and introduce delivery systems that serve the growing needs of US medical professionals and their patients.”

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 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 Labetalol Hydrochloride Injection in Sodium Chloride and Dextrose bags:

CONTRAINDICATIONS

Labetalol HCl in Sodium Chloride Injection and Labetalol HCl in Dextrose Injection are contraindicated in patients with:

- Bronchial asthma or obstructive airway disease
- Severe sinus bradycardia
- Heart block greater than first degree
- Cardiogenic shock
- IV administration of non-dihydropyridine calcium-channel antagonists (e.g., verapamil)
- Hypersensitivity reactions, including anaphylaxis, to labetalol

WARNINGS & PRECAUTIONS

- **Hypotension –** symptomatic postural hypotension (incidence, 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving labetalol HCl injection. Before permitting any ambulation, establish patient's ability to tolerate an upright position and observe the patient at the time of first ambulation.
- **Bradycardia –** bradycardia, including sinus pause, heart block, severe bradycardia, and cardiac arrest have occurred with the use of beta blockers. Monitor heart rate and rhythm in patients receiving labetalol hydrochloride injection.
- **Cardiac Failure –** sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Betablockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Avoid labetalol HCl injection in patients with overt congestive heart failure. If patients develop signs or symptoms of heart failure during administration, discontinue labetalol and treat appropriately.
- **Ischemic Heart Disease –** abrupt cessation of therapy with beta blocking agents in patients with coronary artery disease, can cause exacerbations of angina pectoris and, in some cases, myocardial infarction has been reported. Therefore, even in the absence of overt angina pectoris, after the discontinuation of labetalol HCl injection observe patients for development or worsening of angina. If patient experiences angina or angina markedly worsens or if acute coronary insufficiency develops, promptly reinstitute labetalol HCl injection and manage as unstable angina.
- **Reactive Airway Disease and Nonallergic Bronchospasm –** patients with reactive airways disease should, in general, not receive beta blockers. Labetalol HCl at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease. In the event of bronchospasm, stop the infusion immediately, and treat as appropriate.
- **Use in Patients with Diabetes Mellitus and Hypoglycemia –** in patients with hypoglycemia, or diabetic patients (especially those with labile diabetes) who are receiving insulin or other hypoglycemic agents, beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be masked. Concomitant use of beta-blockers and antidiabetic agents can enhance the glucose-lowering effect of antidiabetic agents. Monitor glycemic levels in patients receiving labetalol HCl injection.
- **Use in Patients with Pheochromocytoma –** intravenous labetalol has been shown to lower blood pressure and relieve symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, monitor blood pressure when administering intravenous labetalol HCl to patients with pheochromocytoma.
- **Hepatic Injury –** severe hepatocellular injury occurs rarely with labetalol therapy. The hepatic injury is usually reversible, but hepatic necrosis and death have been reported. If the patient develops signs or symptoms of liver injury, institute appropriate treatment and investigate the probable cause. Do not restart labetalol in patients without another explanation for the observed liver injury.
- **Use in Patients at Risk of Severe Acute Hypersensitivity Reactions –** patients at risk of anaphylactic reactions may be more reactive to allergen exposure (accidental, diagnostic, or therapeutic). Patients using beta-blockers may be unresponsive to the usual doses of epinephrine used to treat anaphylactic or anaphylactoid reactions. Avoid labetalol HCl injection in patients at high risk of anaphylactic reactions.

- **Intraoperative Floppy Iris Syndrome (IFIS) –** IFIS has been observed during cataract surgery in some patients treated with alpha-1 blockers (labetalol is an alpha/beta blocker). This variant of small pupil syndrome is characterized by the combination of flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. Inform the patient's ophthalmologist to be prepared for possible modifications to the surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling: Hypotension, Bradycardia, Depression of myocardial contractility in patients with overt congestive heart failure, Aggravation of angina, Significant decline in cardiac output following coronary bypass, Bronchospasm in patients with reactive airway disease, Paradoxical hypertensive responses in patients with pheochromocytoma, Hepatic injury, and Acute hypersensitivity reaction.

Clinical Trial Experience
Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol withdrawal. Symptomatic postural hypotension (incidence, 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving labetalol HCl. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with labetalol HCl with the incidence as noted:

Central and Peripheral Nervous Systems
Dizziness in 9%
Paresthesia, most frequently described as tingling of the scalp/skin in 7%

Gastrointestinal System
Nausea in 13%
Vomiting in 4%

Metabolic Disorders
Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8%; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Respiratory System
Bronchospasm

In addition, a number of other less common adverse events have been reported:

Cardiovascular
Hypotension, and rarely, syncope, bradycardia, heart block.

Liver and Biliary System
Hepatic necrosis, hepatitis, cholestatic jaundice, elevated liver function tests.

Hypersensitivity
Rare reports of hypersensitivity (e.g., rash, urticaria, pruritus, angioedema, dyspnea) and anaphylactoid reactions. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.

Clinical Laboratory Tests
Among patients dosed with labetalol tablets, there have been reversible increases of serum transaminases in 4% of patients tested and, more rarely, reversible increases in blood urea.

DRUG INTERACTIONS

Bronchodilators
Labetalol HCl antagonizes the bronchodilatory effect of beta-receptor agonist drugs; therefore, labetalol HCl is contraindicated in patients with bronchial asthma.

Anesthesia
Synergism has been shown between halothane anesthesia and intravenously administered labetalol. During controlled hypotensive anesthesia using labetalol in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure.

Nitroglycerin
Coadministration of labetalol HCl and nitroglycerine will have an additive effect in lowering blood pressure. Additionally, labetalol HCl blunts the reflex tachycardia produced by nitroglycerin. If labetalol is used in patients with angina pectoris on nitroglycerine, monitor patients' blood pressure and adjust labetalol HCl injection dose as needed. In these patients, avoid initiating labetalol HCl tablets.

Calcium Channel Blockers
Coadministration of labetalol HCl with non-dihydropyrindine calcium-channel antagonists (e.g., verapamil) is contraindicated. Avoid the use of labetalol in patients receiving calcium-channel antagonists.

Drug/Laboratory Test Interactions
The presence of labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metanephrine, normetanephrine, and vanillylmandelic acid (VMA) when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol, a specific method, such as a high-performance liquid chromatographic assay with solid phase extraction should be employed in determining levels of catecholamines.

Labetalol has also been reported to produce a false-positive test for amphetamine when screening urine for the presence of drugs using the commercially available assay methods. When patients being treated with labetalol have a positive urine test for amphetamine using these techniques, confirm using more specific methods, such as a gas chromatographic-mass spectrometer technique.

USE IN SPECIFIC POPULATIONS

Pregnancy
The extensive experience with use of labetalol in pregnant women, based on published interventional and observational studies, has not identified a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Untreated hypertension during pregnancy can lead to serious adverse outcomes for the mother and the fetus.

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Labetalol crosses the placenta. Neonates born to mothers who are receiving labetalol during pregnancy, may be at risk for hypotension, bradycardia, hypoglycemia, and respiratory depression. Neonates should be monitored for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and manage accordingly.

Lactation
Available published data report the presence of labetalol in human milk at low levels. There are no data on the effects on the breastfed infant and on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for labetalol and any potential adverse effects on the breastfed infant from labetalol or from the underlying maternal condition.

Females and Males of Reproductive Potential
Based on the published literature, beta blockers, including labetalol, may cause erectile dysfunction and inhibit sperm motility.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Some pharmacokinetic studies indicate that the elimination of labetalol is reduced in elderly patients. Geriatric patients treated with labetalol could initiate therapy at the currently recommended dose of 2 mg/minute by continuous intravenous infusion; however, lower maintenance dosages are generally required for elderly patients than nonelderly patients. Monitor blood pressure and adjust the dosage and duration of infusion accordingly until the desired response is obtained.

DOSAGE AND ADMINISTRATION

General Information
Labetalol HCl in Sodium Chloride Injection and Labetalol HCl in Dextrose Injection are ready-to-use solutions and do not require further dilution. Check for leaks by squeezing the bag firmly. If leaks are found, discard solution, as sterility may be impaired. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the content of the bag unless the solution is clear (colorless to light yellow) and the seal is intact. Do not add any additional medications to the bag.

Once infusion has started, discard any remaining at 24 hours.

Recommended Dosage
The recommended initial dosage is 2 mg/minute by continuous intravenous infusion, which is 2 mL/minute. Monitor blood pressure and adjust the dosage and duration of infusion accordingly. Once supine diastolic blood pressure has begun to rise, transition to oral labetalol HCl.

The usual intravenous dose is in the range of 50 to 200 mg. A total dose of up to 300 mg may be required in some patients, but the safety of doses above 300 mg has not been established.

OVERDOSAGE

Signs and Symptoms of Overdose
Overdosage with labetalol HCl causes excessive hypotension that is posture sensitive and, sometimes, excessive bradycardia. Patients should be placed supine and their legs raised if necessary, to improve the blood supply to the brain. Treat symptoms of overdose with standard supportive care. If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) may be useful for removal of the drug shortly after ingestion.

Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol from the general circulation (<1%).

The oral LD50 value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD50 in these species is 50 to 60 mg/kg.

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

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