Press Release

Hikma launches Labetalol Hydrochloride Injection, USP in prefilled syringe

London, 22 March 2023 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Labetalol Hydrochloride (Labetalol HCl) Injection, USP, in prefilled syringe (PFS) form. The 10mg/2mL PFS has been launched in the US and is used in hospitals for severe hypertension, to lower blood pressure.

Hikma is introducing the first 2mL presentation to the market and we are pleased to expand our portfolio with this launch, broadening the choice of medicines available to hospitals.

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 130 products.

- 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 North America, 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 8,800 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

[1] Source: IQVIA MAT December 2022, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

hikma.

This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

Important Safety Information for Labetalol HCl Injection, USP, 10mg/2mL:

CONTRAINDICATIONS

Labetalol Hydrochloride Injection is 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 *[see Warnings and Precautions (5.1)]*
- Bradycardia *[see Warnings and Precautions (5.2)]*
- Depression of myocardial contractility in patients with overt congestive heart failure *[see Warnings and Precautions (5.3)]*
- Aggravation of angina *[see Warnings and Precautions (5.4)]*
- Significant decline in cardiac output following coronary bypass *[see Warnings and Precautions (5.3)]*
- Bronchospasm in patients with reactive airway disease *[see Warnings and Precautions (5.5)]*
- Paradoxical hypertensive responses in patients with pheochromocytoma *[see Warnings and Precautions (5.7)]*
- Hepatic injury *[see Warnings and Precautions (5.8)]*
- Acute hypersensitivity reaction *[see Warnings and Precautions (5.9)]*

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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
Inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit.

Labetalol HCl Injection, USP, in a prefilled syringe is a ready-to-use solution that does not require further dilution. The prefilled syringe is intended for single dose. Discard any unused portion.

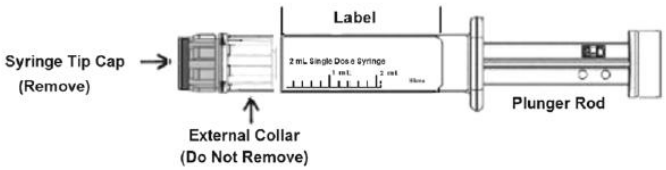
Recommended Dosage
Choose intravenous administration by slow continuous infusion or repeated injection. The usual intravenous dose is in the range of 50 to 200 mg, but the safety of doses above 300 mg has not been established. Once supine diastolic blood pressure has begun to rise, transition to oral labetalol HCl.

Slow Continuous Infusion: Initiate at 2 mg/minute. Monitor blood pressure and adjust the dosage and duration of infusion accordingly.

Repeated Intravenous Injection: Administer 0.25 mg/kg up to 20 mg over 2 minutes. Administer 20 to 80 mg over 2 minutes at 10-minute intervals until a desired supine blood pressure is achieved. The maximum effect usually occurs within 5 minutes of each injection.

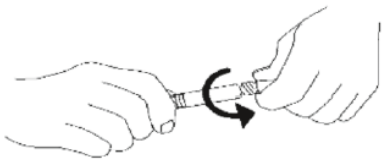
Instructions for Use of Labetalol HCl Injection Prefilled Syringe
CAUTION: Glass syringes may malfunction, break or clog when connected to some Needleless Luer Access Devices (NLADs) and needles. The external collar must remain attached to the syringe *(See Figure 1)*. Spontaneous disconnection of this glass syringe from needles and NLADs with leakage of drug product may occur. Assure that the needle or NLAD is securely attached before beginning the injection. Inspect the glass syringe-needle or glass syringe –NLAD connection before and during drug administration.

Figure 1



1. Push plunger rod slightly to break the stopper loose while tip cap is still on.
2. Remove tip cap by twisting it off. (See Figure 2)

Figure 2



3. Connect the syringe to an appropriate injection connection.

4. Depress plunger rod to deliver the required dose.

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

INDICATIONS AND USAGE

Labetalol HCl Injection is indicated in severe hypertension, to lower blood pressure.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Labetalol Hydrochloride Injection, USP is a preservative-free, clear, colorless to light yellow sterile solution that is available in a single-dose prefilled syringe. It is available in the following presentations:

Product	Strength	Package	NDC Number
Labetalol Hydrochloride Injection, USP	10 mg/2 mL (5 mg/mL) preservative-free	1 single-dose prefilled syringe	0641-6252-01
		Carton of 10 prefilled syringes	0641-6252-10

Storage

Store at 20° to 25°C (68° to 77°F) with excursions permitted between 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature]. DO NOT FREEZE. PROTECT FROM LIGHT.

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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