For the use of a Register Medical Practitioner or a Hospital or a Laboratory only

Labetalol Hydrochloride Injection IP

AMERICAN
Labecanol-XL
Injection

COMPOSITION:
Each ml contains:
Labetalol Hydrochloride IP 5 mg
Water For Injection IP q.s.

Description: Labetalol HCl Injection is a clear, colorless to light yellow aqueous sterile isotonic solution for intravenous injection. It has pH range of 3.0 to 4.0.

CLINICAL PHARMACOLOGY:
Pharmacodynamic Properites: Labetalol lowers blood pressure by blocking peripheral arteriolar α-adrenoreceptors, thus reducing peripheral resistance, and by concurrent ß-blockade, protects the heart from reflex sympathetic drive that would otherwise occur. Cardiac output is not significantly reduced at rest or after moderate exercise. Increases in systolic blood pressure during exercise are reduced but corresponding change in diastolic pressure are essentially normal. All these effect would be expected to benefit hypertensive patients. Labetalol does not adversely affect renal function and particularly suitable for use in hypertensive patients with renal disease.
Pharmacokinetic Properties: The plasma half-life of labetalol is about four hours. About 50% of labetalol in the blood is protein bound. Labetalol is metabolised mainly through conjugation to inactive glucuronide metabolised. These are excreated both in the urine and via the bile, into the faeces. Only negligible amounts of labetalol cross the blood brain barrier in animal studies.

THERAPEUTIC INDICATIONS:
Severe hypertension when rapid control of blood pressure is essential.
Anesthesia when a hypertensive technique is indicated.
Hypertensive episodes following acute myocardial infraction.

Dosage & Administration: Labecanol-XL Injection is intended for IV use in hospitalized patients. Dosage must be individualized depending upon the severity of hypertension and the response of the patient during dosing. Patients should always be kept in a supine position during the period of IV drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position should be established before permitting any ambulation, such as using toilet facilities. Either of two methods of administration of labetalol hydrochloride injection may be used: a) repeated IV injection, or b) slow continuous infusion. **Repeated Intravenous Injection:** Initially, Labecanol-XL Injection should be given in a 20 mg dose (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow IV injection over a 2-minute period. Immediately before the injection and at 5 and 10 minutes after injection, supine blood pressure should be measured to evaluate response. Additional Injections of 40 or 80 mg can be given at 10-minute intervals until a desired supine blood pressure is achieved or a total of 300 mg of Labecanol-XL has been injected. The maximum effect usually occurs within 5 minutes of each injection.

Slow Continuous Infusion: Labecanol-XL Injection is prepared for continuous IV infusion by diluting the vial contents with commonly used IV fluids (see below). Examples of two methods of preparing the infusion solution are: Add 40ml of Labecanol-XL Injection to 160ml of a commonly used IV fluid such that the resultant 200ml of solution contains 200 mg of Labecanol-XL 1 mg/ml. The diluted solution should be administered at a rate of 2 ml/min to deliver 2 mg/min. Alternatively, add 40 ml of Labecanol-XL Injection to 250 ml of a commonly used IV fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2mg/3 ml. The diluted solution should be administered at a rate of 3 ml/min to deliver approximately 2mg/min. The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion, the diluted solution can be infused using a controlled administration mechanism,e.g., graduated burette or mechanically driven infusion pump. Since the half-life of labetalol is 5 to 8 hours, steady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should then be stopped and oral labetalol HCl started (see below). The effective IV dose is usually in the range of 50 to 200 mg. A total dose of up to 300 mg may be required in some patients.

CONTRAINDICATIONS: Labecanol-XL Injection is contraindicated in bronchial asthma, over cardiac failure, greater-than-first-degree heart block, cardiogenic shock, severe bradycardia, other conditions associated with severe and prolonged hypotension, and in patients with a history of hypersensitivity to any component of the product. Beta-blockers, even those with apparent cardioselectivity, should not be used obstructive airway disease including asthma.

WARNING & PRECAUTIONS:
Impaired Hepatic Function: Labecanol-XL Injection should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.**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 Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.**Intraoperative Floppy Iris Syndrome (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 a 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. The patient's ophthalmologist should be prepared for possible modifications to the surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be benefit of stopping alpha-, blocker therapy prior to cataract surgery. **Following Coronary Artery Bypass Surgery:** In one uncontrolled study, patients with low cardiac indices and elevated systemic vascular resistance following intravenous labetalol experienced significant declines in cardiac output with little change in systemic vascular resistance. One of these patients developed hypotension following labetalol treatment. Therefore, use of labetalol should be avoided in such patients.

High Dose Labetalol: Administration of up to 3 g/d as an infusion for up to 2 to 3 days has been anecdotally reported several patients have experienced hypotension or bradycardia.

Jaundice or Hepatic Dysfunction: Severe hepatocellular Injury, confirmed by rechallenge in at least one case, occurs rarely with labetalol therapy. The hepatic injury is usually reversible, but hepatic necrosis and death have been reported. Injury has occurred after both short- and long-term treatment and may be slowly progressive despite minimal symptomatology. Similar hepatic events have been reported with a related compound, dilevalol HCl, including two deaths. Dilevalol HCl is one of the four isomers of labetalol HCl. Thus, for patients taking labetalol, periodic determination of suitable hepatic laboratory tests would be appropriate. Laboratory testing should be done at the very first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has laboratory evidence of liver injury or jaundice, labetalol should be stopped and not restarted.

DRUG INTERACTIONS: Since Labecanol-XL Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration. In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with Labecanol-XL alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded. Drugs possessing beta- blocking properties can blunt the bronchodilator effect of beta receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required. Cimetidine has been shown to increase the bioavailability of Labecanol-XL administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of Labecanol-XL special care should be used in establishing the dose required for blood pressure control in such patients. Synergism has been shown between halothane anesthesia and Intravenously administered Labecanol-XL During controlled hypotensive anesthesia using Labecanol-XL 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. The anesthesiologist should be informed when a patient is receiving Labecanol-XL
Labecanol-XL bunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If Labecanol-XL used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur. Care should be taken if Labecanol-XL is used concomitantly with calcium antagonists of the verapamil type.

Pregnancy & lactation: Teratogenic Effects - Pregnancy Category C: Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at IV doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labecanol-XL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

ADVERSE REACTIONS:
Immune system disorders
Common: Hypersensitivity
Hypersensitivity reactions reported include rash, pruritus, dyspnoea and very rarely drug fever or angioedema.

Cardiac disorders:
Rare: Bradycardia
Very rare: Heart Block

Vascular disorders:
Common: Postural hypotension

Very rare: Exacerbation of the symptoms of Raynaud's syndrome
Pronounced postural hypotension may occur if patient's are allowed to assume the upright position within three hours of receiving Labecanol-XL injection

Respiratory thoratic and mediastinal disorders:
Common: Nasal congestion

Hepatobilary disorders:
Common Raised liver function tests

Very rare: Hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis.
The signs and symptoms of hepatobiliary disorders are usually reversible on withdrawal of the drug.

OVERDOSAGE: 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. If over dosage 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. The following additional measures should be employed if necessary: Excessive bradycardia-administer atropine or epinephrine. Cardiac failure-administer a digitalis glycoside and a diuretic. Dopamine or dobutamine may also be useful. Hypotension administer vasopressors, e.g., norepinephrine. There is pharmacologic evidence that norepinephrine may be the drug of choice. Bronchospasm-administer epinephrine and/or an aerosolized beta 2-agonist. Seizures-administer diazepam.

Shelf life: 24 months

Storage conditions: Store below 25°C.
Protected from light.
Do not freeze.
PRESENTATION: 20 ml Ampoule.

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