of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, therapy with labetalol should be withdrawn (gradually if possible). Ischemic Heart Disease Angina pectoris has not been reported upon labetalol discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of labetalol is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, labetalol administration should be

paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol to patients with radoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol to patients with pheochromocytoma. Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia, it may therefore be necessary to adjust the dose of anti-diabetic drugs. Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protected severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol alpha-adrenergic activity has not been evaluated in this setting. Several deaths have occurred when labetalol HCl injection was used during surgery (including when used in cases to control bleeding). A synergism between labetalol and halothane anesthesia has been shown. Rapid Decreases of Blood Pressure Caution must be observed when reducing severely elevated blood pressure. A number of adverse reactions, including cerebral infarction, optic nerve infarction, angina, and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

PRECAUTIONS: General: Impaired Hepatic Function may diminish metabolism of labetalol. 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 HCl treatment. Therefore, use of labetalol should be avoided in such patients. High-Dose Labetalol HCl Administration of up to 3 g per day as an infusion for up to 2 to 3 days has been anecdotally reported; several patients experienced hypotension or bradycardia. 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. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation. Jaundice or Hepatic Dysfunction. Information for Patients: The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) labetalol HCl injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.. Drug Interactions: Since labetalol HCl 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. 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 labetalol administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol, 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 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. The anesthesiologist should be informed when a patient is receiving labetalol. Labetalol blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur. Care should be taken if labetalol is used concomitantly with calcium antagonists of the verapamil type. When drug products that are alkaline, such as furosemide, have been administered in combination with labetalol, a white precipitate has been noted. Therefore, these drugs should not be administered in the same infusion line. Risk of Anaphylactic Reaction While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nonteratogenic Effects: Hypotension, bradycardia, hypoglycemia, and respiratory depression have been reported in infants of mothers who were treated with labetalol for hypertension during pregnancy.. Labor and Delivery: Labetalol given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery. Nursing Mothers: Small amounts of labetalol (approximatel y 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when labetalol HCl injection is administered to a nursing woman. Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:
Labetalol HCl Injection is usually well tolerated. 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 injection. 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 injection with the incidence per 100 patients as noted: Cardiovascular System Ventricular arrhythmia in 1. Central and Peripheral Nervous Systems Dizziness in 9; tingling of the scalp/skin 7; hypoesthesia (numbness) and vertigo, 1 each. Gastrointestinal System Nausea in 13; vomiting 4; dyspepsia and taste distortion, 1 each. Metabolic Disorders Transient increases in blood urea nitrogen and serum creatinine levels occurred in of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency. Psychiatric Disorders Somnolence/yawningin 3. Respiratory System Wheezing in 1. Skin Pruritus in 1. The incidence of adverse reactions depends upon the dose of labetalol HCl.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 (eg, 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 HCl tablets, there have been reversible increases of serum transaminases in 4% of patients tested, and more rarely, reversible increases in blood urea.)

CONTRAINDICATIONS:
Labetalol hcl injection is contraindicated in bronchodilators asthma, over cardiac failure, greater than first degree block, cardiogenic shock severe bradycardia , other condition associated with severe and prolonged hypotension and inpatient with a history of hypersensitivity to any component of the product. Beta Blockers, even those with appropriate cardioselectivity should not be used in pateints with a history of obstructive airway disease including asthma.

OVERDOSAGE:
Overdosage with labetalol HCl injection 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 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. 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, eg, norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. Bronchospasm-administer epinephrine and/or an aerosolized beta2-agonist. Seizures-administer diazepam. In severe beta-blocker overdose resulting in hypotension and/or bradycardia, glucagon has been shown to be effective when administered in large doses (5 to 10 mg rapidly over 30 seconds, followed by continuous infusion of 5 mg/hr that can be reduced as the patient improves). 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.

PRESENTATION:
Labetalol hydrochloride Injection 5 mg/mL is supplied in: 4 ML(20 ML) (100 mg) in a clear glass ampoule.

Storage: Store in cool & dark place Protect from light. And Retain in carton until time to use. Improper Storage may deteriorate the product

Medicine: - Keep out of reach of children.

Manufactured by:

AMERICAN REMEDIES© Care & Cure with Research

American Remedies Healthcare Pvt. Ltd. (An ISO 9001-2015 Certified Company)

ICO: American Remedies LLC, DE, USA

Gala No. 105 to 111, 1st Flr., Bldg. No. E-15/A, Harihar Complex, Bhiwandi, Mumbai - 421302

At: Vill. Surajpur Nahan Road Paonta Sahib, Distt. Sirmour, Himachal Pradesh-173001

E-mail: info@americanremedies.in

Scan for Batch Certificate

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

℞ Labetalol Injection IP

AMERICAN **Labecanol** Injection

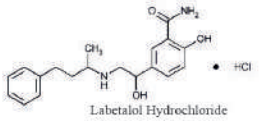
FOR INTRAVENOUS USE ONLY

Composition:

Each ml contains:

Labetalol Hydrochloride	IP	5mg
Water For Injection	IP	q.s

Description:
Labetalol injection, IP is an adrenergic receptor blocking agent that has both selective alpha1-adrenergic and nonselective beta-adrenergic receptor blocking actions in a single substance. Labetalol is a sterile solution of labetalol hydrochloride in water for injection. Labetalol HCl is a white or off-white powder, soluble in water. Labetalol hydrochloride injection is a clear, colorless to light yellow, aqueous, sterile, isotonic solution for intravenous (IV) injection. It has a pH range of 3.5 to 4.5. The structural formula of Labetalol Hydrochloride is



Labetalol Hydrochloride

CLINICAL PHARMACOLOGY
MECHANISM OF ACTION: Labetalol HCl combines both selective, competitive, alpha-1-adrenergic blocking and nonselective, competitive, beta-adrenergic blocking activity in a single substance. In man, the ratios of alpha- to beta-blockade have been estimated to be approximately 1:3 and 1:7 following oral and intravenous (IV) administration, respectively. The principal physiologic action of labetalol is to competitively block adrenergic stimulation of β-receptors within the myocardium (β1-receptors) and within bronchial and vascular smooth muscle (β2-receptors), and α1-receptors within vascular smooth muscle. This causes a decrease in systemic arterial blood pressure and systemic vascular resistance without a substantial reduction in resting heart rate, cardiac output, or stroke volume, apparently because of its combined α- and β-adrenergic blocking activity.

PHARMACODYNAMICS:
Labetalol is a selective alpha-1 and non-selective beta adrenergic blocker used to treat high blood pressure. It works by blocking these adrenergic receptors, which slows sinus heart rate, decreases peripheral vascular resistance, and decreases cardiac output. Labetalol has two asymmetric centers and therefore, exists as a molecular complex of two diastereoisomeric pairs. The capacity of labetalol HCl to block alpha receptors in man has been demonstrated by attenuation of the pressor effect of phenylephrine and by a significant reduction of the pressor response caused by immersing the hand in ice-cold water ("cold-pressor test"). Labetalol HCl's beta1-receptor blockade in man was demonstrated by a small decrease in the resting heart rate, attenuation of tachycardia produced by isoproterenol or exercise, and by attenuation of the reflex tachycardia to the hypotension produced by amyl nitrite. Beta2-receptor blockade was demonstrated by inhibition of the isoproterenol-induced fall in diastolic blood pressure. Both the alpha- and beta-blocking actions of orally administered labetalol HCl contribute to a decrease in blood pressure in hypertensive patients. Labetalol HCl consistently, in dose-related fashion, blunted increases in exercise-induced blood pressure and heart rate, and in their double product. The pulmonary circulation during exercise was not affected by labetalol HCl dosing.

DOSAGE AND ADMINISTRATION:
Labetalol HCl Injection is intended for intravenous 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 intravenous 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 HCl injection may be used: a) repeated intravenous injections, b) slow continuous infusion. Repeated Intravenous Injection: Initially, labetalol HCl injection should be given in a dose of 20 mg labetalol HCl (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow intravenous 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 mg or 80 mg can be given at 10-minute intervals until a desired supine blood pressure is achieved or a total of 300 mg labetalol HCl has been injected. The maximum effect usually occurs within 5 minutes of each injection.

SLOW CONTINUOUS INFUSION: Labetalol HCl Injection is prepared for continuous intravenous infusion by diluting the Ampoule contents with commonly used intravenous fluids (see below). Examples of two methods of preparing the infusion solution are: The contents of either two 20-mL ampoules (40 mL), or one 40-mL ampoule, are added to 160 mL of a commonly used intravenous fluid such that the resultant 200 mL of solution contains 200 mg of labetalol HCl, 1 mg/mL. The diluted solution should be administered at a rate of 2 mL/min to deliver 2 mg/min. Alternatively, the contents of either two 20-mL ampoules (40 mL), or one 40-mL ampoule, of labetalol HCl injection are added to 250 mL of a commonly used intravenous fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2 mg/3 mL. The diluted solution should be administered at a rate of 3 mL/min to deliver approximately 2 mg/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, eg, 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 intravenous 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. Blood Pressure Monitoring: The blood pressure should be monitored during and after completion of the infusion or intravenous injections.

PHARMACOKINETICS AND METABOLISM: Following intravenous infusion, the elimination half-life is about 5.5 hours and the total body clearance is approximately 33 mL/min/kg. The plasma half-life of labetalol following oral administration is about 6 to 8 hours. In patients with decreased hepatic or renal function, the elimination half-life of labetalol is not altered; however, the relative bioavailability in hepatically impaired patients is increased due to decreased "first-pass" metabolism. The metabolism of labetalol is mainly through conjugation to glucuronide metabolites. These metabolites are present in plasma and are excreted in the urine and, via the bile, into the feces. Approximately 55% to 60% of a dose appears in the urine as conjugates or unchanged labetalol within the first 24 hours of dosing. Labetalol has been shown to cross the placental barrier in humans. Labetalol is approximately 50% protein bound. Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol from the general circulation (<1%).

INDICATION AND USAGE: Labetalol HCl Injection is indicated for control of blood pressure in severe hypertension. Labetalol is used parenterally for immediate reduction in blood pressure in severe hypertension or in hypertensive crises when considered an emergency, for the control of blood pressure in patients with pheochromocytoma and pregnant women with preeclampsia, and to produce controlled hypotension during anesthesia to reduce bleeding resulting from surgical procedures

WARNINGS: Hepatic Injury Severe hepatocellular injury, confirmed by rechallenge in at least one case, occurs rarely with therapy with labetalol. 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 also be done at the very first symptom or sign of liver dysfunction (eg, pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has jaundice or laboratory evidence of liver injury, labetalol should be stopped and not restarted. Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol does not abolish the inotropic action of digitalis on heart muscle. In Patients without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can lead, in some cases, to cardiac failure. At the first sign or symptom