

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr LABETALOL HYDROCHLORIDE INJECTION USP

Labetalol hydrochloride

5 mg / mL

For Intravenous (IV) Use

Antihypertensive Agent

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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Pr**LABETALOL HYDROCHLORIDE INJECTION USP**

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous	Solution for injection 5 mg / mL	Dextrose anhydrous, disodium edetate; methylparaben and propylparaben as preservatives and citric acid monohydrate and/or sodium hydroxide to adjust pH and water for injection.

INDICATIONS AND CLINICAL USE

Labetalol Hydrochloride Injection USP (labetalol hydrochloride injection) is indicated for the emergency treatment of severe hypertension when prompt and urgent reduction of blood pressure is essential.

Geriatrics: Lower doses of Labetalol Hydrochloride Injection USP are likely to be required in elderly patients (see WARNINGS AND PRECAUTIONS, Special Populations and DOSAGE AND ADMINISTRATION, Geriatric Patients).

Pediatrics (< 18 years of age): Safety and effectiveness in children have not been established (see WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

Labetalol Hydrochloride Injection USP is contraindicated in patients:

- Who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Exhibiting sinus bradycardia or sick sinus syndrome.
- With uncontrolled congestive heart failure.
- With cardiogenic shock and states of hypoperfusion.

- With asthma or a history of obstructive lung disease.
- With greater than first degree atrioventricular (AV) block.
- With severe peripheral arterial circulatory disorders.

WARNINGS AND PRECAUTIONS

General

Symptomatic postural hypotension is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving Labetalol Hydrochloride Injection USP. Patients should be kept in a supine position during the period of intravenous drug administration because a substantial fall in blood pressure on standing may be anticipated in these patients. The patient's ability to tolerate the upright position should be established before permitting any ambulation (see DOSAGE AND ADMINISTRATION).

Cardiovascular

Cardiac Failure

Cardiac failure should be controlled with digitalis and diuretics before labetalol hydrochloride treatment is initiated. Labetalol Hydrochloride Injection USP should not be given to patients with digitalis-resistant heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. A few patients developed heart failure while on labetalol hydrochloride. Therefore, administration of Labetalol Hydrochloride Injection USP to patients with controlled failure or those likely to develop such failure, must be carried out under careful supervision. The drug does not abolish the inotropic action of digitalis on heart muscle.

Sinus Bradycardia

Severe sinus bradycardia may occur with the use of Labetalol Hydrochloride Injection USP from unopposed vagal activity remaining after blockade of beta₁-adrenergic receptors; in such cases, dosage should be reduced.

Severe Peripheral Artery Disorders

Beta-blockers may aggravate the symptoms of severe peripheral arterial circulatory disorders, mainly due to their blood pressure lowering effect. Caution should be exercised in individuals with such disorders.

Non-dihydropyridine Calcium Channel Blockers

The combination of non-dihydropyridine calcium channel blockers of the verapamil and diltiazem type and beta-blockers warrants caution since additive effects on myocardial contractility, heart rate and AV conduction have been observed. Close medical supervision is recommended (see DRUG INTERACTIONS).

Endocrine and Metabolism

Diabetes and Hypoglycemia

Labetalol Hydrochloride Injection USP should be used with caution in patients subject to hypoglycemic episodes since beta-receptor blocking drugs may mask some of the manifestations of hypoglycemia, particularly tachycardia and may enhance hypoglycemia in patients prone to this condition.

Also, diabetics on insulin or oral hypoglycemic medication may have an increased tendency towards hypoglycemia when treated with these drugs. Patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents should be advised about these possibilities.

Thyrotoxicosis

In patients with thyrotoxicosis, possible deleterious effects from long-term use of labetalol hydrochloride have not been adequately appraised. Beta-blockade may mask the clinical signs of continuing hyperthyroidism or complications, and give a false impression of improvement. Therefore, these patients should be carefully monitored for thyroid function. Abrupt withdrawal of labetalol hydrochloride may be followed by an exacerbation of the symptoms of hyperthyroidism, or may precipitate a thyroid storm.

Pheochromocytoma

While labetalol hydrochloride has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma, paradoxical hypertensive responses have been reported in a few patients with this tumour. Use caution when administering Labetalol Hydrochloride Injection USP to patients with known or suspected pheochromocytoma.

Hepatic/Biliary/Pancreatic

There have been rare reports of severe hepatocellular injury with labetalol hydrochloride therapy. Injury has occurred after both short term and long term treatment and may be slowly progressive despite minimal symptomatology. The hepatic injury is usually reversible but rare cases of hepatic necrosis and death have been reported. Appropriate laboratory testing should be performed at regular intervals during labetalol hydrochloride therapy. Tests should also be done at the first sign or symptom of liver dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained flu-like symptoms). If there is laboratory evidence of liver injury or the patient is jaundiced, Labetalol Hydrochloride Injection USP should be stopped and not restarted.

Immune System

Risk of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge. There may be increased difficulty in treating an allergic-type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacological effects of beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may

not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists, including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Bronchospastic Diseases

Labetalol Hydrochloride Injection USP should not be used in patients with asthma or a history of obstructive airway disease unless there is no suitable alternative treatment available. In such cases, the risk of inducing bronchospasm should be appreciated, therefore, careful monitoring of patients is mandatory and bronchodilators should be used concomitantly. In patients already on therapy, the dose of bronchodilators may have to be increased. In spite of these precautions the patient's respiratory status may worsen, and in such cases Labetalol Hydrochloride Injection USP should be discontinued. If bronchospasm should occur after the use of labetalol hydrochloride, it can be treated with a beta₂- adrenergic receptor stimulant by inhalation, e.g. salbutamol (the dose of which may need to be greater than the usual dose in asthma), and, if necessary, intravenous atropine 1 mg.

Cerebral Hypoperfusion

During treatment with Labetalol Hydrochloride Injection USP, signs of cerebral hypoperfusion may occur if blood pressure is reduced too rapidly. Signs include: confusion, somnolence, lightheadedness, dizziness, nausea, vomiting, pallor, sweating, blurred vision, headache, hallucinations and loss of consciousness. Symptoms and signs of myocardial hypoperfusion include chest pain and ischemic changes in the electrocardiogram. Although they have not been seen with the use of intravenous labetalol hydrochloride, a number of other adverse reactions including cerebral infarction and optic nerve infarction 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.

Ophthalmologic

Animal studies have shown that labetalol binds to the melanin of the uveal tract. The significance of this in humans is not known but periodic ophthalmic examinations are advisable while the patient is taking labetalol hydrochloride.

Peri-Operative Considerations

In patients undergoing surgery: The management of patients being treated with beta-blockers and undergoing surgery is controversial. Although beta-adrenergic-receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli, abrupt discontinuation of therapy with Labetalol Hydrochloride Injection USP may be followed by severe complications (see WARNINGS AND PRECAUTIONS). Some patients receiving beta-adrenergic-blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients with angina undergoing elective surgery, Labetalol Hydrochloride Injection USP should

be withdrawn gradually following the recommendation given under “Abrupt Cessation of Therapy” (see WARNINGS AND PRECAUTIONS).

In emergency surgery, since labetalol hydrochloride is a competitive inhibitor of beta-adrenergic-receptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol.

Skin

Oculomucocutaneous Syndrome

Various skin rashes and conjunctival xerosis have been reported with beta-blockers. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic blocking agent (practolol). This syndrome has not been observed in association with labetalol hydrochloride or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Special Populations

Pregnant Women

Although no teratogenic effects were seen in animal testing, the safety of the use of labetalol hydrochloride during pregnancy has not been established. Labetalol crosses the placental barrier in women and has been found to bind to the eyes of fetal animals. Labetalol Hydrochloride Injection USP should be used in pregnant women only if the expected benefit to the mother justifies the potential risk to the fetus.

Nursing Women

Labetalol has been found in the breast milk of lactating women. If the use of Labetalol Hydrochloride Injection USP is considered essential, then mothers should stop nursing.

Pediatrics (<18 years of age)

Safety and effectiveness in children have not been established.

Geriatric patients

The bioavailability and half-life of labetalol hydrochloride are increased in the elderly. In addition, the hypotensive response is greater in this age group following oral or intravenous administration. Therefore, lower doses of Labetalol Hydrochloride Injection USP are likely to be required in elderly patients (see DOSAGE AND ADMINISTRATION section).

Hepatic impairment

Patients with liver function impairment will likely require lower doses since metabolism of the drug will be diminished (see DOSAGE AND ADMINISTRATION section).

Monitoring and Laboratory Tests

Appropriate liver function laboratory testing should be performed at regular intervals during Labetalol Hydrochloride Injection USP therapy (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic section).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious reported adverse effects of labetalol hydrochloride are severe postural hypotension, jaundice and bronchospasm.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In well controlled clinical trials, the most common transient adverse reactions reported at routinely administered therapeutic doses, were postural hypotension and/or dizziness (16.9%), fatigue/malaise (13.1%), and headache (8.0%). Other transient effects include acute retention of urine and difficulty in micturition. The following summarizes the adverse effects reported.

Cardiovascular: Postural hypotension/dizziness (16.9%), angina pectoris (3.2%), Raynaud's phenomenon (3.2%), pedal edema (1.9%), palpitations (1.3%), bradycardia (<1%).

Gastrointestinal: Nausea/vomiting (6.1%), dyspepsia (1.9%), constipation (1.6%), dry mouth/sore throat (1.6%).

Respiratory: Dyspnea (3.8%), nasal congestion (1.3%).

Dermatological: Drug rash (3.2%), paresthesia (especially "scalp tingling") (3.8%), pruritus (0.6%) and angioedema.

Urogenital: Impotence (2.2%), failure of ejaculation (0.6%), dysuria (0.6%).

Musculoskeletal: Aches/pains (3.5%), muscle cramps (1.3%).

Central Nervous System: Fatigue/malaise (13.1%), headache (8.0%), depression (2.6%), loss of libido (1.3%), dreaming (1.3%).

Miscellaneous: Visual blurring (4.2%), epistaxis (1.6%).

In addition, in the more extensive trials, bronchospasm and severe bradycardia were reported with an incidence of less than 1%. There are rare reports of raised liver function tests, jaundice (both hepatic and cholestatic), and hepatic necrosis (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Abnormal Hematologic and Clinical Chemistry Findings

Elevations of BUN and serum creatinine following bolus injections were reported in 6.8% of patients.

Post-Market Adverse Drug Reactions

Other published or unpublished reports describe other rare, isolated adverse events in patients who were taking labetalol hydrochloride (oral or injectable), as follows: bronchospasm and reduction in peak expiratory flow rate (PEFR), difficulty in micturition including acute urinary retention, ejaculatory failure, Peyronie's disease, toxic myopathy, tremor, taste distortion, hypersensitivity, hypoesthesia, rashes of various types such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriasiform, facial erythema, reversible alopecia and very rarely drug fever. A skin lesion resembling disseminated lupus erythematosus occurred rarely in one patient receiving a high dose of labetalol hydrochloride. There are rare reports of patients who developed lupus-like syndromes while on labetalol hydrochloride which cleared upon discontinuation of treatment. Positive antinuclear factor and antimitochondrial antibodies have been reported in patients receiving the drug, but the significance of these findings is not clear.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Overview

Care should be taken if Labetalol Hydrochloride Injection USP is used concomitantly with either Class I antiarrhythmic agents or calcium antagonists of the verapamil class since these drugs may potentiate the cardiac depressant activities of labetalol hydrochloride.

When used with diuretics and/or other antihypertensive agents the dose of labetalol hydrochloride must be appropriately adjusted (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

Labetalol hydrochloride and halothane have additive hypotensive effects. High doses of halothane (3%) with labetalol hydrochloride predispose the patient to the myocardial depressant effects of halothane and an undesirable reduction in myocardial performance. The anesthesiologist should be informed when a patient is receiving labetalol hydrochloride.

Labetalol hydrochloride blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. When labetalol hydrochloride is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

In one survey, 2.3% of patients taking labetalol hydrochloride in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol hydrochloride alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is not recommended. Where such co-administration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

The presence of a metabolite of labetalol hydrochloride in the urine may result in falsely elevated levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol hydrochloride, specific radioenzymatic or high performance liquid chromatographic assay techniques should be used to determine levels of catecholamines or their metabolites.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment:

The administration of intravenous Labetalol Hydrochloride Injection USP should be restricted to hospitalized patients. **DOSAGE MUST BE INDIVIDUALIZED** according to the patient's weight, the severity of their hypertension and to their response during dosing.

Patients should be kept supine during the period of intravenous drug administration because a substantial fall in blood pressure on standing may be anticipated in these patients. The patient's ability to tolerate the upright position (e.g. use of toilet facilities) should be established prior to them getting up, especially within the three hours post-injection.

The blood pressure should be monitored prior, during and after completion of the infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic blood pressure during intravenous treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as an indicator of effectiveness in addition to the response of the diastolic pressure.

To reduce blood pressure in general cases:

Labetalol Hydrochloride Injection USP should be given in an initial dose of 0.25 mg/kg, up to a maximum of 20 mg (dosing for an 80 kg patient) by slow intravenous injection over a two-minute period. Dosage varies between 0.25 and 2 mg/kg. Additional injections of 40 mg or 80 mg can be given at ten-minute intervals until desired blood pressure is reached.

To reduce blood pressure very quickly:

A dose of 50 mg of Labetalol Hydrochloride injection USP can be given into the vein over a period of one minute. If necessary this dose can be repeated every five minutes up to three times until the blood pressure has been lowered. The total dose should not exceed 200 mg.

To lower blood pressure during an operation:

While under anesthetic, 10-20 mg Labetalol Hydrochloride injection USP (depending on age and health) can be injected into the vein. If after 5 minutes blood pressure has not been reduced, a dose of 5-10 mg can be given every 5 minutes until blood pressure is low enough.

Geriatric Patients: Lower doses of Labetalol Hydrochloride Injection USP are likely to be required in elderly patients due to increased relative bioavailability (see WARNINGS AND PRECAUTIONS, Special Populations). Close monitoring and strict observation of adverse reactions are recommended during and after the administration of Labetalol Hydrochloride Injection USP.

Pediatrics: Safety and effectiveness in children have not been established.

Hepatic Impairment: Patients with liver function impairment may require lower doses since metabolism of the drug may decrease in these patients (see WARNINGS AND PRECAUTIONS, Special Populations).

Two methods of administration of Labetalol Hydrochloride Injection USP may be used:

- repeated intravenous injection, or
- slow continuous infusion.

Repeated Intravenous Injection

Prior to the first injection, measure Supine Diastolic Blood Pressure (SuDBP).

- Inject first dose (0.25 mg/kg , up to a maximum dose of 20 mg) by slow intravenous injection.
- Five minutes and ten minutes after injection, repeat measurement of SuDBP to evaluate the patient's response. The maximum effect usually occurs within 5 to 10 minutes of each injection but may be longer.
- No further injections are required if SuDBP:
 - 1) is less than 95 mmHg; or
 - 2) has decreased more than 30 mmHg

If SuDBP is greater than 95 mmHg, give patient a second injection and continue to monitor SuDBP and dose patient as indicated above.

Dosing of labetalol hydrochloride should be limited to a maximum of 300 mg.

Slow Continuous Infusion

- Prepare a 1 mg/ml solution of Labetalol Hydrochloride Injection USP by diluting the vial contents with commonly used intravenous fluids (e.g. Sodium Chloride Injection USP

0.9% and Dextrose Injection USP 5%; see section below Compatibility With Commonly Used Intravenous Fluids)

- To gradually reduce blood pressure, slowly drip solution into the vein
 - The amount of solution required will be determined by the response during dosing and may be adjusted until the optimal blood pressure is achieved.
1. To reduce high blood pressure in pregnancy
 - Administer 20 mg of Labetalol Hydrochloride USP injection over 60 minutes
 - The dose may then be doubled every 30 minutes until blood pressure has been reduced or the dose has reached 160 mg per hour
 - A higher dose may be used occasionally if the potential benefits justifies the potential risk to the fetus.
 2. To reduce high blood pressure after a heart attack
 - Administer 15 mg of Labetalol Hydrochloride injection USP injection over 60 minutes
 - The dose may then be gradually increased up to a maximum of 120 mg per hour if needed.
 3. To reduce high blood pressure for other reasons such as severe hypertension
 - Administer 2 mg/min of Labetalol Hydrochloride injection USP injection until blood pressure has reached 95 mmHg.
 - The total dose given is usually between 50 mg and 200 mg. Higher doses up to 300 mg may be used when lower doses are not effective.

Compatibility with Commonly Used Intravenous Fluids

Labetalol Hydrochloride Injection USP was tested for compatibility with commonly used intravenous fluids at final concentrations of 1.25 mg and 3.75 mg labetalol hydrochloride per mL of the mixture. Labetalol Hydrochloride Injection USP was found to be compatible with and stable (24 hrs, refrigerated or at room temperature) in Sodium Chloride Injection USP 0.9% and Dextrose Injection USP 5%. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

There are two methods that can be used to prepare the infusion solution:

1. The contents of two 20 mL vials (40 mL) of labetalol hydrochloride are added to 160 mL of a commonly used intravenous fluid (e.g. Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 5%). The resultant 200 mL of solution will contain 200 mg of labetalol hydrochloride at a concentration of 1 mg/mL. This diluted solution should be administered at a rate of 2 mL/min to infuse labetalol hydrochloride at a rate of 2 mg/min.
2. Alternatively, the contents of two 20 mL vials (40 mL) of Labetalol Hydrochloride Injection USP can be added to 250 mL of a commonly used intravenous fluid. The resultant solution will contain 200 mg of labetalol hydrochloride, approximately 2 mg/3 mL. The diluted solution should be administered at a rate of 3 mL/min to deliver labetalol hydrochloride at a rate of approximately 2 mg/min.

Both methods could be used when high blood pressure needs to be reduced in cases other than after a heart attack or during a pregnancy. However, the rate of infusion of the diluted solution may be adjusted downward according to the patient's age, weight, health, the severity of hypertension, prior therapy, and their response during treatment. 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 hydrochloride 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 medication started when it has been established that the supine diastolic blood pressure has begun to rise. 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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms

The signs and symptoms associated with Labetalol Hydrochloride Injection USP overdose are excessive hypotension which is posture-sensitive, and sometimes, excessive bradycardia.

Treatment

Patients should be laid supine and their legs raised, if necessary. Hemodialysis removes less than 1% of circulating labetalol, and is therefore not recommended as a method to manage overdoses.

If overdose occurs, provide general supportive and specific symptomatic treatment. Based on expected pharmacologic actions and recommendations for other beta-blockers, the following additional measures should be employed if necessary, including stopping Labetalol Hydrochloride Injection USP when clinically warranted;

Excessive Bradycardia: Administer atropine intravenously to induce vagal blockage. If bradycardia persists, isoproterenol may be administered cautiously. In refractory cases, the use of a cardiac pacemaker may be considered.

Congestive Heart Failure: Conventional therapy with cardiac glycosides and diuretics.

Hypotension: Administer vasopressors, e.g. norepinephrine.

Bronchospasm: Administer a beta2-stimulating agent and/or a theophylline preparation.

Heart block (second or third degree): Monitor and treat with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Hypoglycemia: Administer intravenous glucose. Repeated dose of intravenous glucose or possibly glucagon may be required.

Oliguric renal failure has been reported after massive overdosage of labetalol hydrochloride orally. In one case, the use of dopamine to increase blood pressure may have aggravated the renal failure.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Labetalol Hydrochloride Injection USP (labetalol hydrochloride) is an adrenergic receptor blocking agent possessing both α_1 (post-synaptic) and beta-receptor blocking activity. Its action on beta-receptors is four times stronger than that on alpha-receptors. It antagonizes β_1 - and β_2 -receptors equally.

The mechanism of the antihypertensive action of labetalol has not been fully established. It is considered that labetalol lowers blood pressure by partially blocking the alpha-adrenoreceptors in the peripheral arterioles, thus causing vasodilation and a resulting reduction of peripheral resistance. At the same time, blockade of the beta-adrenoreceptors in the myocardium prevents reflex tachycardia and subsequent elevation of cardiac output. Peripheral vasodilation is achieved with incomplete blockade of alpha-adrenoreceptors in the arterioles and the barostatic reflexes remain sufficiently active to reduce the incidence of postural hypotension.

Pharmacodynamics

At rest, labetalol slightly reduces the heart rate, increases the stroke volume but does not significantly affect cardiac output. It reduces exercise-induced increases in systolic pressure and heart rate, again without significantly influencing cardiac output.

Following oral administration to hypertensive patients, labetalol decreases plasma renin activity and aldosterone levels, both at rest and during exercise, particularly when these were elevated prior to treatment. Labetalol is significantly more efficacious in hypertensive patients with high baseline plasma noradrenaline levels.

Following a bolus intravenous injection, the maximum antihypertensive effect occurs within 5 to 10 minutes in the majority of patients. However, in some patients the peak effect occurs considerably later.

Pharmacokinetics

Distribution: Rapid and extensive distribution within tissue compartments occurs after intravenous administration. The drug is approximately 50% bound to plasma proteins.

Metabolism: Labetalol is metabolized mostly by conjugation with glucuronic acid; the resulting metabolite is inactive.

Excretion: Labetalol and its metabolites are rapidly excreted in urine, and *via* bile into the feces. The plasma half-life of labetalol is approximately 5.5 hours after intravenous administration.

STORAGE AND STABILITY

Store between 20 and 25°C. Protect from freezing and from light. Multi-dose vials: Discard 28 days after initial puncture.

The stopper is not made with natural rubber latex.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL contains: Labetalol hydrochloride 5 mg. **Non-medicinal ingredients:** Dextrose anhydrous 45 mg, disodium edetate 0.1 mg; methylparaben 0.08% (w/v) and propylparaben 0.01% (w/v) as preservatives and citric acid monohydrate and/or sodium hydroxide to adjust pH and water for injection.

Labetalol Hydrochloride Injection USP, 5 mg/mL, is available in multidose vials of 20 mL, boxes of 1.

PART II: SCIENTIFIC INFORMATION

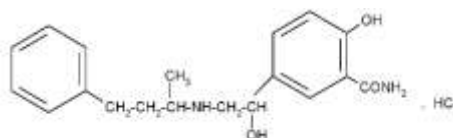
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: labetalol hydrochloride

Chemical Name: 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl] benzamide hydrochloride

Structural Formula:



Molecular Formula: $C_{19}H_{24}N_2O_3 \cdot HCl$

Molecular Weight: 364.87 g/mol

Physical Characteristics: Labetalol hydrochloride is a white to off-white powder with a melting point around 180°C with decomposition.

Solubility: Labetalol hydrochloride is soluble in water and in alcohol; it is insoluble in ether and chloroform.

pH: The pH of a 1% w/v solution of labetalol hydrochloride is between 4.0 and 5.0.

CLINICAL TRIALS

Study Results

In a clinical pharmacologic study in severe hypertensives, an initial 0.25 mg/kg injection of labetalol administered to patients in the supine position decreased blood pressure by an average of 11/7 mmHg. Additional injections of 0.5 mg/kg at 15 minute intervals up to a total cumulative dose of 1.75 mg/kg of labetalol caused further dose-related decreases in blood pressure. Some patients required cumulative doses of up to 3.25 mg/kg. The maximal effect of each dose level occurred within 5 minutes. Following discontinuation of intravenous treatment with labetalol, the blood pressure rose gradually and progressively, approaching pretreatment baseline values within an average of 16 to 18 hours in the majority of patients.

Similar results were obtained in the treatment of patients with severe hypertension requiring urgent blood pressure reduction with an initial dose of 20 mg (which corresponds to 0.25 mg/kg for an 80 kg patient) followed by additional doses of either 40 mg or 80 mg at 10-minute intervals to achieve the desired effect or up to a cumulative dose of 300 mg.

Labetalol hydrochloride administered as a continuous intravenous infusion with a mean dose of 136 mg (27 to 300 mg) over a period of 2 to 3 hours (mean of 2 hours and 39 minutes) lowered the blood pressure by an average of 60/35 mmHg.

DETAILED PHARMACOLOGY

Effects on Cardiovascular System Dogs:

Intravenous labetalol hydrochloride, in doses of 0.1 to 10 mg/kg, caused a dose-dependent decrease in blood pressure and heart rate. Doses up to 1 mg/kg resulted in progressive shifts to the right of the dose-pressor response curve for noradrenaline. There was no further increase in B-blockade with the higher doses. Beta-adrenergic blockade was seen with doses of 0.1, 0.5 and 1.0 mg/kg as shown by antagonism of isoproterenol-induced vasodilation and tachycardia.

Intravenous labetalol hydrochloride, in doses of 0.1 to 3.0 mg/kg, caused a dose-dependent reduction in arterial blood pressure (11-16%), heart rate (16-27%), aortic blood flow (10-38%), and cardiac contractibility (9-52%). Changes in anaesthetized dogs lasted for more than one hour.

Consistent reductions in stroke volume (21%) occurred at the highest dose and in total peripheral resistance at 1 and 3 mg/kg.

Oral doses of 0.25 to 5 mg/kg lowered systolic blood pressure by 10 to 35 mmHg for about 5 hours with no consistent changes in heart rate.

Labetalol hydrochloride has not been shown to possess intrinsic sympathomimetic activity.

Intravenous labetalol hydrochloride, in doses of 0.03 to 1 mg/kg, caused direct vasodilation of resistant blood vessels in dogs rendered devoid of adrenergic tone.

Using the guinea pig intradermal wheal test, it was demonstrated that labetalol possesses local anaesthetic activity approximately equipotent to that of propranolol.

Humans:

Intravenous labetalol hydrochloride, in doses of 10, 40 and 160 mg caused dose-related inhibition of phenylephrine-induced increase in mean blood pressure and of isoproterenol-induced tachycardia. After 40 mg of labetalol hydrochloride, a 2-fold increase in the dose of phenylephrine (β -blockade) and an 8-fold increase in the dose of isoproterenol (β -blockade) were required to elicit responses equivalent to pretreatment levels. The tachycardia induced by Valsalva manoeuvre was also abolished by the 40 mg IV dose.

Doses of 0.5 mg/kg of labetalol hydrochloride administered IV to 12 hypertensive patients resulted in the following statistically significant mean percentage changes: blood pressure was lowered by 18.5% ($p < 0.001$) and total peripheral vascular resistance by $13.5 \pm 22\%$ ($p < 0.02$). No significant changes in resting heart rate or cardiac output were observed.

Labetalol hydrochloride significantly reduced the pressor response to immersion of the hand in ice-cold water for 60 seconds (**cold pressor test**), signifying the postsynaptic β -blocking action of the drug.

After oral treatment with labetalol hydrochloride (average dose 1200 mg), plasma renin and angiotensin II levels were reduced, especially if elevated prior to treatment. Intravenous labetalol hydrochloride, in doses of 1-2 mg/kg, reduced plasma levels of angiotensin II and aldosterone in hypertensive patients.

Effects on Pulmonary Function

A single 400 mg oral dose of labetalol hydrochloride administered to healthy male subjects caused a reduction in Peak Expiratory Flow Rate (PEFR) at rest and during exercise.

In 11 hypertensive asthmatic subjects, a 300 mg oral dose of labetalol hydrochloride caused a slight reduction in resting FEV₁, and significantly reduced the effect of inhaled salbutamol in FEV₁.

Other Effects

Labetalol hydrochloride administered to 17 hypertensive men in daily oral doses of 600 to 1200 mg caused a small increase in fasting blood glucose levels but no alteration in insulin activity or response to an oral glucose tolerance test.

TOXICOLOGY

Acute Toxicity

Animal	Sex	Route of Administration	LD ₅₀ (in mg/kg)
Mouse	M	PO	655
Mouse	F	PO	577
Mouse	M	IV	53
Mouse	F	IV	49
Rat	M	PO	2 379
Rat	F	PO	2 055
Rat	M	IV	51
Rat	F	IV	50
Dog	M	IV	34
Dog	F	IV	38

Signs of Toxicity

Mice: hypoactivity, dyspnea, prostration, piloerection, ataxia, clonic convulsions.

Rats: hypoactivity, dyspnea, salivation, clonic convulsions.

Four beagle dogs were treated with single oral doses of labetalol hydrochloride 500, 750 and 1000 mg/kg. No deaths resulted. The following signs were observed in dogs treated with 750 mg/kg or higher: emesis, redness of the mucous membranes, dry nose, mild sedation, slight tachycardia, bradypnea and hypothermia.

In beagle dogs, death occurred within 15 minutes of an IV dose of 40 mg/kg and was preceded by prostration. Survivors (5/12) from doses up to 100 mg/kg experienced temporary lethargy, hypotension and bradycardia.

Subacute Toxicity

In rats, labetalol hydrochloride was administered by gavage in doses of 0, 50, 110 and 250 mg/kg/day (24 rats/dose) for 3 months. Polydipsia, dilute polyuria, proteinuria, elevated serum liver enzymes, polycythemia and nephrocalcinosis were noted. Cellular casts were found in the urine of animals in the high dose group.

Labetalol hydrochloride was administered IV to beagle dogs (10/sex) in doses of up to 20 mg/kg/day for 15 days. No drug-induced toxicity was noted.

Chronic Toxicity

Labetalol hydrochloride was administered by gavage to Wistar rats for 1 year in doses of 1, 100, 140, and 200 mg/kg/day (32 rats/dose). A slight, but statistically significant lengthening of the clotting time was found in all treated groups. Increased plasma levels of alkaline phosphatase, SGOT and SGPT were noted towards the end of the study period. Increases in heart weights were observed in all treated groups.

Labetalol hydrochloride was administered orally to beagle dogs in doses of 0, 25, 50 and 100 mg/kg once daily, 7 days per week for 52 weeks (6 dogs/dose).

Muscle tremors, abnormal gait, vomiting and loose stools of abnormal colour were observed at 50 and 100 mg/kg doses. Occult blood was occasionally seen in the feces of animals in the high dose group.

One male and one female in the high dose group died during testing. Both showed gastrointestinal mucosal congestion and the female had increased blood urea and SGPT levels. Cause of death was not established.

Body weight gain was significantly lower in high dose males.

Four dogs developed minor corneal ulcers. Reflex tear secretion was normal in all animals. Heart rate was reduced at all doses (ECG recordings).

No drug-related changes in gross weight of organs or histopathological findings were noted.

Reproduction and Teratologic Studies

Labetalol hydrochloride was administered by gavage to AHA rats in doses of 0, 50, 100 and 200 mg/kg/day (32 rats/dose) for 10 weeks prior to mating and throughout the mating period. A dose-related reduction in fertility was observed in the treated animals (F0 generation). No reproductive impairment was noted in the subsequent F1 and F2 generations.

Primiparous Wistar rats were administered labetalol hydrochloride by gavage throughout pregnancy (19 days) in doses of 0, 125, 150, 175, 200, 250 and 300 mg/kg/day (8 rats/dose). No congenital malformations were observed. There was a retardation of fetal growth in the 250 and 300 mg/kg dose groups.

Mated female New Zealand white rabbits were administered labetalol hydrochloride by gavage from day 7 through day 19 of gestation, in doses of 0, 50, 100 and 200 mg/kg/day (14 rabbits/dose). There were no apparent drug-related effects on the course of pregnancy or fetal development.

Mutagenicity Studies

Studies with labetalol hydrochloride, using dominant lethal assays in mice and rats, and exposing microorganisms according to modified Ames tests, did not show any evidence of drug-related mutagenicity.

Carcinogenicity Studies

Labetalol hydrochloride was admixed in the diet of CR/H Glaxo mice in doses of 0, 100, 140 and 200 mg/kg/day for 18 months (100 mice/dose). No drug-related carcinogenicity was apparent.

Sprague-Dawley CD rats were fed labetalol hydrochloride in doses of 0, 100, 140 and 225 mg/kg/day for 24 months (110 rats/dose). Increased incidences of ovarian cysts, corneal lesions, reactive lymphoid hyperplasia of the cervical lymph nodes, and enlargement of seminal vesicles were noted in the active treatment groups. No drug-related carcinogenicity was apparent.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III : PATIENT MEDICATION INFORMATION

LABETALOL HYDROCHLORIDE INJECTION USP

Labetalol Hydrochloride Injection

You or your caregiver should read this carefully before you are given Labetalol Hydrochloride Injection USP. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Labetalol Hydrochloride Injection USP.

What is Labetalol Hydrochloride Injection USP used for?

Labetalol Hydrochloride Injection USP is used in the hospital for the emergency treatment of very high blood pressure. It is given to you when your blood pressure needs to be lowered quickly.

How does Labetalol Hydrochloride Injection USP work?

Labetalol Hydrochloride Injection USP is a fast acting blood pressure lowering medication that belongs to a group of drugs called “beta-blockers”. They work by:

- making your heart beat more slowly and less forcefully, and
- lowering your blood pressure by relaxing your blood vessels so that your blood flows more easily.

What are the ingredients in Labetalol Hydrochloride Injection USP?

Medicinal ingredient: labetalol hydrochloride

Non-medicinal ingredients: Dextrose anhydrous 45 mg, disodium edetate 0.1 mg; methylparaben 0.08% (w/v) and propylparaben 0.01% (w/v) as preservatives and citric acid monohydrate and/or sodium hydroxide to adjust pH and water for injection.

Labetalol Hydrochloride Injection USP comes in the following dosage forms:

Solution for Injection: 5 mg/mL.

Labetalol Hydrochloride Injection USP will not be used if you:

- Are allergic or hypersensitive to labetalol hydrochloride or to any of the other ingredients in Labetalol Hydrochloride Injection USP.
- Have heart failure and you notice that your symptoms are getting worse. For example you feel more tired, are out of breath more often, or have swelling of the ankles.
- Have severe heart damage and your heart is not able to pump enough blood to meet your body's needs.
- Have a slow or irregular heartbeat.

- Have a problem with your heart’s electrical conduction (that causes you to have chest pain, difficulty breathing, nausea, fatigue and fainting).
- Have asthma or other lung problems (like bronchitis or emphysema).
- Have serious problems with blood flow in your feet and legs (severe peripheral artery disease).
- Are less than 18 years old.

To help avoid side effects and ensure proper use, you or your caregiver should talk to your healthcare professional before you are given Labetalol Hydrochloride Injection USP. You or your caregiver should talk about any health conditions or problems you may have, including if you:

- Have a history of heart problems.
- Have a history of fainting.
- Have diabetes and take medicine to control your blood sugar or have low blood sugar (hypoglycemia).
- Have a condition called pheochromocytoma (a tumour of the adrenal gland).
- Have thyroid problems.
- Have liver problems.
- Have had allergic reactions or have allergies.
- Are pregnant or trying to become pregnant. Labetalol Hydrochloride Injection USP is not usually recommended for use during pregnancy. Your doctor will consider the benefit to you versus the risk to your unborn baby.
- Are breastfeeding. You should not breastfeed while using Labetalol Hydrochloride Injection USP.
- Are scheduled for surgery and will be given an anesthetic.
- Develop a skin rash while taking Labetalol Hydrochloride Injection USP.

You or your caregiver should tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Labetalol Hydrochloride Injection USP:

- Drugs used to treat high blood pressure, such as:
 - Diuretics (“water pills”)
 - ACE inhibitors
 - Calcium channel blockers (e.g. diltiazem, verapamil)
- Anesthetic drugs used during surgery (e.g. halothane)
- Drugs used to prevent angina (e.g. nitroglycerin)
- Drugs used to treat heartburn and stomach ulcers (e.g. cimetidine)
- Drugs used to treat depression (e.g. tricyclic antidepressants)
- Drugs used to treat Multiple Sclerosis (e.g. fingolimod)

How Labetalol Hydrochloride Injection USP is given:

You should **only** be given Labetalol Hydrochloride Injection USP:

- If you are in a hospital or clinic that has the proper monitoring and support equipment

- By a healthcare professional that has been specifically trained in the use of intravenous anti- hypertensives

Adult dose: Your healthcare professional will decide the best dose for you. It will depend on:

- your age
- your weight
- your health
- the severity of your hypertension
- previous therapy and how you respond during treatment
- Labetalol Hydrochloride Injection USP is given to you as an injection. It is injected directly into your vein (intravenously). It may be given to you as a:
 - Repeated intravenous injection, or
 - Slow continuous infusion

During treatment

- You should be kept lying on your back during treatment. This is because you may experience a considerable drop in your blood pressure while you are standing.

After treatment

- Your doctor will monitor you to see if you can tolerate standing.

For elderly patients and patients with liver problems:

Smaller doses are generally used in older patients, and those with liver problems.

Overdose:

If you think you have been given too much Labetalol Hydrochloride Injection USP, tell your healthcare professional, the hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using Labetalol Hydrochloride Injection USP?

These are not all the possible side effects you may feel when taking Labetalol Hydrochloride Injection USP. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Side effects may include:

- Dizziness
- Headache
- Nausea/Vomiting
- Tiredness

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
<ul style="list-style-type: none"> • Hypotension (low blood pressure): dizziness or lightheadedness leading to fainting can occur when changing positions, for example from lying down to standing up 		√	
<ul style="list-style-type: none"> • Chest pain 			√
UNCOMMON			
<ul style="list-style-type: none"> • Bradycardia: decreased heart rate that causes you to be dizzy or faint 		√	
<ul style="list-style-type: none"> • Allergic reactions: rash, swelling of the lips, face or neck, difficulty breathing or speaking 			√
<ul style="list-style-type: none"> • Congestive heart failure: irregular heartbeat, low heart rate, or other changes in heart symptoms 		√	
<ul style="list-style-type: none"> • Narrowing of the airways (bronchospasm) or other lung 		√	
<ul style="list-style-type: none"> • Liver disorders: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite 			√
UNKNOWN FREQUENCY			
<ul style="list-style-type: none"> • Lupus-like syndrome: joint pain, muscle pain, chest pain when you cough or breathe, breathing difficulties (shortness of breath or labored breathing) 		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Labetalol Hydrochloride Injection USP will be stored by your healthcare professional, hospital, or clinic.

If you want more information about Labetalol Hydrochloride Injection USP:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website www.pfizer.ca or by calling **1-800-463-6001**.

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