PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-LABETALOL

Labetalol Hydrochloride Tablets USP

100 mg and 200 mg of labetalol hydrochloride

Antihypertensive Agent

Apotex Inc.
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Weston, Ontario
M9L 1T9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablets / 100 mg and 200 mg	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol, purified water, titanium dioxide. The 100 mg tablets also contain the following colouring agents: D&C Yellow #10 Aluminum Lake 16%, FD&C Yellow #6 Aluminum Lake 40%.

INDICATIONS AND CLINICAL USE

APO-LABETALOL (labetalol hydrochloride tablets) is indicated for the treatment of hypertension.

APO-LABETALOL is usually used in combination with other drugs, particularly a thiazide diuretic (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

However, APO-LABETALOL may be tried alone as an initial agent in those patients in whom, in the judgement of the physician, treatment should be started with an alpha- beta-blocker rather than with a diuretic.

APO-LABETALOL may be used in combination with diuretics and/or other antihypertensive agents to treat severe hypertension (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

The combination of labetalol hydrochloride tablets with a diuretic has been found to be compatible. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with labetalol hydrochloride tablets.

Geriatrics: Lower doses of APO-LABETALOL 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

APO-LABETALOL 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

Postural hypotension and syncope may occur in patients treated with APO-LABETALOL (labetalol hydrochloride tablets), particularly if the initial dose is too high or if dose titration is too rapid (see DOSAGE AND ADMINISTRATION). Treatment should start with small doses without additional alpha- or beta-adrenergic blocking drugs.

Cardiovascular

Abrupt Cessation of Therapy

Patients with angina should be warned against abrupt discontinuation of beta-adrenergic blocking agents. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of APO-LABETALOL is planned in patients with angina pectoris, the dosage should be gradually reduced over a period of about two weeks and the patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, APO-LABETALOL therapy should be discontinued stepwise and under conditions of closer observation.

If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with APO-LABETALOL be re-instituted promptly, at least temporarily.

Cardiac Failure

Cardiac failure should be controlled with digitalis and diuretics before APO-LABETALOL treatment is initiated. APO-LABETALOL 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 contractibility and precipitating cardiac failure. A few patients developed heart failure while on labetalol hydrochloride tablets. Therefore, administration of APO-LABETALOL 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 tablets from unopposed vagal activity remaining after blockade of beta$_1$-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

APO-LABETALOL 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 tablets 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 APO-LABETALOL may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

Pheochromocytoma

While labetalol hydrochloride tablets have 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 APO-LABETALOL to patients with known or suspected pheochromocytoma.

Hepatic/Biliary/Pancreatic

There have been rare reports of severe hepatocellular injury with labetalol hydrochloride tablet 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 APO-LABETALOL 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, APO-LABETALOL should be stopped and not restarted.

In patients with chronic liver disease the oral bioavailability of labetalol is enhanced due to reduced first pass metabolism. Lower doses of APO-LABETALOL are likely to be required in these patients (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

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.

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 APO-LABETALOL.

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

In emergency surgery, since APO-LABETALOL 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 tablets 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 tablets 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. APO-LABETALOL 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 APO-LABETALOL is considered essential, then mothers should stop nursing.

Pediatrics (< 18 years of age): Safety and effectiveness in children have not been established.

Geriatrics: The bioavailability and half-life of labetalol hydrochloride tablets are increased in the elderly. In addition, the hypotensive response is greater in this age group following administration. Therefore, lower doses of APO-LABETALOL are likely to be required in elderly patients.

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 APO-LABETALOL therapy (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic section).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious reported adverse effects of labetalol hydrochloride tablets 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 list 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%) and bradycardia (<1.0%).

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

Respiratory: Dyspnea (3.8%) and 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%) and dysuria (0.6%).

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

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

Miscellaneous: Visual blurring (4.2%) and 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

Occasional elevations of serum transaminases and blood urea have been reported following oral administration.

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 APO-LABETALOL 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 APO-LABETALOL must be appropriately adjusted (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

Labetalol hydrochloride tablets and halothane have additive hypotensive effects. High doses of halothane (3%) with labetalol hydrochloride tablets 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 APO-LABETALOL.

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

Cimetidine has been shown to increase the oral bioavailability of labetalol hydrochloride tablets. As cimetidine might be given to patients with hypertension also receiving APO-LABETALOL, special care should be used in establishing the dose required for blood pressure control in such patients.

In one survey, 2.3% of patients taking labetalol hydrochloride tablets in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol hydrochloride tablets 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-Food Interactions

When taken with food, the bioavailability of unchanged drug is increased although peak plasma levels remain the same. APO-LABETALOL should be taken preferably after food.

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 non-specific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with APO-LABETALOL, specific radioenzymatic or high performance liquid chromatographic assay techniques should be used to determine levels of catecholamines or their metabolites.

DOSAGE AND ADMINISTRATION

Dosing Considerations

APO-LABETALOL (labetalol hydrochloride) tablets should be taken preferably after food.

Recommended Dose and Dosage Adjustment

The dosage of APO-LABETALOL must always be adjusted in accordance with the individual requirements of the patient. The recommended initial dose is 100 mg twice daily whether used alone or with a diuretic. Thereafter, the dose should be adjusted semi-weekly or weekly according to the response.

The usual maintenance dose is 200 to 400 mg twice daily. Patients may require up to 1200 mg per day, in two divided doses.

Optimal doses are usually lower in patients also receiving a diuretic and/or other antihypertensive agents since an additive antihypertensive effect can be expected.

Hepatic Impairment

Patients with liver function impairment will likely require lower doses since metabolism of the drug will be diminished.

Geriatric Patients

Lower doses of APO-LABETALOL are likely to be required in elderly patients (see WARNINGS AND PRECAUTIONS, Special Populations).

OVERDOSAGE

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

Symptoms

The signs and symptoms associated with labetalol hydrochloride tablet overdosage are excessive hypotension which is posture-sensitive, and sometimes, excessive bradycardia.

Treatment

Patients should be laid supine and their legs raised, if necessary. Gastric lavage or pharmacologically-induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Hemodialysis removes less than 1% of circulating labetalol hydrochloride, and is therefore not recommended.

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 APO-LABETALOL 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 $beta_2$-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 tablets 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 is an adrenergic receptor blocking agent possessing both $alpha_1$-(post-synaptic) and beta-receptor blocking activity. Its action on beta-receptors is four times stronger than that on alpha-receptors. It antagonizes $beta_1$- and $beta_2$-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.

Pharmacokinetics

Labetalol produces a significant fall in blood pressure in 1 to 4 hours after the first oral dose. The maximum blood pressure lowering effect at any particular dose level is usually achieved within 24 to 72 hours.

Absorption: Labetalol is well absorbed from the gastrointestinal tract with peak blood levels occurring 1 to 2 hours after oral dosing.

A single oral dose of 200 mg produced average peak plasma levels of 360 mcg per 100 mL.

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

Metabolism: The drug undergoes extensive "first pass" metabolism following oral administration. The bioavailability of oral compared to intravenous (i.v.) labetalol is approximately 25%. When taken with food, the bioavailability of unchanged drug is increased although peak plasma levels remain the same. The drug 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 6 to 8 hours following oral administration

STORAGE AND STABILITY

APO-LABETALOL Tablets should be stored at room temperature 15°C to 30°C. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-LABETALOL 100 mg Tablets: Each orange, capsule-shaped tablet, scored and engraved "LAB 100" on one side, "APO" on the other contains 100 mg labetalol hydrochloride. Available in bottles of 100; unit dose packages of 100; Apotex Long-Term Care unit dose packages (Apo-LTC Paks) of 620 and 700.

APO-LABETALOL 200 mg Tablets: Each white, capsule-shaped tablet, scored and engraved "LAB 200" on one side, "APO" on the other contains 200 mg labetalol hydrochloride. Available in bottles of 100 and 500; unit dose packages of 100; Apotex Long-Term Care unit dose packages (Apo-LTC Paks) of 620 and 700.

APO-LABETALOL (labetalol hydrochloride) Tablets contain 100 mg or 200 mg of labetalol hydrochloride. APO-LABETALOL Tablets also contains the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol, purified water, titanium dioxide. APO-LABETALOL 100 mg Tablets also contain the following colouring agents: D&C Yellow #10 Aluminum Lake 16%, FD&C Yellow #6 Aluminum Lake 40%.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

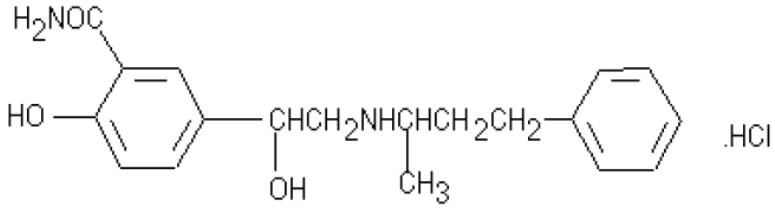
Proper/Common Name: Labetalol Hydrochloride

Chemical Names:

1) Benzamide, 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3- phenylpropyl)amino]ethyl]-, monohydrochloride;

2) 5-[1-Hydroxy-2-[(1-methyl-3-phenylpropyl)amino]- ethyl]salicylamide mono-hydrochloride.

Structural Formula:



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

Molecular Weight: 364.87 g/mol

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

Solubility: In water = 1:60; in ethanol = 1:60; in ether = almost insoluble; in chloroform = almost insoluble

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

CLINICAL TRIALS

Comparative Bioavailability Studies

A standard, randomized, two-way crossover, single-dose bioavailability study was conducted in sixteen (16) healthy, adult, male volunteers under fasting conditions to evaluate the relative bioavailability of single oral doses (1 x 200 mg) of APO-LABETALOL (labetalol hydrochloride) 200 mg Tablets manufactured by Apotex Inc., and Trandate® (labetalol hydrochloride) 200 mg Tablets manufactured by Roberts Pharmaceutical Canada Inc. The results are summarized in the

following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Labetalol (1 x 200 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	299.4 341.5 (52.6)	304.3 362.2 (64.2)	98.4	88.3-109.7
AUC_I (ng.h/mL)	344.0 386. 6 (49.2)	349.5 408.8 (59.5)	98.4	89.1-108.8
C_{max} (ng/mL)	122.5 130.3 (35.1)	125.2 148.0 (68.7)	97.8	77.3-123.8
T_{max}§ (h)	0.98 (38.2)	0.81 (41.5)		
$T_{½}$§ (h)	5.44 (33.0)	5.71 (44.2)		

* APO-LABETALOL (labetalol hydrochloride) 200 mg Tablets manufactured by Apotex Inc.

† Trandate® (labetalol hydrochloride) 200 mg Tablets manufactured by Roberts Pharmaceutical Canada Inc. were purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only."

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 mm Hg. 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 i.v. 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.

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25) Product Monograph. TRANDATE® (Labetalol hydrochloride tablets), Paladin Labs Inc., Date of revision: June 16, 2016. Control number: 190689.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

APO-LABETALOL
Labetalol Hydrochloride Tablets USP

Read this carefully before you start taking APO-LABETALOL and each time you get a refill. 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 APO-LABETALOL.

What is APO-LABETALOL used for?
APO-LABETALOL is used to treat high blood pressure (also known as hypertension) in adults. APO-LABETALOL can be used alone or with other medicines to treat this condition.

How does APO-LABETALOL work?
APO-LABETALOL belongs to a group of drugs called "beta-blockers".

- It makes your heart beat more slowly and less forcefully.
- It lowers your blood pressure by relaxing your blood vessels so that your blood flows more easily.

This medicine does not cure your disease but helps to control it. Therefore it is important to continue taking APO-LABETALOL regularly even if you feel fine.

What are the ingredients in APO-LABETALOL?
Medicinal ingredient: labetalol hydrochloride
Non-medicinal ingredients:.colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol, purified water, titanium dioxide. APO-LABETALOL 100 mg Tablets also contain the following colouring agents: D&C Yellow #10 Aluminum Lake 16%, FD&C Yellow #6 Aluminum Lake 40%.

APO-LABETALOL comes in the following dosage forms:
Tablets: 100 mg and 200 mg

Do not use APO-LABETALOL if you:

- Are allergic or hypersensitive to labetalol hydrochloride or to any of the other ingredients in APO-LABETALOL.
- 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, talk to your healthcare professional before you take APO-LABETALOL. 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. APO-LABETALOL 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 APO-LABETALOL.
- Are scheduled for surgery and will be given an anesthetic.
- Develop a skin rash while taking APO-LABETALOL.

Other warnings you should know about:
Do not stop taking APO-LABETALOL suddenly. This could cause chest pain or a heart attack. If your doctor decides that you should stop taking APO-LABETALOL, your dose may be reduced so that you need to use less and less before you stop the medicine completely.

The results of urine tests may be affected by taking APO-LABETALOL. If you need to have a urine test, tell your doctor that you have been given APO-LABETALOL tablets.

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 APO-LABETALOL:
- 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 to take APO-LABETALOL:
Your doctor will determine your dose based on your individual medical needs and will tell you when and how to take APO-LABETALOL. Take APO-LABETALOL exactly as prescribed.
APO-LABETALOL should be taken preferably after food.

Usual adult dose:
Starting daily dose: 100 mg twice a day
Daily maintenance dose: 200 to 400 mg twice a day
Maximum daily dose: 1200 mg per day (600 mg twice a day)

Your doctor may:
- Start you on a different dose or change your dose over time depending on how APO-LABETALOL works for you.
- Add another medicine like a diuretic (“water pill”) or an ACE inhibitor for you to take along with APO-LABETALOL to treat your high blood pressure.

Do not stop taking APO-LABETALOL or change your dose without first consulting your doctor. This can be dangerous.

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 taken too much APO-LABETALOL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using APO-LABETALOL?
These are not all the possible side effects you may feel when taking APO-LABETALOL. 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			
• **Hypotension (low blood pressure**): dizziness or lightheadedness leading to fainting can occur when changing positions, for example from lying down to standing up		✓	
• **Chest pain**			✓
UNCOMMON			
• **Bradycardia:** decreased heart rate that causes you to be dizzy or faint		✓	
• **Allergic reactions:** rash, swelling of the lips, face or neck, difficulty breathing or speaking			✓

• **Congestive heart failure:** irregular heartbeat, low heart rate, or other changes in heart symptoms		✓	
• Narrowing of the airways (**bronchospasm**) or other lung effects		✓	
• **Liver disorders:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite			✓
UNKNOWN FREQUENCY			
• **Lupus-like syndrome:** joint pain, muscle pain, chest pain when you cough or breath, 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:
Store at room temperature 15°C to 30°C. Protect from light.

Keep out of reach and sight of children.

If you want more information about APO-LABETALOL:

- 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). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products) or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc. Toronto, Ontario, M9L 1T9.

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