Product Monograph

Including Patient Medication Information

PrAPO-LABETALOL

Labetalol hydrochloride tablets

For oral use

100 mg and 200 mg

USP

Antihypertensive

Apotex Inc.
150 Signet Drive
Weston, Ontario
M9L 1T9

Date of Revision: JAN 07, 2026

Submission Control Number: 300161

Recent Major Label Changes

None at time of the most recent authorization

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part I: Healthcare Professional Information

1. Indications

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 4.1 Dosing Considerations and 9.2 Drug Interactions Overview).

However, APO-LABETALOL may be used alone as an initial agent in those patients in whom, in the judgement of the healthcare professional, 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 4.1 Dosing Considerations and 9.2 Drug Interactions Overview).

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.

1.1. Pediatrics

Pediatrics (< 18 years of age):

No data are available to Health Canada. Therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): Evidence from experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Therefore, lower doses of APO-LABETALOL are likely to be required in geriatric patients (see 7.1.4 Geriatrics and 4.2 Recommended Dose and Dosage Adjustment, *Geriatric patients*).

2. Contraindications

APO-LABETALOL is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging
- 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

3. Serious Warnings and Precautions Box

Severe hepatocellular injury

- Injury has occurred after both short term and long-term treatment with labetalol hydrochloride 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 (see 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic and Monitoring and Laboratory Tests).

4. Dosage and Administration

4.1. Dosing Considerations

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

4.2. 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 (see 7 Warnings and Precautions, General).

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

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

Geriatrics: Lower doses of APO-LABETALOL are likely to be required in elderly patients (see 7.1.4 Geriatrics).

Pediatrics: Health Canada has not authorized an indication for pediatric use.

4.2.1. Discontinuing Treatment

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.

4.4. Administration

APO-LABETALOL should be taken preferably after food.

4.5. Missed Dose

If a patient misses a dose, advise them to take the dose as soon as possible and continue with their regular schedule. However, a patient should not take 2 doses the same day.

5. Overdose

Symptoms

The signs and symptoms associated with labetalol hydrochloride tablets 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, 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablets, 100 mg and 200 mg of labetalol hydrochloride	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol and 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%.

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.

7. Warnings and Precautions

(Please see 3 Serious Warnings and Precautions Box)

General

Postural hypotension and syncope may occur in patients treated with APO-LABETALOL, particularly if the initial dose is too high or if dose titration is too rapid (see 4.2 Recommended Dose and Dosage Adjustment). 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.

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 heart 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 9.2 Drug Interactions Overview).

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 (see 7 Warnings and Precautions, Monitoring and Laboratory Tests). 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.

Immune

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.

Monitoring and Laboratory Tests

Appropriate liver function laboratory testing should be performed at regular intervals during APO-LABETALOL therapy (see 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

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

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 7 Warnings and Precautions, Cardiovascular; Endocrine and Metabolism; Immune). 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 4.2.1 Discontinuing Treatment.

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, healthcare professionals should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

7.1. Special Populations

7.1.1. 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.

7.1.2. Breastfeeding

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.

7.1.3. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics (≥ 65 years of age): 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 (see 4.2 Recommended Dose and Dosage Adjustment, Geriatric).

8. Adverse Reactions

8.1. Adverse Reaction Overview

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

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 (< 1.0%)

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 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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

8.5. Post-Market Adverse 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.

9. Drug Interactions

9.2. 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 tablets (see 7 Warnings and Precautions, Cardiovascular).

When used with diuretics and/or other antihypertensive agents the dose of APO-LABETALOL must be appropriately adjusted (see 4.1 Dosing Considerations).

9.4. Drug-Drug Interactions

Halothane: 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 anaesthesiologist should be informed when a patient is receiving APO-LABETALOL.

Nitroglycerin: 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: 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.

Tricyclic antidepressants: 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.

Fingolimod: 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.

9.5. 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 (see 4.1 Dosing Considerations and 10.3 Pharmacokinetics, Metabolism).

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

The presence of a metabolite of labetalol hydrochloride tablets in the urine may result in falsely elevated levels of urinary catecholamines when measured by a nonspecific trihydroxy indole (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.

10. Clinical Pharmacology

10.1. 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.

10.2. 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.

10.3. 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 i.v. 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.

Elimination

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.

Special Populations and Conditions

Hepatic impairment*:* 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 4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment, *Hepatic impairment*).

11. Storage, Stability and Disposal

APO-LABETALOL Tablets should be stored at room temperature 15°C to 30°C. Protect from light. Keep out of reach and sight of children.

Part II: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance: labetalol hydrochloride

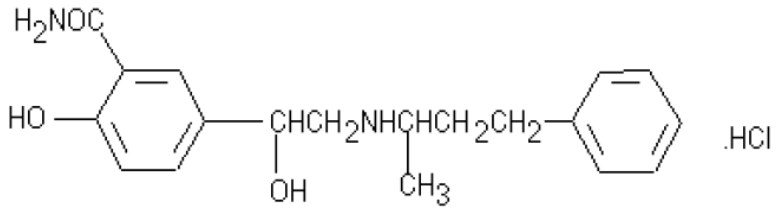
Chemical names:

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.

Molecular formula and molecular mass: $C_{19}H_{24}N_2O_3$.HCl and 364.87 g/mol

Structural formula:



Physiochemical properties: Labetalol hydrochloride is a white to off-white powder with a melting point around 180°C. Labetalol hydrochloride is soluble in water and in alcohol; it is insoluble in ether and chloroform; in water = 1:60; in ethanol = 1:60; in ether = almost insoluble; in chloroform = almost insoluble. The pH of a 1% w/v solution of labetalol hydrochloride is between 4.0-5.0.

14. Clinical Trials

14.2. Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of APO-LABETALOL tablets, 200 mg (Apotex Inc.) and TRANDATE® tablets, 200 mg (Roberts Pharmaceutical Canada Inc.) was conducted in healthy adult male subjects under fasting conditions. Comparative bioavailability data from 16 subjects that were included in the

statistical analysis are presented in the following table:

Summary Table of the Comparative Bioavailability Data

Labetalol (1 x 200 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% 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}[3] (h)	0.83 (0.50 - 2.0)	0.75 (0.50 - 1.33)		
T½[4] (h)	5.44 (33.0)	5.71 (44.2)		

[1] APO-LABETALOL (labetalol as labetalol hydrochloride) tablets, 200 mg (Apotex Inc.)

[2] TRANDATE® (labetalol as labetalol hydrochloride) tablets, 200 mg (Roberts Pharmaceutical Canada Inc.)

[3] Expressed as the median (range) only

[4] Expressed as the arithmetic mean (CV %) only

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.

16. Non-Clinical Toxicology

The non-clinical toxicology data, on which the original indication was authorized, is not available.

17. Supporting Product Monographs

1. TRANDATE® (Tablets, 100 mg and 200 mg), control 293154, product monograph, Endo Operations Ltd. (2025-05-23)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-LABETALOL

Labetalol hydrochloride tablets

This Patient Medication Information is written for the person who will be taking **APO-LABETALOL**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **APO-LABETALOL**, talk to a healthcare professional.

Serious warnings and precautions box

Liver disorders: APO-LABETALOL may cause severe liver problems. This rare and serious side effect has occurred in patients taking labetalol hydrochloride tablets for both short and long periods. It also developed progressively, and with very little symptoms. It is usually reversible, but there has been rare cases of hepatic necrosis (cell death in the liver), and even death.

What APO-LABETALOL is used for:
APO-LABETALOL is used in adults (18 years of age or older) to treat high blood pressure (also known as hypertension). It can be used alone or with other medicines to treat this condition.

How does APO-LABETALOL works:
APO-LABETALOL belongs to a group of medicines called “beta-blockers”. It lowers blood pressure by:

- making your heart beat more slowly and less forcefully;
- relaxing your blood vessels so that your blood flows more easily.

This medicine does not cure your disease but helps to control it.

The ingredients in APO-LABETALOL are:

Medicinal ingredient: Labetalol hydrochloride

Non-medicinal ingredients: Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol and 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 form:
Tablets: 100 mg and 200 mg.

Do not use APO-LABETALOL if you:

- are allergic to labetalol hydrochloride or any of the other ingredients in APO-LABETALOL.
- have heart failure and your symptoms are getting worse (e.g., 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 called atrioventricular block (also known as "AV block").
- have asthma or a history of lung problems (e.g., bronchitis or emphysema).
- have serious problems with blood flow in your feet and legs.

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 heart failure. Your healthcare professional will ensure your condition is under control before taking APO-LABETALOL.
- have chest pain (angina pectoris).
- are taking any other medicines.
- have or are at risk for diabetes. APO-LABETALOL may make you more prone to low blood sugar, especially if you also take insulin or oral diabetes medications.
- have a condition called pheochromocytoma (a tumour of the adrenal gland).
- have thyroid problems.
- have liver problems.
- have a history of severe allergic reactions.
- are pregnant, think you might be pregnant or are planning on becoming pregnant. APO-LABETALOL is not usually recommended for use during pregnancy. Your healthcare

professional will consider the benefit of you being treated with APO-LABETALOL against the risk to your unborn baby.

- are breastfeeding or planning to breastfeed. You should not breastfeed while taking APO-LABETALOL.
- are going to have an operation or surgery. Let the medical staff of the operation or surgery know, in particular the anesthetist, that you are taking APO-LABETALOL.
- are 65 years of age or older.

Other warnings you should know about:
APO-LABETALOL can cause serious side effects, including:

- **Heart failure:** Patients taking APO-LABETALOL can develop heart failure. Your healthcare professional will check you for signs and symptoms of heart failure during your treatment with APO-LABETALOL.
- **Bradycardia** (abnormally slow heartbeat): Your heart rate may lower while you are taking APO-LABETALOL. If it gets too low, your dose may be reduced or your healthcare professional may tell you how to safely stop your treatment with APO-LABETALOL.
- **Allergic reactions:** While you are taking APO-LABETALOL:
  - a severe allergic reaction may be harder to treat.
  - you may be more likely to have a severe allergic reaction if you have a history of them.

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.
Check-ups and testing: Based on your health history, your healthcare professional may perform blood tests regularly during your treatment with APO-LABETALOL. This is to monitor:

- your blood sugar levels;
- the health of your heart, liver, and thyroid.

It is also recommended that you get regular eye exams while taking APO-LABETALOL to monitor the health of your eyes.

Taking APO-LABETALOL may also affect the results of urine tests. If you need to have a urine test, tell your healthcare professional that you are taking APO-LABETALOL.

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:

- medicines used to treat high blood pressure, chest pain and heart rhythm problems (e.g., verapamil, diltiazem, diuretics (also known as “water pills”), nitroglycerin).
- insulin, or medications taken by mouth to treat high levels of sugar in the blood (diabetes).
- epinephrine, used to treat severe allergic reactions.
- anesthetics, medicines used during surgery (e.g., halothane).
- medicines used to reduce the amount of acid in the stomach (e.g., cimetidine).
- medicines used to treat depression (e.g., tricyclic antidepressants).
- medicines used to treat multiple sclerosis (e.g., fingolimod).

How to take APO-LABETALOL:

- Take APO-LABETALOL exactly as your healthcare professional has told you to.
- APO-LABETALOL should be taken preferably after food.
- It is important to continue taking APO-LABETALOL regularly even if you feel fine.
- Your healthcare professional may add another medicine like a diuretic (“water pill”) 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 consulting your healthcare professional. This can be dangerous. If you suddenly stop taking APO-LABETALOL, this could cause chest pains or a heart attack. If your healthcare professional decides that you should stop taking APO-LABETALOL, your dose will be reduced slowly over a period of 2 weeks before you stop taking the medicine completely. Your healthcare professional will closely monitor your health during this time.

Usual dose:

Your healthcare professional will decide how much APO-LABETALOL you should take each day depending on your condition.

They may also change your dose depending on how you respond to the treatment.

Usual starting dose: 100 mg twice a day.
Usual maintenance dose: 200 mg to 400 mg twice a day.
Maximum dose: 1200 mg per day (600 mg twice a day).

Overdose:

Symptoms of overdose with APO-LABETALOL may include:

- very low blood pressure (may occur when you go from lying or sitting to standing up);
- an abnormally slow or irregular heart beat;
- heart failure (your heart doesn't pump enough blood for your body's needs);
- difficulty breathing, tightness in your chest;
- low blood sugar.

If you think you, or a person you are caring for, have taken too much APO-LABETALOL, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:
If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

Possible side effects from using APO-LABETALOL:
These are not all the possible side effects you may have when taking APO-LABETALOL. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with APO-LABETALOL may include:

- dizziness
- headache
- nausea or vomiting
- lack of energy
- general feeling of discomfort
- aches and pains
- muscle cramps
- shaking (tremor)
- blurred vision
- nosebleeds
- indigestion
- change in taste
- constipation
- dry mouth
- sore throat
- stuffy nose

- "pins and needles" sensation on the skin
- itchy skin
- inability to keep or maintain an erection
- loss of sex drive

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
Common			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).		✓	
Chest pain			✓
Raynaud's phenomenon (episodes of reduced blood flow): cold feeling in fingers and toes (and sometimes nose, lips and ears), prickly or stinging feeling, change in skin colour to white then blue.		✓	
Depression (sad mood that won't go away): difficulty sleeping, sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations,		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
family, gatherings and activities with friends, reduced libido (sex drive), or thoughts of death or suicide.			
Rare			
Bradycardia (abnormally slow heartbeat): decreased heart rate that causes you to be dizzy or faint.		✓	
Allergic reactions: rash, hives swelling of the lips, face, tongue, throat or neck, difficulty breathing, swallowing or speaking, wheezing, drop in blood pressure, feeling sick to your stomach, or vomiting			✓
Congestive heart failure (heat does not pump blood as well as it should): shortness of breath, fatigue, weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, or reduced ability to exercise.		✓	
Bronchospasm (when there is a sudden narrowing of the airway):		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
difficulty breathing with wheezing or coughing.			
Liver disorders: yellowing of the skin or eyes (jaundice), right upper stomach area pain, swelling, unusual dark urine, nausea, vomiting, or unusual tiredness.			✓
Unknown			
Lupus-like syndrome: joint pain, muscle pain, fatigue, fever, chest pain when you cough or breath.		✓	
Hypoglycemia (low blood sugar): thirst, frequent urination, hunger, nausea and dizziness, fast heartbeat, tingling trembling, nervousness, sweating, low energy.		✓	
Peyronie's disease (a condition where scar tissue forms under the skin of the penis): penile pain, shortening of the penis, erection problems, or significant bend to the penis.		✓	
Toxic myopathy (muscle damage caused by medications): muscle weakness (especially of		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
your upper arms, shoulders and thighs), muscle cramps, stiffness and spasms, fatigue with exercise, lack of energy.			
Skin reactions: rash, itchiness, flushing, red patches of skin covered with thick, silvery scales, dry cracked skin that may bleed, burning, or soreness.		✓	
Angioedema (swelling of tissue under the skin): difficulty breathing, swollen face, hands and feet, genitals tongue, throat, swelling of the digestive tract causing diarrhea, nausea or vomiting.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare 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 the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); 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.

Last Revised: JAN 07, 2026