

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>Pr</sup>**TRANDATE**<sup>®</sup>

Labetalol hydrochloride tablets

100 mg and 200 mg

USP

Antihypertensive Agent

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# PrTRANDATE<sup>®</sup>

Labetalol hydrochloride tablets

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablet 100 mg, 200 mg	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol, purified water and titanium dioxide.  The 100 mg tablets also contains: D&C Yellow #10 Aluminum Lake and Sunset Yellow Aluminum Lake 40%.

### INDICATIONS AND CLINICAL USE

TRANDATE<sup>®</sup> (labetalol hydrochloride tablets) is indicated for the treatment of hypertension.

TRANDATE<sup>®</sup> is usually used in combination with other drugs, particularly a thiazide diuretic (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

However, TRANDATE<sup>®</sup> 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.

TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> with a diuretic has been found to be compatible. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with TRANDATE<sup>®</sup>.

**Geriatrics:** Lower doses of TRANDATE<sup>®</sup> 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**

TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> (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 TRANDATE<sup>®</sup> 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, TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> be re-instituted promptly, at least temporarily.

### **Cardiac Failure**

Cardiac failure should be controlled with digitalis and diuretics before TRANDATE<sup>®</sup> treatment is initiated. TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup>. Therefore, administration of TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> from unopposed vagal activity remaining after blockade of beta<sub>1</sub>-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**

TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

### **Pheochromocytoma**

While TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> to patients with known or suspected pheochromocytoma.

### **Hepatic/Biliary/Pancreatic**

There have been rare reports of severe hepatocellular injury with TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> 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, TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup>.

## **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 TRANDATE<sup>®</sup> 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, TRANDATE<sup>®</sup> should be withdrawn gradually following the recommendation given under “Abrupt Cessation of Therapy” (see WARNINGS AND PRECAUTIONS).

In emergency surgery, since TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> 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. TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> are increased in the elderly. In addition, the hypotensive response is greater in this age group following administration. Therefore, lower doses of TRANDATE<sup>®</sup> 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 TRANDATE® therapy (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic section).

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The most serious reported adverse effects of TRANDATE® (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 (<1.0%).

**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 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 TRANDATE<sup>®</sup> (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 TRANDATE<sup>®</sup>. There are rare reports of patients who developed lupus-like syndromes while on TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup>.

When used with diuretics and/or other antihypertensive agents the dose of TRANDATE<sup>®</sup> must be appropriately adjusted (see DOSAGE AND ADMINISTRATION).

## **Drug-Drug Interactions**

TRANDATE<sup>®</sup> and halothane have additive hypotensive effects. High doses of halothane (3%) with TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup>.

TRANDATE<sup>®</sup> blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. When TRANDATE<sup>®</sup> is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Cimetidine has been shown to increase the oral bioavailability of TRANDATE<sup>®</sup>. As cimetidine might be given to patients with hypertension also receiving TRANDATE<sup>®</sup>, 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 TRANDATE<sup>®</sup> in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with TRANDATE<sup>®</sup> 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. TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup>, 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

TRANDATE<sup>®</sup> (labetalol hydrochloride) should be taken preferably after food.

### Recommended Dose and Dosage Adjustment

The dosage of TRANDATE<sup>®</sup> 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.

### **Geriatrics Patients**

Lower doses of TRANDATE<sup>®</sup> 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.
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### **Symptoms**

The signs and symptoms associated with TRANDATE<sup>®</sup> overdose 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 TRANDATE<sup>®</sup> 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<sub>2</sub>-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 TRANDATE<sup>®</sup> (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**

TRANDATE<sup>®</sup> (labetalol hydrochloride) is an adrenergic receptor blocking agent possessing both alpha<sub>1</sub>-(post-synaptic) and beta-receptor blocking activity. Its action on beta-receptors is four times stronger than that on alpha-receptors. It antagonizes beta<sub>1</sub>- and beta<sub>2</sub>-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 µg 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.

**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**

Store between 15 °C and 30 °C.

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

TRANDATE<sup>®</sup> (labetalol hydrochloride tablets) contains either 100 mg or 200 mg of labetalol hydrochloride.

TRANDATE<sup>®</sup> tablets also contain the following excipients: Colloidal silicon dioxide, Croscarmellose Sodium, Hydroxypropyl Cellulose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Methylcellulose, Polyethylene glycol, Purified Water and Titanium dioxide.

The 100 mg tablets also contains: D&C Yellow #10 Aluminum Lake and Sunset Yellow Aluminum Lake 40%.

**100 mg Tablets:** Each orange, capsule-shaped tablet contains: labetalol HCl 100 mg. Scored and engraved LAB 100 on one side, PLB on the other side. Bottles of 100.

**200 mg Tablets:** Each white, capsule-shaped tablet contains: labetalol HCl 200 mg. Scored and engraved LAB 200 on one side, PLB on the other side. Bottles of 100.

## PART II: SCIENTIFIC INFORMATION

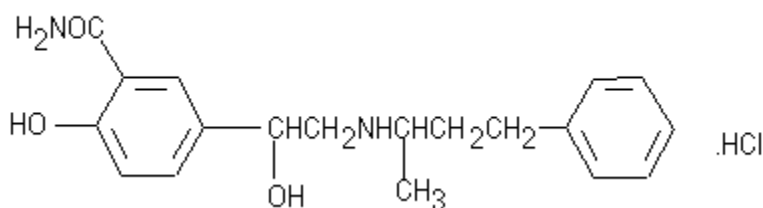
### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper Name: Labetalol hydrochloride

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

Structural Formula:



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

Molecular Weight: 364.9 g/mol

Physicochemical Properties: Labetalol hydrochloride is a white to off-white powder with a melting point around 185°C

Solubility: 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

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



## REFERENCES

1. Adam WR, Meagher EJ, Barter CE. Labetalol, beta-blockers, and acute deterioration of chronic airway obstruction. *Clin Exp Hyperten* 1982; A4(8):1419-1428.
2. Bellamy GR, Hunyor SN, *et al.* Magnitude and mechanisms of the antihypertensive action of labetalol, including ambulatory assessment. *Br J Clin Pharmacol* 1983; 16:916.
3. Brogden RN, Heel RC, *et al.* Labetalol: a review of its pharmacology and therapeutic use in hypertension. *Drugs* 1978; 15(4):251-270.
4. Cummings AMM, Brown JJ, *et al.* Blood pressure reduction by incremental infusion of labetalol in patients with severe hypertension. *Br J Clin Pharmacol* 1979; 8:359-364.
5. Eisalo A, Virta P. Treatment of hypertension in the elderly with labetalol. *Acta Med Scan* 1982; Suppl 665:129-133.
6. Farmer JB, Kennedy I, *et al.* Pharmacology of AH 5158: a drug which blocks both  $\alpha$ - and  $\beta$ -adrenoceptors. *Br J Pharmacol* 1972; 45:660-675.
7. George RB, Burford JG, *et al.* Effects of a new alpha and beta adrenergic antagonist in hypertensive patients with reversible chronic airways obstruction. *Chest* 1981; 80(3):356.
8. Homeida M, Jackson L, Roberts CJC. Decreased first-pass metabolism of labetalol in chronic liver disease. *Br Med J* 1978; 2:1048-1050.
9. Jackson SHD, Beevers DG. Comparison of the effects of single doses of atenolol and labetalol on airways obstruction in patient with hypertension and asthma. *Br J Clin Pharmacol* 1983; 15:553-556.
10. Kanto JH. Current status of labetalol, the first alpha- and beta-blocking agent. *Int J Clin Pharmacol Ther Toxicol* 1985; 23(11):617-628.
11. Kelly JG, McGarry K *et al.* Bioavailability of labetalol increases with age. *Br J Clin Pharmacol* 1982; 14:304-305.
12. Lund-Johansen P. Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983; 75 (Suppl 4A):24-31.
13. MacCarthy EP, Bloomfield SS. Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. *Pharmacother* 1983; 3(4):193-219.
14. Maconochie JG, Woodings EP, Richards DA. Effects of labetalol and propranolol on histamine-induced bronchoconstriction in normal subjects. *Br J Clin Pharmacol* 1977; 4:157-162.

15. Mazzola C, Guffanti E, *et al.* Respiratory effects of labetalol in anginous or hypertensive patients. *Curr Ther Res* 1982; 31(2):219-231.
16. Morgan T, Gilles A, *et al.* The effect of labetalol in the treatment of severe drug-resistant hypertension. *Med J Austr* 1978; 1:393-396.
17. Papademetriou V, Notargiacomo AV, *et al.* Treatment of severe hypertension with intravenous labetalol. *Clin Pharmacol Ther* 1982; 32(4):431-435.
18. Prichard BNC. Combined alpha- and beta-receptor inhibition in the treatment of hypertension. *Drugs* 1984; 28(Suppl 2):51-68.
19. Richards DA, Woodings EP, *et al.* The effects of oral AH5158, a combined - and - adrenoceptor antagonist, in healthy volunteers. *Br J Clin Pharmacol* 1974; 1:505-510.
20. Richards DA, Turner P (eds). Proceedings of a symposium on labetalol - April 1976. *Br J Clin Pharmacol* 1976; 3(Suppl 3):677-678.
21. Richards DA, Woodings EP, Maconochie JG. Comparison of the effects of labetalol and propranolol in healthy men at rest and during exercise. *Br J Clin Pharmacol* 1977; 4:15-21.
22. Richards DA, Prichard BNC. Proceedings of the second symposium on labetalol - March 1979. *Br J Clin Pharmacol* 1979; 8(Suppl 2):85S-244S.
23. Richards DA, Robertson JIS, Prichard BNC. Proceedings of the third symposium on labetalol - June 1981. *Br J Clin Pharmacol* 1982; 13(Suppl 1):1S-141S.
24. Weber MA, Drayer JIM, Kaufman CA. The combined alpha- and beta-adrenergic blocker labetalol and propranolol in the treatment of high blood pressure: similarities and differences. *J Clin Pharmacol* 1984; 24:103-112.

## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PART III: PATIENT MEDICATION INFORMATION

#### **Pr**TRANDATE®

(Labetalol hydrochloride tablets USP)

Read this carefully before you start taking **TRANDATE®** 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 **TRANDATE®**.

#### **What is TRANDATE® used for?**

TRANDATE® is used to treat high blood pressure (also known as hypertension) in adults. TRANDATE® can be used alone or with other medicines to treat this condition.

#### **How does TRANDATE® work?**

TRANDATE® 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 TRANDATE® regularly even if you feel fine.

#### **What are the ingredients in TRANDATE®?**

Medicinal ingredient: labetalol hydrochloride

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol, purified water and titanium dioxide.

The 100 mg tablets also contains: D&C Yellow #10 Aluminum Lake and Sunset Yellow Aluminum Lake 40%.

#### **TRANDATE® comes in the following dosage forms:**

Tablets: 100 mg and 200 mg

**Do not use TRANDATE<sup>®</sup> if you:**

- Are allergic or hypersensitive to labetalol hydrochloride or to any of the other ingredients in TRANDATE<sup>®</sup>.
- 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 TRANDATE<sup>®</sup>. 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. TRANDATE<sup>®</sup> 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 TRANDATE<sup>®</sup>.
- Are scheduled for surgery and will be given an anesthetic.
- Develop a skin rash while taking TRANDATE<sup>®</sup>.

**Other warnings you should know about:**

**Do not** stop taking TRANDATE<sup>®</sup> suddenly. This could cause chest pain or a heart attack. If your doctor decides that you should stop taking TRANDATE<sup>®</sup>, 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 TRANDATE<sup>®</sup>. If you need to have a urine test, tell your doctor that you have been given TRANDATE<sup>®</sup> 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 TRANDATE®:**

- 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 TRANDATE®:**

Your doctor will determine your dose based on your individual medical needs and will tell you when and how to take TRANDATE®. Take TRANDATE® exactly as prescribed.

TRANDATE® 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 TRANDATE® works for you.
- Add another medicine like a diuretic (“water pill”) or an ACE inhibitor for you to take along with TRANDATE® to treat your high blood pressure.

**Do not** stop taking TRANDATE® 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 TRANDATE<sup>®</sup>, 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 TRANDATE<sup>®</sup>?**

These are not all the possible side effects you may feel when taking TRANDATE<sup>®</sup>. 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	
<b>COMMON</b>			
<ul style="list-style-type: none"> <li><b>Hypotension (low blood pressure):</b> dizziness or lightheadedness leading to fainting can occur when changing positions, for example from lying down to standing up</li> </ul>		✓	
<ul style="list-style-type: none"> <li><b>Chest pain</b></li> </ul>			✓
<b>UNCOMMON</b>			
<ul style="list-style-type: none"> <li><b>Bradycardia:</b> decreased heart rate that causes you to be dizzy or faint</li> </ul>		✓	
<ul style="list-style-type: none"> <li><b>Allergic reactions:</b> rash, swelling of the lips, face or neck, difficulty breathing or speaking</li> </ul>			✓
<ul style="list-style-type: none"> <li><b>Congestive heart failure:</b> irregular heartbeat, low heart rate, or other changes in heart symptoms</li> </ul>		✓	
<ul style="list-style-type: none"> <li>Narrowing of the airways (<b>bronchospasm</b>) or other lung effects</li> </ul>		✓	
<ul style="list-style-type: none"> <li><b>Liver disorders:</b> yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite</li> </ul>			✓
<b>UNKNOWN FREQUENCY</b>			
<ul style="list-style-type: none"> <li><b>Lupus-like syndrome:</b> joint pain, muscle pain, chest pain when you cough or breath, breathing difficulties (shortness of breath or labored breathing)</li> </ul>		✓	

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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

#### **3 ways to report:**

- Online at [MedEffect](#);
  - By calling 1-866-234-2345 (toll-free);
  - By completing a Consumer Side Effect Reporting Form and sending it by:
    - Fax to: 1-866-678-6789 (toll-free), or
    - Mail to: Canada Vigilance Program  
Health Canada, Postal Locator 0701E  
Ottawa, ON  
K1A 0K9
- Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

*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 between 15 °C and 30 °C.

Keep out of reach and sight of children.

### **If you want more information about TRANDATE®:**

- 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](#); the manufacturer's website [www.paladin-labs.com](http://www.paladin-labs.com), or by calling 1-888-867-7426.

This leaflet was prepared by Paladin Labs Inc.

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