

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

TRANDATE 100mg & 200mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 100 mg or 200 mg of labetalol hydrochloride. TRANDATE tablets contain lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Trandate tablets 100 mg are circular biconvex tablets with orange film coat, each containing labetalol hydrochloride 100 mg, marked TRANDATE 100 on one face.

Trandate tablets 200 mg are circular biconvex tablets with orange film coat, each containing labetalol hydrochloride 200 mg, marked TRANDATE 200 on one face.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRANDATE tablets are indicated for the treatment of all forms of hypertension, and all grades of hypertension (mild, moderate and severe) when oral antihypertensive therapy is desirable.

TRANDATE tablets are also indicated for the treatment of patients with angina pectoris coexisting with hypertension.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Adults

Treatment may start with one 100 mg tablet twice daily but in some patients, including those already being treated with antihypertensive medicines, the elderly, and those of low body weight and for patients with newly diagnosed mild hypertension one 50 mg tablet twice daily may be more appropriate. The first dose is best taken at night before retiring.

If the blood pressure is not controlled by the initial dosage, increases should be made at intervals of one to two weeks. By prescribing tablets of increasing strength, the dose can be maintained until a total daily dose of 800 mg is reached. Daily doses of up to 2400 mg have been given in the treatment of severe and refractory hypertension. In such patients it is preferable to administer labetalol three or four times daily. Blood pressure should be monitored regularly and the dose adjusted as required.

Satisfactory control of blood pressure will be obtained in most patients at a total daily dosage of 200mg (one 100 mg tablet twice daily) to 400 mg (one 200 mg tablet twice daily).

In severe hypertension, particularly that of pregnancy, the dosage may be increased on a daily basis until adequate control of blood pressure is obtained.

For hospital in-patients daily increases in dosage may be made if the need to reduce blood pressure is urgent. If it is necessary to reduce the blood pressure rapidly in very severe hypertension, intravenous labetalol is indicated.

In hypertensive patients with angina, the dose of labetalol will be that required to control the hypertension.

Children

Not applicable.

Use with other agents

Hypertension is usually controlled by labetalol alone. Diuretic therapy is not usually necessary in patients receiving labetalol tablets, but may be introduced or continued if required. Diuretics usually increase the antihypertensive action of labetalol.

If labetalol tablets are prescribed together with another antihypertensive medicine, such as methyldopa or clonidine, an additive effect may be expected in patients who are responsive to both medicines. When transferring patients from other medicines, labetalol tablets should be introduced as recommended above and the dosage of the existing therapy progressively decreased.

Abrupt withdrawal of clonidine or beta-adrenoceptor blockers is undesirable.

Method of administration

Tablets should be taken with food.

4.3 CONTRAINDICATIONS

- Cardiogenic shock.
- Uncontrolled, incipient or digitalis-refractory heart failure.
- Sick sinus syndrome (including sino-atrial block).
- Second or third degree heart block.
- Prinzmetal's angina.
- History of wheezing or asthma.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Bradycardia (<45-50 bpm).
- Hypotension.
- Hypersensitivity to labetalol or to any of the excipients listed in 6.1.
- Severe peripheral circulatory disturbances.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking medicines. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Gradual discontinuance of the medicine should be considered if any such reaction is not otherwise explicable.

The occurrence of intraoperative floppy iris syndrome (IFIS, a variation of Horner's syndrome) has been observed during cataract surgeries in some patients who were being treated with tamsulosine, or have been treated with tamsulosine in the past. IFIS has also been reported when other alpha-1- blockers were being used, and the possibility of a class effect cannot be excluded. Since IFIS can lead to a higher chance of complications during cataract surgeries, the ophthalmologist needs to be informed if alpha-1-blockers are currently being used, or have been used in the past.

There have been rare reports of severe hepatocellular injury with labetalol therapy. The hepatic injury is usually reversible and has occurred after both short term and long term

treatment. Appropriate laboratory testing should be done at the first sign or symptom of liver dysfunction. If there is laboratory evidence of liver injury or the patient is jaundiced, labetalol should be stopped and not restarted.

Due to negative inotropic effects, special care should be taken with patients whose cardiac reserve is poor and heart failure should be controlled before starting labetalol therapy.

Patients, particularly those with ischaemic heart disease, should not interrupt/discontinue abruptly labetalol therapy. The dosage should be gradually reduced, i.e. over 1-2 weeks, if necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop.

It is not necessary to discontinue labetalol therapy in patients requiring anaesthesia but the anaesthetist must be informed and the patient should be given intravenous atropine prior to induction. During anaesthesia labetalol may mask the compensatory physiological responses to sudden haemorrhage (tachycardia and vasoconstriction). Close attention must therefore be paid to blood loss and the blood volume maintained. If beta-blockade is interrupted in preparation for surgery, therapy should be discontinued for at least 24 hours. Anaesthetic agents causing myocardial depression (e.g. cyclopropane, trichloroethylene) should be avoided. Labetalol may enhance the hypotensive effects of halothane.

In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta-blockers should be used with great caution as aggravation of these disorders may occur.

Beta-blockers may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to bradycardia, the dosage should be reduced.

Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of obstructive airways disease unless no alternative treatment is available. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken. If bronchospasm should occur after the use of labetalol it can be treated with a beta2-agonist by inhalation, e.g. salbutamol (the dose of which may need to be greater than the usual dose in asthma), and, if necessary, intravenous atropine 1 mg.

Due to a negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block. Patients with liver or kidney insufficiency may need a lower dosage, depending on the pharmacokinetic profile of the compound. The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly.

Patients with a history of psoriasis should take beta-blockers only after careful consideration.

Risk of anaphylactic reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Labetalol interferes with laboratory tests for catecholamines.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant use not recommended

- Calcium antagonists such as verapamil and to a lesser extent diltiazem have a negative influence on contractility and atrio-ventricular conduction.
- Digitalis glycosides used in association with beta-blockers may increase atrio-ventricular conduction time.
- Clonidine: Beta-blockers increase the risk of rebound hypertension. When clonidine is used in conjunction with non-selective beta-blockers, such as propranolol, treatment with clonidine should be continued for some time after treatment with the beta-blocker has been discontinued.
- Monoamine oxidase inhibitors (except MOA-B inhibitors).

Use with caution

- Class I antiarrhythmic agents (e.g. disopyramide, quinidine) and amiodarone may have potentiating effects on atrial conduction time and induce negative inotropic effect.
- Insulin and oral antidiabetic drugs may intensify the blood sugar lowering effect, especially of nonselective beta-blockers. Beta-blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).
- Anaesthetic drugs may cause attenuation of reflex tachycardia and increase the risk of hypotension.
- Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking agent. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided.
- Cimetidine, hydralazine and alcohol may increase the bioavailability of labetalol.
- Several different drugs or drug classes may enhance the hypotensive effects of labetalol: ACE inhibitors; angiotensin-II antagonists; aldesleukin, alprostadil; anxiolytics; hypnotics; moxislyte; diuretics; alpha-blockers.
- Several different drugs or drug classes may antagonise the hypotensive effects of labetalol: NSAIDs, corticosteroids; oestrogens; progesterones.

Take into account

- Calcium antagonists: dihydropyridine derivatives such as nifedipine. The risk of hypotension may be increased. In patients with latent cardiac insufficiency, treatment with beta-blockers may lead to cardiac failure.
- Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effect of betablockers.
- Sympathomimetic agents may counteract the effect of beta-adrenergic blocking agents.
- Concomitant use of tricyclic antidepressants, barbiturates, phenothiazines or other antihypertensive agents may increase the blood pressure lowering effect of labetalol. Concomitant use of tricyclic antidepressants may increase the incidence of tremor.
- Labetalol has been shown to reduce the uptake of radioisotopes of metaiodobenzylguanidine (MIBG), and may increase the likelihood of a false negative study. Care should therefore be taken in interpreting results from MIBG scintigraphy. Consideration should be given to withdrawing labetalol for several days at least before MIBG scintigraphy, and substituting other beta or alpha-blocking drugs.
- Antimalarials such as mefloquine or quinine may increase the risk of bradycardia.
- Ergot derivatives may increase the risk of peripheral vasoconstriction.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Although no teratogenic effects have been demonstrated in animals, labetalol should only be used during the first trimester if the potential benefit outweighs the potential risk.

Labetalol crosses the placental barrier and the possibility of the consequences of alpha- and beta-adrenoceptor blockade in the foetus and neonate should be borne in mind. Perinatal and

neonatal distress (bradycardia, hypotension, respiratory depression, hypoglycaemia, hypothermia) has been rarely reported. Sometimes these symptoms developed a day or two after birth. Response to supportive measures (e.g. intravenous fluids and glucose) is usually prompt but with severe preeclampsia, recovery may be slower. This may be related to diminished liver metabolism in premature babies.

Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period. Intra-uterine and neonatal deaths have been reported with labetalol but other medicines (e.g. vasodilators, respiratory depressants) and the effects of pre-eclampsia, intra-uterine growth retardation and prematurity were implicated. Such clinical experience warns against unduly prolonging high dose labetalol and delaying delivery and against co-administration of hydralazine.

Breast-feeding

Labetalol is excreted in breast milk. Breastfeeding is therefore not recommended.

Nipple pain and Raynaud's phenomenon of the nipple have been reported (see section 4.8).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 UNDERSIRABLE EFFECTS

Most side-effects are transient and occur during the first few weeks of treatment with labetalol. They include:

Blood and lymphatic system disorders

Rare reports of positive anti-nuclear antibodies unassociated with disease, hyperkalaemia, particularly in patients who may have impaired renal excretion of potassium, thrombocytopenia.

Psychiatric disorders

Depressed mood and lethargy, hallucinations, psychoses, confusion, sleep disturbances, nightmares.

Nervous system disorders

Headache, tiredness, dizziness, tremor has been reported in the treatment of hypertension of pregnancy.

Eye disorders

Impaired vision, dry eyes.

Cardiac disorders

Bradycardia, heart block, heart failure, hypotension.

Vascular disorders

Ankle oedema increase of an existing intermittent claudication, postural hypotension, cold or cyanotic extremities, Raynaud's phenomenon, paraesthesia of the extremities.

Respiratory, thoracic and mediastinal disorders

Bronchospasm (in patients with asthma or a history of asthma), nasal congestion, interstitial lung disease.

Gastrointestinal disorders

Epigastric pain, nausea, vomiting, diarrhoea.

Hepato-biliary disorders

Raised liver function tests, jaundice (both hepatocellular and cholestatic), hepatitis and hepatic necrosis.

Skin and subcutaneous tissue disorders

Sweating, tingling sensation in the scalp, usually transient, also may occur in a few patients early in treatment, reversible lichenoid rash systemic lupus erythematosus, exacerbation of psoriasis.

Musculoskeletal, connective tissue and bone disorders

Cramps, toxic myopathy.

Renal and urinary disorders

Acute retention of urine, difficulty in micturition.

Reproductive system and breast disorders

Ejaculatory failure.

Frequency 'not known': Nipple pain, Raynaud's phenomenon of the nipple (see section 4.6).

General disorders and administration site conditions

Hypersensitivity (rash, pruritus, angioedema and dyspnoea), drug fever, masking of the symptoms of thyrotoxicosis or hypoglycaemia, reversible alopecia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 OVERDOSE

Symptoms of overdosage are bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. Absorption of any drug material still present in the gastro-intestinal tract can be prevented by gastric lavage, administration of activated charcoal and a laxative.

Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 mcg/min, or dobutamine, starting with a dose of approximately 2.5 mcg/min, until the required effect has been obtained. If this does not produce the desired effect, intravenous administration of 8-10 mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed, if necessary, by an IV infusion of glucagon at 1-3 mg/hour.

Administration of calcium ions, or the use of a cardiac pacemaker, may also be considered.

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

Labetalol does have membrane stabilising activity which may have clinical significance in overdosage.

Haemodialysis removes less than 1% labetalol from the circulation.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Alpha and beta blocking agents, ATC code: C07AG01

Mechanism of action

Labetalol lowers blood pressure by blocking peripheral arteriolar alpha-adrenoceptors thus reducing peripheral resistance, and by concurrent beta-blockade, protects the heart from the reflex sympathetic drive that would otherwise occur. Cardiac output is not significantly reduced at rest or after moderate exercise. Increases in systolic pressure during exercise are reduced but corresponding changes in the diastolic pressure are essentially normal.

In patients with angina pectoris coexisting with hypertension, the reduced peripheral resistance decreases myocardial afterload and oxygen demand. All these effects would be expected to benefit hypertensive patients and those with coexisting angina.

5.2 PHARMACOKINETIC PROPERTIES

The plasma half-life of labetalol is about four hours. About 50% of labetalol in the blood is protein bound. Labetalol is metabolised mainly through conjugation to inactive glucuronide metabolites. These are excreted both in urine and via the bile into the faeces.

Only negligible amounts of the drug cross the blood brain barrier in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

lactose, maize starch, pregelatinized maize starch, magnesium stearate, Pharmacoat 606, Opaspray M-1-3499D, methyl hydroxybenzoate and propyl hydroxybenzoate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or identified as part of the registration of this medicine.

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE bottle containing 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

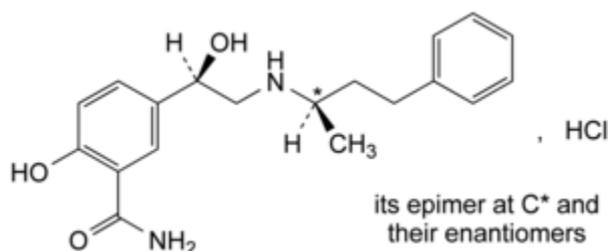
Not applicable.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical formula

Labetalol hydrochloride is a dry powder. The chemical name is: 2-hydroxy-5[1-hydroxy-2(1-methyl-3-phenylpropyl amino) ethyl] benzamide hydrochloride.

(Ph. Eur. monograph 0923)



$C_{19}H_{25}ClN_2O_3$

CAS number
32780-64-6

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland, New Zealand

9. DATE OF FIRST APPROVAL

19 March 2020

10. DATE OF REVISION OF THE TEXT

7 January 2022

Summary table of changes

Section changed	Summary of new information
All sections	New Data Sheet
4.6	Nipple pain and Raynaud's phenomenon of the nipple have been reported
4.8	Frequency 'not known': Nipple pain, Raynaud's phenomenon of the nipple