Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trandate 200mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg Labetalol hydrochloride

Excipients with known effect:
Lactose monohydrate 49.56 mg
Methyl hydroxybenzoate (E218) 5.6 micrograms
Propyl hydroxybenzoate (E216) 4.6 micrograms
Sunset yellow (E110)
Sodium benzoate (E211)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.
Circular, biconvex, orange-coloured, film-coated tablets engraved 'Trandate 200' on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of all forms of hypertension, including hypertension of pregnancy.

In the treatment of patients with angina pectoris with and without co-existing hypertension.

In the long term management of hypertensive episodes following acute myocardial infarction.

4.2 Posology and method of administration

Posology
Adults:

Hypertension

Treatment should start with 100mg twice daily. In patients already being treated with antihypertensives and in those of low body weight this may be sufficient to control blood pressure. In others, increases in dose of 100mg twice daily should be made at fortnightly intervals. Many patients' blood pressure is controlled by 200mg twice daily and up to 800mg daily may be given as a twice daily regimen. In severe, refractory hypertension, daily doses up to 2400mg have been given. Such doses should be divided into a three or four times a day regimen.

Elderly

Use of the 100 mg dosage in elderly is subject to the prescriber's evaluation.
In elderly patients, reduced daily doses compared to adults.

In the hypertension of pregnancy

The initial dose of 100mg twice daily may be increased, if necessary, at weekly intervals by 100mg twice daily. During the second and third trimester, the severity of the hypertension may require further dose titration to a three times daily regimen, ranging from 100mg tds to 400mg tds.

The lowest effective dose should be used, and the maximum dose limited to 1200mg daily whenever possible. A total daily dose of 2400mg must not be exceeded.

Hospital in-patients with severe hypertension, particularly of pregnancy, may have daily increases in dosage.

General

If rapid reduction of blood pressure is necessary, see the SPC for Trandate Injection. If long-term control of hypertension following the use of Trandate Injection is required, oral therapy with Trandate tablets should start with 100mg twice daily.

Additive hypotensive effects may be expected if Trandate tablets are administered together with other antihypertensives e.g. diuretics, methyldopa etc. When transferring patients from such agents, Trandate tablets should be introduced with a dosage of 100mg twice daily and the previous therapy gradually decreased. Abrupt withdrawal of clonidine or beta-blocking agents is undesirable.

Angina co-existing with hypertension

In patients with angina pectoris co-existing with hypertension, the dose of Trandate will be that required to control the hypertension.

Paediatric population

Safety and efficacy in children have not been established.

Method of administration

Trandate tablets should be taken orally with food.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1
- 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
- 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 drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Gradual discontinuance of the drug 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 tamsulosin, or have been treated with tamsulosin 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 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 therapy should be stopped and not re-started.

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 Trandate therapy. Evidence of recrudescence of such conditions should be regarded as a signal to review therapy.

Patients particularly those with ischemic heart disease, should not interrupt/ discontinue abruptly Trandate therapy. The dosage should gradually be reduced, ie. 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 Trandate therapy in patients requiring anaesthesia but the anaesthetist must be informed and the patient should be given intravenous atropine prior to induction. During anaesthesia Trandate 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 (eg. cyclopropane, trichloroethylene) should be avoided. Trandate 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 the bradycardia, the dosage should be reduced.

Beta-blockers, even those with apparent cardio-selectivity, should not be used in patients with asthma or 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 Trandate, it can be treated with a $beta_2$-agonist by inhalation, e.g. salbutamol (the dose of which may need to be greater than the usual in asthma) and, if necessary, intravenous atropine 1mg.

Adequate supervision must be maintained to permit any necessary adjustment of dosage of the bronchodilator employed.

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.

The label will state "Do not take Trandate if you have a history of wheezing or asthma as it can make your breathing worse."

<u>Trandate film coated tablets contain :</u>

Lactose monohydrate: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Methyl hydroxybenzoate (E218) and propyl hydroxybenzoate (E216): May cause allergic reactions (possibly delayed).

Sunset yellow (E110): May cause allergic reactions.

Sodium benzoate: This medicine contains 0.3mg of sodium benzoate (E211) in each film-coated tablet.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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.
- Monoamineoxidase inhibitors (except MOA-B inhibitors).

Use with caution:

- Class I antiarrhythmic agents (eg. 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 non-selective 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; moxisylyte; diuretics; alpha-blockers.
- Several different drugs or drug classes may antagonise the hypotensive effects of labetalol: NSAIDs, corticosteroids; oestrogens; progesterones; xamoterol.

Take into account:

- Calcium antagonists: dihydropyridine derivates 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 beta-blockers.
- Sympathicomimetic 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 halofantrine, mefloquine or quinine may increase the risk of bradycardia.
- Ergot derivatives may increase the risk of peripheral vasoconstriction.
- Tropisetron may increase the risk of ventricular arrhythmia.
- Labetalol interferes with laboratory tests for catecholamines.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

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

Trandate crosses the placental barrier and the possible 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 have developed a day or two after birth. Response to supportive measures (e.g. intravenous fluids and glucose) is usually prompt but with severe pre-eclampsia, particularly after prolonged intravenous labetalol, 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 Trandate but other drugs (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
Trandate is excreted in breast milk. Breast-feeding 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 Undesirable effects

The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

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

System organ class	Adverse reactions	Frequency
Blood and the lymphatic system disorders	Rare reports of positive antinuclear antibodies unassociated with disease	Not known
	Hyperkalaemia, particularly in patients who may have impaired renal excretion of potassium	Not known
	Thrombocytopenia	Not known
Psychiatric disorders	Depressed mood and lethargy	Not known
	Hallucinations	Not known
	Psychoses	Not known
	Confusion	Not known
	Sleep disturbances	Not known
	Nightmares	Not known
Nervous system disorders	Headache	Not known
	Tiredness	Not known
	Dizziness	Not known
	Tremor been reported in the treatment of hypertension of pregnancy	Not known
Eye disorders	Impaired vision	Not known
	Dry eyes	Not known
Cardiac disorders	Bradycardia	Not known
	Heart block	Not known
	Heart failure	Not known
	Hypotension	Not known

Vascular disorders	Ankle oedema	Not known
	Increase of an existing intermittent claudication	Not known
	Postural hypotension	Not known
	Cold or cyanotic extremities	Not known
	Raynaud's phenomenon	Not known
	Paraesthesia of the extremities	Not known
Respiratory, thoracic and mediastinal disorders	Bronchospasm (in patients with asthma or a history of asthma)	Not known
	Nasal congestion	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Epigastric pain	Not known
	Nausea	Not known
	Vomiting	Not known
	Diarrhoea	Not known
Hepatobiliary disorders	Raised liver function tests	Not known
	Jaundice (both hepatocellular and cholestatic)	Not known
	Hepatitis	Not known
	Hepatic necrosis	Not known
Skin and subcutaneous tissue disorders	Sweating, tingling sensation in the scalp, usually transient, may occur in a few patients early in treatment	Not known
	Reversible lichenoid rash,	Not known
	Systemic lupus erythematosus	Not known
	Exacerbation of psoriasis	Not known
Musculoskeletal, connective tissue and bone disorders	Cramps	Not known
	Toxic myopathy	Not known
Renal and urinary disorders	Acute retention of urine	Not known
	Difficulty in micturition	Not known
Reproductive system and breast disorders	Ejaculatory failure	Not known
	Nipple pain, Raynaud's phenomenon of the nipple	Not known
General disorders and administration site conditions	Hypersensitivity (rash, pruritus, angioedema and dyspnoea)	Not known
	Drug fever	Not known
	Masking of the symptoms of thyrotoxicosis or hypoglycaemia	Not known
	Reversible alopecia	Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

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

After an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. 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 5mcg/min, or dobutamine, starting with a dose of approximately 2.5mcg/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 1-3mg/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 hydrochloride from the circulation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C07AG 01 - alpha and beta blocking agents.

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

In patients with angina pectoris co-existing 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 co-existing angina.

5.2 Pharmacokinetic properties

The plasma half-life of labetalol is about 4 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.

5.3 Preclinical safety data

Not applicable since Trandate Tablets has been used in clinical practice for many years and its effects in man are well known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core Tablet
Lactose Monohydrate
Magnesium Stearate
Maize Starch
Pregelatinised Maize Starch

Film Coat
Hypromellose (E464)
Opaspray Orange M-1-3499D*
Methyl hydroxybenzoate (E218)
Propyl Hydroxybenzoate (E216)
Industrial Methylated Spirit, 99%
Purified Water

*Opaspray orange contains:

Sodium benzoate (E211), titanium dioxide (E171), sunset yellow (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Securitainers: 5 years

Blister packs: 3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Securitainer: Polypropylene container with tamper-evident polyethylene lid containing 50 or 250 tablets.

Blister packs: Calendar blister pack composed of hard tempered aluminium foil and opaque PVC blister containing 56 tablets as 4x14 tablets per strip.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

RPH Pharmaceuticals AB
Box 603
101 32 Stockholm
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8 MARKETING AUTHORISATION NUMBER

PA1638/006/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 19 July 2008

10 DATE OF REVISION OF THE TEXT

September 2022