SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trandate 5mg/ml solution for injection
Labetalol Hydrochloride 5mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Labetalol hydrochloride 5mg/ml

3 PHARMACEUTICAL FORM

Solution for injection

A colourless or very pale yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trandate Injection/Labetalol Injection is indicated for the treatment of:-

1. Severe hypertension, including severe hypertension of pregnancy, when rapid control of blood pressure is essential.
2. Anaesthesia when a hypotensive technique is indicated.
3. Hypertensive episodes following acute myocardial infarction.

4.2 Posology and method of administration

Adults:

Trandate Injection/Labetalol Injection is intended for intravenous use in hospitalised patients. The plasma concentrations achieved after intravenous dose of labetalol in severe hypertension are substantially greater than those following oral administration of the drug and provide a greater degree of blockade of alpha-adrenoceptors necessary to control the more severe disease.

Patients should, therefore, always receive the drug whilst in the supine or left lateral position. Raising the patient into the upright position, within three hours of intravenous labetalol administration, should be avoided since excessive postural hypotension may occur.

Bolus injection

If it is essential to reduce blood pressure quickly, as for example, in hypertensive encephalopathy, a dose of 50mg of labetalol hydrochloride should be given by intravenous injection over a period of at least one minute. If necessary, doses of 50mg may be repeated at five minute intervals until a satisfactory response occurs. The total dose should not exceed 200mg. After bolus injection, the maximum effect usually occurs within five minutes and the effective duration of action is usually about six hours but may be as long as eighteen hours.

Intravenous infusion

An alternative method of administering labetalol is intravenous infusion of a solution made by diluting the contents of two ampoules (200mg) to 200ml with Sodium Chloride and Dextrose Injection BP or 5% Dextrose Intravenous Infusion BP. The resultant infusion solution contains 1mg/ml of labetalol hydrochloride. It should be administered using a paediatric giving set fitted with a 50ml graduated burette to facilitate dosage.

In the hypertension of pregnancy: The infusion can be started at the rate of 20mg per hour and this dose may be doubled every thirty minutes until a satisfactory reduction in blood pressure has been obtained or a dosage of 160mg per hour is reached. Occasionally, higher doses may be necessary.

In hypertensive episodes following acute myocardial infarction: The infusion should be commenced at 15mg per hour and gradually increased to a maximum of 120mg per hour depending on the control of blood pressure.

In hypertension due to other causes: The rate of infusion of labetalol hydrochloride should be about 2mg (2ml of infusion solution) per minute, until a satisfactory response is obtained; the infusion should then be stopped. The effective dose is usually in the range of 50-200mg depending on the severity of the hypertension. For most patients it is unnecessary to administer more than 200mg but larger doses may be required especially in patients with phaeochromocytoma. The rate of infusion may be adjusted according to the response, at the discretion of the physician. The blood pressure and pulse rate should be monitored throughout the infusion.

It is desirable to monitor the heart rate after injection and during infusion. In most patients, there is a small decrease in the heart rate; severe bradycardia is unusual but may be controlled by injecting atropine 1-2 mg intravenously. Respiratory function should be observed particularly in patients with any known impairment.

Once the blood pressure has been adequately reduced, maintenance therapy with labetalol tablets should be instituted with a starting dose of one 100 mg tablet twice daily (see labetalol tablet SmPC for further details). Trandate Injection/Labetalol Injection has been administered to patients with uncontrolled hypertension already receiving other hypotensive agents, including beta-blocking drugs, without adverse effects.

In hypotensive anaesthesia: Induction should be with standard agents (e.g. sodium thiopentone) and anaesthesia maintained with nitrous oxide and oxygen with or without halothane. The recommended starting dose of

Trandate Injection/Labetalol Injection is 10-20 mg intravenously depending on the age and condition of the patient. Patients for whom halothane is contra-indicated usually require a higher initial dose of labetalol hydrochloride (25-30 mg). If satisfactory hypotension is not achieved after five minutes, increments of 5-10 mg should be given until the desired level of blood pressure is attained.
Halothane and labetalol act synergistically therefore the halothane concentration should not exceed 1-1.5% as profound falls in blood pressure may be precipitated.
Following Trandate Injection/Labetalol Injection the blood pressure can be quickly and easily adjusted by altering the halothane concentration and/or adjusting table tilt. The mean duration of hypotension following 20-25 mg of labetalol hydrochloride is fifty minutes.
Hypotension induced by Trandate Injection/Labetalol Injection is readily reversed by atropine 0.6 mg and discontinuation of halothane.
Tubocurarine and pancuronium may be used when assisted or controlled ventilation is required. Intermittent Positive Pressure Ventilation (IPPV) may further increase the hypotension resulting from Trandate Injection/Labetalol Injection and/or halothane.
Children:
Safety and efficacy have not been established.

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.
- Severe peripheral circulatory disturbances.
- Where peripheral vasoconstriction suggests low cardiac output, the use of Trandate Injection/Labetalol Injection to control hypertensive episodes following acute myocardial infarction is contra-indicated.

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 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 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 labetalol therapy.

Patients, particularly those with ischemic heart disease, should not interrupt/discontinue abruptly labetalol therapy. The dosage should gradually be 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 the 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 $beta_2$-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.

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 use to treat allergic reaction.

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

Sodium
This medicinal product contains less than 1mmol sodium (23mg) per dose, 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 (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 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.

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 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

Although no teratogenic effects have been demonstrated in animals, labetalol should only be used during the first trimester of pregnancy 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 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 labetalol 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.
Labetalol 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

Trandate Injection/Labetalol Injection is usually well tolerated. Excessive postural hypotension may occur if patients are allowed to assume an upright position within three hours of receiving Trandate Injection/Labetalol Injection. Most side-effects are transient and occur during the first few weeks of treatment with labetalol. They include:
Blood and the lymphatic system disorders
Rare reports of positive antinuclear 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, 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.
Nipple pain, Raynaud's phenomenon of the nipple (frequency not known)

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 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 Yellow Card Scheme on the MHRA website (www.mhra.gov.uk/yellowcard).

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 1-3 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 hydrochloride from the circulation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Labetalol lowers the blood pressure primarily 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 coexisting 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 Injection/Labetalol Injection 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

Hydrochloric acid dilute (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

Trandate Injection/Labetalol Injection has been shown to be incompatible with sodium bicarbonate injection BP 4.2% w/v

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Protect from light. Store below 30°C

6.5 Nature and contents of container

Type I Glass ampoules: 5 ampoules of 20ml (per pack).

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

RPH Pharmaceuticals AB
Box 603
101 32 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER(S)

PL 36301/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/03/2009

10 DATE OF REVISION OF THE TEXT

02/06/2023