APPROVED PROFESSIONAL INFORMATION FOR Labetalol 5 mg/ mL RBC

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Labetalol 5 mg/mL RBC

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Labetalol 5 mg/mL RBC contains Labetalol Hydrochloride 5 mg.

Sugar free.

For the full list of excipients, (see section 6.1)

3. PHARMACEUTICAL FORM

Injection:

Labetalol 5 mg/mL RBC is a clear, colorless to light yellow color solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Labetalol 5 mg/mL RBC is indicated for:

- Severe hypertension, including severe hypertension of pregnancy, when rapid control of blood pressure is essential.
- May be used to achieve controlled hypotension during anaesthesia.

4.2 Posology and method of administration

Posology

Adults

Labetalol 5 mg/mL RBC is intended for intravenous use in hospitalised patients.

The plasma concentrations achieved after intravenous doses of Labetalol 5 mg/mL RBC in severe hypertension are substantially greater than those following oral administration of the medicine.

Patients should therefore always receive Labetalol 5 mg/mL RBC whilst in the supine position.

Raising the patient into the upright position within three hours of intravenous Labetalol 5 mg/mL RBC administration should be avoided since excessive postural hypotension may occur.

The blood pressure and heart rate should be monitored after injection and during infusion.

It is desirable to monitor the Blood Pressure and 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 to 2 mg I.V. Respiratory function should be observed particularly in patients with any known impairment.

Once the Blood Pressure has been adequately reduced by bolus injection or infusion, maintenance therapy with Labetalol 5 mg/mL RBC tablets should be substituted with a starting dose of 100 mg twice daily.

Labetalol 5 mg/mL RBC has been administered to patients with uncontrolled hypertension already receiving other hypotensive medicines, including beta-blocking medicines, without adverse effects.

Severe hypertension (Adults)

Bolus injection:

If it is essential to reduce the blood pressure quickly, as, for example, in hypertensive encephalopathy, a dose of 50 mg should be given by I.V injection (over a period of at least 1 min) and, if necessary, repeated at 5 min intervals until a satisfactory response occurs. The total dose should not exceed 200 mg. The maximum effect usually occurs within 5 min and the duration of action is usually about 6 h but may be as long as 18 h.

Intravenous infusion

The resultant infusion solution contains 1 mg/mL of Labetalol 5 mg/mL RBC. An intravenous infusion of a solution made by diluting the contents of two 20 mL ampoules or eight 5 mL

ampoules (200 mg) to 200 mL with sodium chloride and dextrose injection BP is given. It should be administered using a volume-controlled infusion pump to facilitate accurate dosage.

Hypertension due to other causes

The rate of infusion of Labetalol 5 mg/mL RBC should be about 2 mg (2 mL 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 to 200 mg depending on the severity of the hypertension. For most patients, it is unnecessary to administer more than 200 mg but doses up to 300 mg may be required, especially in patients with pheochromocytoma. The rate of infusion may be adjusted according to the response, at the discretion of the medical practitioner.

Abrupt withdrawal of clonidine or beta-blocking medicines is undesirable. For long-term control of hypertension following the use of labetalol injection, oral therapy with labetalol tablets should start at 100 mg twice daily.

Special population

Severe hypertension of pregnancy

In case of severe hypertension of pregnancy, a slower and increasing rate of infusion should be used. Infusion rate should be started at 20 mg/hour. The dose may be doubled every 30 minutes until a satisfactory response is obtained or a dosage of 160 mg/hour is reached.

Hypotensive anaesthesia

In hypotensive anaesthesia, induction should be with standard medicines (e.g., sodium thiopentone) and anaesthesia maintained with halogenated inhalation anaesthetics. The recommended starting dose of Labetalol 5 mg/mL RBC is 10 to 20 mg intravenously, depending on the age and condition of the patient. If satisfactory blood pressure reduction is not achieved after five minutes, increments of 5 to 10 mg should be given until the desired level of blood pressure is attained.

The mean duration of hypotension following 20 to 25 mg of Labetalol 5 mg/mL RBC is fifty minutes.

Paediatric population

The safety and efficacy of Labetalol 5 mg/mL RBC in paediatric patients aged 0 to 18 years have not been established. No data is available.

Method of administration

Intravenous.

An alternative method of administering Labetalol 5 mg/mL RBC is intravenous infusion of a solution made by diluting the contents of two ampoules (200 mg) to 200 mL with Sodium Chloride and Dextrose Injection BP or 5 % Dextrose Intravenous Infusion BP. The resultant infusion solution contains 1 mg/mL of labetalol hydrochloride.

4.3 Contraindications

Labetalol 5 mg/mL RBC is contra-indicated in:

- Patients with hypersensitivity to labetalol or any of the excipients in Labetalol 5 mg/mL RBC. (see section 6.1).
- Non-selective beta-blockers should not be used in patients with asthma or a history of obstructive airways disease.
- Second- or third-degree heart block (unless pacemaker is in *situ*), cardiogenic shock and other conditions associated with severe and prolonged hypotension or severe bradycardia.
- Uncompensated heart failure.
- Unstable/uncontrolled heart insufficiency.
- Sick sinus syndrome (including sinus atrial block) unless pacemaker in *situ*.
- Prinz metal angina.
- Sinus node dysfunction.
- Women who are breastfeeding their infants (see section 4.6).
- Untreated phaeochromocytoma.
- Metabolic acidosis.

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

4.4 Special warnings and precautions for use

Hepatobiliary disorders

Care should be taken in liver disease. There have been reports of severe hepatocellular injury with LABETALOL 5 MG/ ML RBC therapy, including fatal liver toxicity. The hepatic injury is usually reversible on stopping treatment and has occurred after both short and long-term treatment. However, hepatic necrosis, in some cases with fatal outcome, has been reported. Appropriate laboratory testing should be done at the first sign or symptom of liver dysfunction. Laboratory evidence of liver injury or the patient is jaundiced, LABETALOL 5 MG/ ML RBC therapy should be stopped immediately and not restarted.

Particular care should be taken when LABETALOL 5 MG/ ML RBC is to be used in patients with hepatic impairment, as these patients metabolise labetalol more slowly than normal patients without hepatic impairment.

Peripheral vascular disease

LABETALOL 5 MG/ ML RBC should be used with caution in patients with peripheral vascular disease as their symptoms may be exacerbated. Caution is advised in patients with peripheral arteriolar disease (Raynaud's syndrome, claudication intermittens) as LABETALOL 5 MG/ ML RBC may exacerbate their symptoms. Alpha-block may counter the unfortunate effect of beta-blockers.

Symptomatic bradycardia

If the patient develops symptomatic bradycardia, the dosage of LABETALOL 5 MG/ ML RBC should be reduced, or should be stopped.

First-degree atrio ventricular block

Given the negative effect of beta-adrenoceptor blocking medicines on atrioventricular conduction time, LABETALOL 5 MG/ ML RBC should be administered with caution to patients with digoxin-resistant heart failure first-degree atrio-ventricular block.

Special care should be taken with patients who suffer from heart failure or poor left ventricular systolic function. Heart failure should be controlled with appropriate therapy before use of labetalol.

Diabetes mellitus

Care should be taken in case of uncontrolled or difficult-to-control diabetes mellitus.

As with other beta-adrenoceptor blocking medicines LABETALOL 5 MG/ ML RBC may mask the symptoms of hypoglycaemia (tachycardia and tremor) in diabetic patients (see section 4.5). The hypoglycaemic effect of insulin and oral hypoglycaemic medicines may be enhanced by beta blockers. This statement is based on the fact that a slight increase in blood sugar level occurs following the administration of LABETALOL 5 MG/ ML RBC, and the possibility of interactions with LABETALOL 5 MG/ ML RBC and insulin or oral anti-diabetic medicines.

Thyrotoxicosis

Beta blockers may mask the symptoms of thyrotoxicosis, but the thyroid function is not altered.

Hypersensitivity to beta blockers

Risk of anaphylactic reaction: While receiving LABETALOL 5 MG/ ML RBC, 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 (adrenaline) used to treat allergic reactions.

Adrenaline

If patients receiving LABETALOL 5 MG/ ML RBC require epinephrine (adrenaline) treatment, a reduced dosage of epinephrine (adrenaline) should be used, as concomitant administration of LABETALOL 5 MG/ ML RBC with epinephrine (adrenaline) may result in bradycardia and hypertension (see section 4.5).

Skin rashes and/or dry eyes

There have been common reports of skin rashes and/or dry eyes associated with the use of LABETALOL 5 MG/ ML RBC. Gradual discontinuance of LABETALOL 5 MG/ ML RBC should be considered if any such reaction is not otherwise explicable.

Inhalation anaesthetics

Care should be taken with concomitant treatment with inhalation anaesthetics (see section 4.5). LABETALOL 5 MG/ ML RBC may enhance the hypotensive effects of volatile anaesthetics.

Sudden haemorrhage

During anaesthesia LABETALOL 5 MG/ ML RBC 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.

Renal impairment

Caution is advised when LABETALOL 5 MG/ ML RBC is used in patients with severe renal impairment (GFR = 15 to 29 ml/min/1,73m²).

Intraoperative floppy iris syndrome

The occurrence of Intraoperative Floppy Iris Syndrome (IFIS), a variation of Small Pupil Syndrome, has been observed during cataract surgery in some patients on, or previously treated with, tamsulosin. Isolated reports have also been received with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural

complications during the cataract operation, current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

Cardiovascular disorders

Heart failure or poor left ventricular function

Special care should be taken with patients who suffer from heart failure or poor left ventricular systolic function.

LABETALOL 5 MG/ ML RBC is contraindicated in uncontrolled heart failure but may be used with caution in patients who are well managed and free of symptoms (see section 4.3). Heart failure should be controlled with appropriate therapy before use of LABETALOL 5 MG/ ML RBC.

Use of beta blockers implies a risk of inducing or exacerbating heart failure or obstructive lung disease. In case of heart failure, the myocardial contractility should be maintained, and the failure should be compensated. Patients with reduced contractility, particularly the elderly, should be monitored regularly for development of heart failure.

It is strongly recommended not to stop treatment with LABETALOL 5 MG/ ML RBC abruptly especially in patients with heart failure and patients with angina pectoris (risk of exacerbation of angina, myocardial infarction and ventricular fibrillation).

Metabolic acidosis and pheochromocytoma

Care should be taken in cases of metabolic acidosis and pheochromocytoma. In patients with pheochromocytoma, LABETALOL 5 MG/ ML RBC may be administered only after adequate alpha- blockade is achieved.

Calcium antagonists

Care should be taken if LABETALOL 5 MG/ ML RBC is used concomitantly with calcium antagonists, particularly the "calcium entry blockers", which influence contractility and AV conduction negatively.

Bronchospasm

Caution must be observed if LABETALOL 5 MG/ ML RBC is used to treat asthmatic patients or individuals prone to bronchospasm. Any resultant bronchospasm may be controlled by an inhaled beta agonist; the required dose may be greater than the normal anti-asthmatic dose. If further treatment is required, intravenous atropine 1 mg may be given.

Beta blockers have negative inotropic effect but does not affect the positive inotropic effect of digitalis.

Concurrent use of LABETALOL 5 MG/ ML RBC may result in an increased plasma concentration of the following medicines: hypoglycaemic medicines, phenothiazine's and various anti-dysrhythmic medicines. Such interactions can have life-threatening consequences (see section 4.5).

Caution should be taken to prevent occasional exaggerated hypotensive response, particularly in the presence of hypovolaemia.

Safety and efficacy in children has not been established.

Sodium contents

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 medicines 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

Use with caution:

- Class I antidysrhythmic medicines (e.g., disopyramide, quinidine) and amiodarone may have potentiating effects on atrial conduction time and induce negative inotropic effect.
- Insulin and oral antidiabetic medicines 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 medicines may cause attenuation of reflex tachycardia and increase the risk of hypotension. Continuation of beta-blockade reduces the risk of dysrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking medicine. Anaesthetic medicines causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided.
- Cimetidine, hydralazine and alcohol may increase the bioavailability of labetalol.
- Several different medicines or medicine classes may enhance the hypotensive effects of labetalol: ACE inhibitors; angiotensin-II antagonists; aldesleukin, alprostadil; anxiolytics; hypnotics; moxisylyte; diuretics; alpha-blockers.
- Several different medicines or medicine 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 medicines may decrease the hypotensive effect of beta-blockers.

- Sympathicomimetic medicines may counteract the effect of beta-adrenergic blocking medicines.
- Concomitant use of tricyclic antidepressants, barbiturates, phenothiazines or other antihypertensive medicines 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 medicines.
- 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.
- Concomitant treatment with alpha stimulating adrenergics may increase the risk of increased blood pressure (e.g. phenylpropanolamine and adrenaline), while concomitant treatment with beta stimulating adrenergics results in a mutual reduced effect (antidote effect).

4.6 Fertility, pregnancy and lactation

Pregnancy

Based on experience during human pregnancy Labetalol 5 mg/mL RBC is not expected to increase the risk of congenital malformations.

Due to the pharmacological action of alpha- and beta-adrenoceptor blockade adverse effects on the foetus and neonate when used in the later stages of pregnancy (bradycardia, hypotension, respiratory depression, hypoglycaemia), should be borne in mind, as Labetalol 5 mg/mL RBC crosses the placental barrier (see section 5).

Beta-blockers may reduce uterine blood flow.

Breastfeeding

Safety in breastfeeding has not been established.

Labetalol 5 mg/mL RBC is excreted in breast milk in small amounts (approximately 0,004 to 0,07 % of the maternal dose). Adverse events such as sudden death syndrome, diarrhoea and hypoglycaemia have been reported in breastfed neonates.

Mothers breastfeeding their infants should not be treated with Labetalol 5 mg/mL RBC (see section 4.3).

Fertility

There are no data on the effects of Labetalol 5 mg/mL RBC on fertility.

4.7 Effects on the 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

Labetalol 5 mg/mL RBC Injection is usually well tolerated. Excessive postural hypotension may occur if patients are allowed to assume an upright position within three hours of receiving Labetalol 5 mg/mL RBC Injection.

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

Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Immune system

Frequent: Hypersensitivity including rash; pruritus; dyspnoea

Less frequent: Drug fever; angioedema

Blood and the lymphatic system disorders

Less frequent: rare reports of positive antinuclear antibodies unassociated with disease, hyperkalaemia, particularly in patients who may have impaired renal excretion of potassium, thrombocytopenia.

Psychiatric disorders

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

Nervous system disorders

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

Eye disorders

Less frequent: Impaired vision, dry eyes.

Cardiac disorders

Frequent: Congestive heart failure

Less frequent: Bradycardia; heart block

Vascular disorders

Frequent: #Postural hypotension; confusion; disorientation if patients are allowed to assume the upright position within three hours of receiving Labetalol 5 mg/mL RBC.

Less frequent: Exacerbation of the symptoms of Raynaud's syndrome

Respiratory, Thoracic and Mediastinal disorders

Frequent: #Nasal congestion

Less frequent: Bronchospasm

Gastrointestinal disorders

Less frequent: Epigastric pain, nausea, vomiting, diarrhoea.

Hepato-biliary disorders

Frequent: Raised liver function tests

Less frequent: Hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis

Skin and subcutaneous tissue disorders

Less frequent: 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 and connective tissue disorders

Frequent: Muscle rigidity

Less frequent: Trismus, toxic myopathy

Renal and urinary disorders

Less frequent: Acute retention of urine, difficulty in micturition.

Reproductive system and breast disorders

Frequent: Erectile dysfunction

Undesirable effects indicated by a hash (#) are usually transient and occur during the first few weeks of treatment.

General disorders and administration site conditions

Less frequent: Hypersensitivity (angioedema), masking of the symptoms of thyrotoxicosis or hypoglycaemia, reversible alopecia.

Description of selected adverse reactions

Immune system disorders

Hypersensitivity reactions reported include rash (including reversible lichenoid rash), pruritus, dyspnoea and very rarely drug fever or angioedema.

Vascular disorders

Postural hypotension is more common at very high doses or if the initial dose is too high or doses are increased too rapidly.

Hepatobiliary disorders

The signs and symptoms of hepatobiliary disorders are usually reversible on withdrawal of Labetalol 5 mg/mL RBC.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. By reporting side effects, you can help provide more information on the safety of Labetalol 5 mg/ mL RBC.

4.9 Overdose

Symptoms

Profound cardiovascular effects are to be expected, e.g., excessive, posture-sensitive hypotension and sometimes bradycardia. Oliguric renal failure has been reported after massive overdosage of labetalol, orally. Overdosage with Labetalol 5 mg/mL RBC causes excessive hypotension, which is posture-dependent, and excessive bradycardia.

Treatment

Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain.

The use of dopamine to increase blood pressure may aggravate renal failure.

Haemodialysis removes less than 1 % Labetalol 5 mg/mL RBC hydrochloride from the circulation.

Further management should be as clinically indicated or as recommended by the national poison centre, where available.

Atropine 1 to 2 mg should be given intravenously to relieve bradycardia. Massive overdosage with Labetalol 5 mg/mL RBC in man has not been reported, but profound cardiovascular effects are to be expected.

If further measures are required to obtain adequate circulatory pressure, vasopressors may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha and beta-blocking medicines

ATC code C07AG01

Pharmacological classification: A 7.1.3 Vascular medicines, vasodilators, other hypotensives.

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 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. All these effects would be expected to benefit hypertensive patients.

5.2 Pharmacokinetic properties

Intravenous labetalol hydrochloride reduces blood pressure without producing tachycardia or increasing plasma renin levels.

Distribution

About 50 % of labetalol in the blood is protein bound. Labetalol crosses the placental barrier and is secreted in breast milk.

Biotransformation

Labetalol is metabolised mainly through conjugation to inactive glucuronide metabolites.

Elimination

The glucuronide metabolites are excreted both in the urine and via the bile, into the faeces.
Less than 5 % of the labetalol dose is excreted unchanged in urine and bile. The plasma half-life of labetalol is about 4 h.

Special populations

Hepatic impairment

Labetalol undergoes significant but variable first-pass metabolism when given by the oral route.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid Monohydrate

Dextrose anhydrous

Edetate Disodium Dihydrate

Methylparaben

Nitrogen

Propylparaben

Sodium Hydroxide

Water for Injection

6.2 Incompatibilities

Labetalol 5 mg/mL RBC has been shown to be incompatible with sodium bicarbonate injection Blood Pressure.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Labetalol 5 mg/mL RBC:

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of the container

Labetalol 5 mg/mL RBC packed in glass vials:

- Each 20 mL vial is comprised of a 20 mL, 20 mm neck moulded Type-I clear glass vial with a 20 mm grey Bromobutyl uncoated rubber stopper and a 20 mm flip-off Misty grey color seal.

Pack sizes: 1 X 20 mL Multiple-Dose Vials

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RBC PHARMACEUTICALS (PTY) LTD.

23 Kiaat Street, ERF 926, Extension 7,

Noordwyk, Midrand, Gauteng,

South Africa, 1687

8. REGISTRATION NUMBERS

57/7.1.3/0906

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 September 2025

10. DATE OF REVISION OF TEXT

TBA