SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Labetalol 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg labetalol hydrochloride.

Excipient with known effect: Each tablet contains 32 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet

Orange, round, biconvex, film-coated tablets coded 'LTL 100' on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Labetalol Tablets are indicated for the treatment of:

- Mild, moderate and severe hypertension
- Hypertension in pregnancy
- Angina pectoris with existing hypertension

4.2 Posology and method of administration

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 in to a three or four times a day regimen.

Elderly

In elderly patients, an initial dose of 50mg twice daily is recommended. This has provided satisfactory control in some cases.

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 to 400mg three times a day. A total daily dose of 2400mg should 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, labetalol injection should be used. If long-term control of hypertension following the use of labetalol injection is required, oral therapy with labetalol tablets should start with 100mg twice daily. Additive hypotensive effects may be expected if labetalol tablets are administered together with other antihypertensives e.g. diuretics, methyldopa etc. where the hypotensive effects will be additive. When transferring patients from such agents, labetalol 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 labetalol will be that required to control the hypertension.

Paediatric population
The safety and efficacy of labetalol in children has not been established.

Method of administration

Labetalol tablets should be taken orally with food.

4.3 Contraindications

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

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 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 performed 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 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 treatment is initiated.

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 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 pre-op. 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 $beta_2$-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 used to treat allergic reaction. (see section 4.5).

The label will carry the following warning: 'Important warning: Do not take this medicine if you have a history of wheezing or asthma as it can make your breathing worse'.

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

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.

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.

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.

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).

Cimetidine, hydralazine and alcohol may increase the plasma concentration of labetalol.

Other drugs/drug classes
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 effects of beta-blockers.

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 Pregnancy and lactation

Pregnancy
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 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 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.

Breast-feeding
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

Most side-effects are transient and resolve within 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 during 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, 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, systematic lupus erythematosus, exacerbation of psoriasis.

Musculoskeletal, connective tissue and bone disorders
Cramps, toxic myopathy.

Renal and urinary disorders
Acute urinary retention, difficulty in micturition.

Reproductive system and breast disorders
Ejaculatory failure
Frequency 'not known': Nipple pain, Raynaud's phenomenon of the nipple

General disorders and administration site conditions
Hypersensitivity (rash, pruritis, angioedema, 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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdosage are hypotension, bradycardia, 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 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 8-10mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed, if necessary, by an i.v. infusion of glucagon at an administration rate of 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

Pharmacotherapeutic group: Alpha and Beta blocking agents and other diuretics
ATC code: C07CG

Mechanism of action and pharmacodynamic effects
Labetalol hydrochloride 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 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 Labetalol tablets have 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
Starch
Povidone
Isopropanol
Sodium Starch Glycollate
Magnesium Stearate

Coating
Hydroxy Propyl Methyl Cellulose
Mastercote FA 1293 (E110)
Triacetin
Water
IMS

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Polypropylene container with a low density polyethylene lid incorporating a tear-off sealing band containing 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 250, 500 and 1000 tablets.

PVdC coated PVC/Aluminium blister packs (60g/m^2 PVdC on 250µm PVC/20µm Al) containing 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Limited
220 Butterfield
Great Marlings
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8. MARKETING AUTHORISATION NUMBER(S)

PL 11311/0375

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01/02/1990
Date of latest renewal: 29/07/2009

10 DATE OF REVISION OF THE TEXT

18/02/2022