# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Labetalol Tablets BP 400mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400mg labetalol hydrochloride.
For excipients, see 6.1

## 3. PHARMACEUTICAL FORM

Orange, circular, biconvex, film-coated tablets engraved '400 LAB' on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic Indications

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

Labrocol Tablets are also indicated for the treatment of patients with angina pectoris coexisting with hypertension.

### 4.2. Posology and Method of Administration

Route of administration: Oral

Labetalol tablets should be taken with food.

Adults:

*Hypertension:* Treatment should start with one 100mg tablet 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.

*In hypertensive patients with angina:* The recommended dose of labetalol tablets will be that required to control the hypertension.

*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 drug, such as methyldopa or clonidine, an additive effect may be expected. When transferring patients from other drugs, labetalol tablets should be introduced with a dosage of 100mg twice daily and the dosage of the existing therapy progressively decreased.

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

Children: Safety and efficacy in children has not been established.

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

## 4.3. Contra-Indications

Labetalol tablets are contraindicated in patients with

- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome (including sino-atrial block)
- Second and third degree heart block
- Printzmetal's angina
- History of bronchospasm and bronchial asthma
- Untreated phaeochromocytoma
- Metabolic acidosis
- Bradycardia (<45-50 bpm)
- Hypotension
- Hypersensitivity to labetalol or any of the excipients used in the tablet
- Severe peripheral circulatory disturbances

## 4.4. Special Warnings and Special Precautions For Use

Severe hepatocellular injury has rarely been reported and can occur after both short and long term treatment but is usually reversible. At the first sign or symptom of liver problems laboratory testing should be performed and if there is any evidence of liver injury, or if the patient is jaundiced then labetalol should be discontinued and not re-started.

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. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable.

Care should be taken in patients whose cardiac reserve is poor. Heart failure should be controlled with a cardiac glycoside and diuretic therapy before treatment is initiated. Labetalol should not normally be given to patients with digitalis-resistant heart failure or atrio-ventricular block.

Especially in patients with ischaemic heart disease, treatment should not be discontinued suddenly. 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.

Caution is required when administering anaesthetic agents to patients receiving Labetalol. The anaesthetist must always be informed of the use of a beta-adrenoceptor blocking drug. The patient should receive intravenous atropine prior to induction. When it has been decided to interrupt a beta-blockade 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.

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.

Labetalol should not be used to treat asthmatic patients or individuals prone to bronchospasm unless there is no alternative. The label will carry the following

warning: “Do not take this medicine if you have a history of wheezing or asthma. Consult your doctor or pharmacist first”. The risk of inducing bronchospasm must be appreciated and appropriate precautions taken. Any resultant bronchospasm may be controlled by an inhaled selectively-acting bronchodilator such as salbutamol; the required dose may be greater than the normal anti-asthmatic dose. If further treatment is required, intravenous atropine 1mg should be given.

Beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzmetal’s angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers should not be used for these patients, and beta-1 selective blockers only with the utmost care.

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

In patients with a history of severe anaphylactic reaction the use of beta-blockers may mean the patient is more reactive to repeated challenge. These patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat allergic reaction.

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

Patient with rare hereditary problems of galactose intolerance, the Lapp lactose 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 propanolol, treatment with clonidine should be continued for some time after treatment when the beta-blocker has been discontinued.
- Monoamineoxidase inhibitors (exception MOA-B inhibitors).

*Precautions for use:*

- Class I anti-arrhythmic drugs (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 non-selective beta-blockers).
- Beta-adrenergic 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 agent causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided.
- Cimetidine, hydralazine and alcohol may increase the bioavailability of labetalol.

*Take into account:*
- Calcium antagonists: dihydropyridine derivates such as nifedipine. The risk of hypotension may be increase. 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.

## 4.6 Fertility, pregnancy and lactation

Labetalol should only be used in pregnancy if considered essential by the physician. Labetalol tablets should only be given in the first trimester if the physician considers that 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 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 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.

Breast-feeding

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

Side effects usually occur in the first few weeks of treatment and most are transient. Effects include headache, tiredness, depressed mood, lethargy, dizziness, sweating, nasal congestion and rarely ankle oedema. A few patients may get a transient tingling in the scalp early in treatment. Postural hypotension is uncommon except at very high doses or if the initial dose it too high or doses are increased too rapidly.

Reports of other effects include acute retention of urine, difficulty in micturition, ejaculatory failure, epigastric pain, nausea and vomiting. There have been rare reports of positive anti-nuclear antibodies unassociated with disease as well as rare reports of systemic lupus erythematosus and very rarely drug fever. There are rare reports of bradycardia and heart block. There are very rare reports of toxic myopathy.

In the treatment of hypertension of pregnancy, tremor has been reported.

If the initial dose is too high, adjustment of the dose is too rapid or the patient is on a very high dose, then postural hypotension may occur; this is otherwise uncommon.

There are rare reports of hypersensitivity including rash, pruritus, angioedema, dyspnoea and a reversible lichenoid rash. Reports of other effects which are not necessarily related to labetalol include blurred vision, eye irritation and cramps.

On rare occasions labetalol has been associated with jaundice (both hepatocellular and cholestatic), raised liver function tests, hepatitis and hepatic necrosis. It is therefore recommended that treatment with labetalol should be discontinued should a patient develop jaundice, since the latter has been shown to be reversible on stopping the drug.

Other possible side effects of beta-blockers are: heart failure, cold or cyanotic extremities, Raynaud's phenomenon, paraesthesia of the extremities, increase of an existing intermittent claudication, hallucinations, psychoses, confusion, sleep disturbances, nightmares, diarrhoea, bronchospasm (in patients with asthma or a history of asthma), masking of the symptoms of thyrotoxicosis or hypoglycaemia.

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

## 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 administrating 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 2.5 mcg/min, until the required effect has been obtained. In refractory cases Isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of 8-10mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed – if appropriate – 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. Labetolol does have membrane stabilizing activity which may have clinical significance in overdosage.

Haemodialysis removes less than 1% labetalol from the circulation.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic Properties

Labetalol lowers the blood pressure primarily by blocking alpha-adrenoceptors in peripheral arterioles and thereby reducing the peripheral resistance. Concurrent beta-blockade protects the heart from the reflex sympathetic drive normally induced by peripheral vasodilatation. Cardiac output is not significantly reduced at rest or after moderate exercise. Increases in systolic pressure during exercise are, however, reduced after labetalol; corresponding changes in the diastolic pressure are essentially normal.

In patients with coexisting angina the reduced peripheral resistance leads to a decreased left ventricular afterload, and hence, reduced myocardial oxygen demand. All these effects would be expected to benefit hypertensive patients with coexisting angina.

### 5.2. Pharmacokinetic Properties

Labetalol is rapidly absorbed following oral administration with peak plasma concentrations reported to occur 1-2 hours after administration. Labetalol is subject to considerable first-pass metabolism. The bioavailability of labetalol varies between individuals and is reported to increase with food. 50% of labetalol is protein bound in the blood.

The elimination half-life is reported to be 8 hours at steady state.

Labetalol is mainly metabolized in the liver with excretion via the urine and faeces. 5% labetalol remains unchanged in the urine.

Neither the half-life or plasma clearance are reported to be affected in patients with impaired renal function.

Labetalol crosses the placenta and is excreted in breast milk.

### 5.3. Pre-clinical Safety Data

Not required.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of Excipients

Lactose, maize starch, magnesium stearate, hydroxypropylmethylcellulose, colour containing titanium dioxide (E171) and sunset yellow (E110), methyl hydroxybenzoate and propyl hydroxybenzoate.

### 6.2. Incompatibilities

Not known.

### 6.3. Shelf-Life

Securitainer
3 years

Blister: PVC/Aluminium
2 years

### 6.4. Special Precautions for Storage

Store in a cool, dry place, protect from light.

### 6.5 Nature and contents of container

Securitainer.

Pack sizes: 28, 30, 50, 56, 60, 84, 90, 112, 120 and 250.

Blister: PVC/Aluminium

Pack Size 56

### 6.6. Instructions for Use, Handling and Disposal

Not applicable.

**7. MARKETING AUTHORISATION HOLDER**

Sandoz Ltd
Woolmer Way
Bordon
Hampshire
GU35 9QE

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0082

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION**

14 January 1985 / 17 July 1996

## 10 DATE OF REVISION OF THE TEXT

25/07/2022