# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Labetalol 5 mg/ml solution for injection/ infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 5 mg of labetalol hydrochloride.

Excipient with known effect: 1 ml contains 49.5 mg Glucose monohydrate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection/infusion.

A clear, colourless solution in a clear glass ampoule.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

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

### 4.2 Posology and method of administration

**Posology**

Labetalol injection is intended for I.V. use in hospitalised patients.

**Populations**

**Adults**:

| Indication | Dosage |
|---|---|
| **Severe Hypertension** | Bolus injection:<br>If it is essential to reduce the blood pressure quickly a dose of 50 mg should be given by I.V. injection (during 1 minute) and, if necessary, be repeated at 5-minute intervals until a satisfactory response occurs. The total dose should not exceed 200 mg.<br><br>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:<br><br>A 1 mg/ml solution of labetalol should be used, i.e. the contents of two 20 ml ampoules (200 mg) diluted to 200 ml with the compatible I.V. infusion fluids indicated in section 6.6.<br>The infusion rate will normally be about 160 mg/h but may be adjusted accorded to the response at the discretion of the physician. The effective dose is usually 50 to 200 mg, but the infusion should be continued until a satisfactory response is obtained and larger doses may be needed, especially in patients with phaeochromocytoma. |

| | |
|---|---|
| | 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/h, then doubled every 30 minutes until a satisfactory response is obtained or a dosage of 160 mg/h is reached. |
| **Achieving a controlled hypotension during anaesthesia** | To achieve a controlled hypotension during anaesthesia, the recommended starting dose of labetalol for injection is 10 to 20 mg intravenously depending on the age and condition of the patient.<br><br>If satisfactory hypotension is not achieved after 5 min, increments of 5 to 10 mg should be given until the desired level of blood pressure is attained.<br><br>The mean duration of hypotension following 20 to 25 mg of labetalol is 50 minutes. |
| **Hypertension Due to Other Causes** | Infuse at a rate of 120-160 mg/h until a satisfactory response is obtained, then stop infusion. The effective dose is usually 50 to 200 mg, but larger doses may be needed, especially in patients with phaeochromocytoma. |

**Paediatric population:**
The safety and efficacy of labetalol in paediatric patients aged 0 to 18 years have not been established. No data are available.

**Method of administration**
Precautions to be taken before handling or administering the medicinal product:
Patients should always receive the medicinal product whilst in the supine or left lateral position.
Raising the patient into the upright position within 3 h of I.V. labetalol administration should be avoided since excessive postural hypotension may occur.

**4.3 Contraindications**

- Labetalol is contraindicated in patients known to have hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Non-selective beta-blockers should not be used for patients with asthma or a history of obstructive airway disease
- Labetalol is contraindicated in 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
- Prinzmetal angina
- Sinus node dysfunction
- Untreated phaeochromocytoma

**4.4 Special warnings and precautions for use**

**Liver disease**
Care should be taken in liver disease. There have been very 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. However, hepatic necrosis, in some cases with fatal outcome, has been reported. Appropriate laboratory tests 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.

Particular care should be taken when labetalol is used in patients with hepatic impairment as these patients metabolise labetalol more slowly than patients without hepatic impairment.

**Renal impairment**
Caution is advised when labetalol is used for patients with severe renal impairment (GFR = 15-29 mL/min / 1.73m$^2$).

**Peripheral vascular disease**
Labetalol should be used with caution in patients with peripheral vascular disease as their symptoms may be exacerbated. Caution is advised in patients with peripheral arterial disease (Raynauds syndrome, claudicatio intermittens), as labetalol may exacerbate their symptoms. Alpha-block may counter the unfortunate effect of beta-blockers.

**Symptomatic bradycardia**
If the patient develops symptomatic bradycardia, then the dosage of labetalol should be reduced.

**First-degree atrio ventricular block**
Given the negative effect of beta-adrenoceptor blocking medicinal products on atrioventricular conduction time, labetalol should be administered with caution to patients with first-degree atrio-ventricular block.

**Diabetes mellitus**
Care should be taken in case of uncontrolled or difficult-to-control diabetes mellitus. As with other beta-adrenoceptor blocking medicinal products, labetalol may mask the symptoms of hypoglycaemia (tachycardia and tremor) in diabetic patients. The hypoglycaemic effect of insulin and oral hypoglycaemic agents may be enhanced by beta blockers.

Labetalol S.A.L.F. contains 49.5 mg/ml of glucose monohydrate. This should be taken into account in patients with diabetes mellitus.

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

**Hypersensitivity to beta blockers**
Risk of anaphylactic reaction: When 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 an allergic reaction.

**Adrenaline**
If patients receiving labetalol require adrenaline treatment, a reduced dosage of adrenaline should be used as concomitant administration of labetalol with adrenaline may result in bradycardia and hypertension (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Upon severe influence of adrenaline as in phaeochromocytoma, labetalol may cause a paradoxical blood pressure elevation.

**Skin rashes and/or dry eyes**
There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking medicinal products. The reported incidence is small and in most cases, the symptoms have cleared when the treatment was withdrawn. Gradual discontinuance of the medicinal product should be considered if any such reaction is not otherwise explicable.

**Intraoperative Floppy Iris Syndrome**
The occurrence of intraoperative Floppy Iris Syndrome (IFIS, a variant of Small Pupil Syndrome) has been observed during cataract surgery in some patients on, or previously treated with, 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.

**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 is contraindicated in uncontrolled heart failure, but may be used with caution in patients who are well managed and free of symptoms. Heart failure should be controlled with appropriate therapy before use of labetalol.

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 Hydrochloride abruptly, especially in patients with heart failure and patients with angina pectoris (risk of exacerbation of angina, myocardial infarction and ventricular fibrillation).

**Inhalation anaesthetics**
Care should be taken with concomitant treatment with inhalation anaesthetics (see section 4.5 Interaction with other medicinal products and other forms of interaction). Labetalol need not be discontinued prior to anaesthesia but patients should receive I.V. atropine prior to induction. Labetalol may enhance the hypotensive effects of volatile anaesthetics.

**Metabolic acidosis and phaeochromocytoma**
Care should be taken in case of metabolic acidosis and phaeochromocytoma. In patients with phaeochromocytoma, labetolol may be administered only after an adequate alpha-blockade is achieved.

**Calcium antagonists**
Care should be taken if labetalol is used concomitantly with calcium antagonists, particularly the "calcium entry blockers", which influence contractility and AV conduction negatively.

Care should be taken with concomitant administration of adrenaline, verapamil or a class-1 antiarrhythmics (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

**Sudden haemorrhage**
During anaesthesia, labetalol may mask the compensatory physiological responses of sudden haemorrhage (tachycardia and vasoconstriction). Close attention must therefore be paid to blood loss and the blood volume maintained.

**Administration**
It desirable to monitor the blood pressure and heart rate after the 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 intravenously.

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 tablets should be substituted with a starting dose of 100 mg twice daily.
Labetalol injection has been administered to patients with uncontrolled hypertension already receiving other hypotensive agents, including beta-blockers medicinal products, without adverse effects.

**4.5 Interaction with other medicinal products and other forms of interactions**

The hypotensive effect of labetalol may be reduced when used in combination with prostaglandin synthetase inhibitors (NSAIDs). Dosage adjustments may therefore be necessary. Additive synergism may occur with other antihypertensive agents.

Labetalol fluoresces in alkaline solution at an excitation wavelength of 334 nanometres and a fluorescence wavelength of 412 nanometres, and may therefore interfere with the assays of certain fluorescent substances including catecholamines.

The presence of labetalol metabolites in the urine may result in falsely elevated levels or urinary catecholamines, metanephrine, normetanephrine and vanillylmandelic acid, (VMA) when measured by fluorimetric or photometric methods. In screening patients suspected of having a phaeochromocytoma and being treated with labetalol hydrochloride, a specific method such as high performance liquid chromatography with a solid phase extraction should be employed in determining levels of catecholamines.

Labetalol has been shown to reduce the uptake of radioisotopes of metaiodobenzylguanidine (MIBG). Care should therefore be taken in interpreting results from MIBG scintigraphy.

Concomitant administration of labetalol and adrenaline may result in bradycardia and hypertension (see section 4.4 Special warnings and precautions for use).

Care should be taken if labetalol is used concomitantly with either Class I antiarrhythmic agents or calcium antagonists of the verapamil type.

Increased risk of myocardial depression in combination with Class I antiarrhythmic (e.g. disopyramide and quinidine) and amiodarone (Class II antiarrhythmics).

Risk of marked bradycardia and hypotension in combination with calcium antagonists with negative inotropic effect (e.g., verapamil, diltiazem), especially in patients with an impaired ventricular function and/or conduction disorders. In case of change from a calcium antagonist to a beta-blocker or reverse, new intravenous therapy must not be initiated before at least 48 hours after withdrawal of the former treatment.

Concomitant treatment with calcium antagonists which are dihydropyridine derivatives (e.g. nifedipine) may increase the risk of hypotension and may lead to heart failure in patients with latent cardial insufficiency. Digitalis glycosides in combination with beta blockers may increase the atrioventricular conduction time. Labetalol may enhance the digoxin's effect of reducing ventricular rate.

Beta-blockers, especially non-selective beta blockers, may increase the risk of hypoglycaemia in diabetic patients and mask the symptoms of hypoglycaemia, such as tachycardia and tremor, and delay the normalisation of blood sugar after insulin-induced hypoglycemia, especially non-selective beta blockers. Dose adjustments of oral antidiabetics and insulin may be necessary.

Care should be taken at general anaesthesia of patients using beta blockers. Beta blockers reduce the risk of arrhythmias during anaesthesia, but may lead to reduction of the reflectoric tachycardia and increase the risk of hypotension during anaesthesia. As anaesthetic, an agent with as low as possible degree of negative inotropic effect should be used. Heart function must be closely monitored and bradycardia due to vagal dominance should be corrected by intravenous administration of atropine 1-2 mg intravenously (withdrawal prior to surgery, see section 4.2 Posology and method of administration).

For withdrawal in patients using both beta blockers and clonidine, gradual discontinuation of the beta blocker must be done several days before discontinuation of clonidine. This is to reduce the potential rebound hypertensive crisis which is a consequence of withdrawal of clonidine. Accordingly, when changing from clonidine to a beta-blocker, it is important to discontinue clonidine gradually and start treatment with beta blocker several days after the clonidine has been withdrawn.

Concomitant treatment with cholinesterase inhibitors can increase the risk of bradycardia.

Concomitant treatment with 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).

Concomitant use of ergotamine derivatives may increase the risk of vasospastic reactions in some patients.

Labetalol has been shown to increase the bioavailability of imipramine by more than 50% through the inhibition of its 2-hydroxylation. Labetalol in combination with imipramine may increase the effect of imipramine and concomitant use of tricyclic antidepressants. Concomitant use of tricyclic antidepressants may increase the incidence of tremor.

Labetalol may enhance the hypotensive effect of volatile anaesthetics.
Enhanced blood pressure reduction may occur in case of concomitant use of e.g. nitrates, antipsychotics (phenothiazine derivatives such as chloropromazine) and other antipsychotics, antidepressants.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**
Based on experience during human pregnancy, labetalol is not expected to increase the risk of congenital malformations. Animal studies do not indicate teratogenicity. However toxicity on embryo-foetal development has been noted (see section 5.3). 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 crosses the placental barrier. Close monitoring 24 - 48 hours after birth is required. Beta-blockers may reduce uterine blood flow.

Labetalol should only be used during pregnancy if the benefits for the mother outweigh the risks for the foetus.

**Breast-feeding**:
Labetalol is excreted in breast milk in small amounts (approximately 0.004- 0.07% of the maternal dose). No adverse effects have been reported so far. Caution should be exercised when labetalol is administered to breast feeding women.
Nipple pain and Raynaud's phenomenon of the nipple have been reported (see section 4.8).

**Fertility**

There are no human data on the potential effects of labetalol on fertility. Non-clinical data is considered insufficient.

**4.7 Effects on ability to drive and use machines**

Not relevant.

**4.8 Undesirable effects**

**Summary of the safety profile**
The most common undesirable effects observed with labetalol injection, and collected from post-marketing reports include: congestive heart failure, postural hypotension, hypersensitivity, drug fever, raised liver function tests, nasal congestion, and erectile dysfunction.

**Tabulated list of adverse reactions**
The following convention has been used for the classification of frequency:
Very common ≥1/10
Common ≥1/100 and <1/10
Uncommon ≥1/1000 and <1/100
Rare ≥1/10,000and <1/1000
Very rare <1/10,000
Not known (cannot be estimated from the available data)

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

| System organ class | | Side effects |
|---|---|---|
| Immune System Disorders | Common | Hypersensitivity, Drug fever |
| Cardiac Disorders | Common | Congestive heart failure |
| | Rare | Bradycardia |
| | Very rare | Heart block |
| Vascular Disorders | Common | #Postural Hypotension |
| | Very rare | Exacerbation of the of Raynaud's Syndrome |
| Respiratory, Thoracic and Mediastinal disorders | Common | # Nasal Congestion |
| | Uncommon | Bronchospasm |
| Hepatobiliary Disorders | Common | Raised liver function tests |
| | Very rare | Hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis |
| Reproductive System and Breast Disorders | Common | Erectile dysfunction |
| | Not known | Nipple pain, Raynaud's phenomenon of the nipple |

**Description of selected adverse reactions:**

**Immune system disorders**
Hypersensitivityreactions reported include rash, pruritus, dyspnoea and very rarely drug feverand angioedema.

**Vascular disorders**
Pronounced postural hypotension may occur if patients are allowed to assume the upright position within 3 h of receiving labetalol injection.

**Hepatobiliary disorders**
Thesigns and symptoms of hepatobiliary disorders are usually reversible onwithdrawal of the medicinal product.

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 and signs:
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. In one case, the use of dopamine to increase the blood pressure may have aggravated the renal failure.

Treatment:
Patients should be laid supine with the legs raised.
Parenteral adrenergic/anticholinergic therapy should be administered as needed to improve the circulation.

Haemodialysis removes less than 1% labetalol hydrochloride from the circulation.

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

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

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

Mechanism of action
Labetalol lowers the blood pressure by blocking peripheral arteriolar alpha-adrenoceptors, thus reducing the peripheral resistance, and by concurrent beta-blockade, protects the heart from reflex sympathetic drive that would otherwise occur.

Pharmacodynamic effects
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 the diastolic pressure are essentially normal. All of these effects would be expected to be benefit for hypertensive patients.

**5.2 Pharmacokinetic properties**

**Pharmacokinetics**
Labetalol chemically consists of four stereoisomers with different pharmacodynamic effects.

Distribution
Approximately 50% of labetalol in the blood is protein bound. Only negligible amounts of labetalol cross the blood brain barrier in animal studies. 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 patient populations**

**Hepatic Impairment**
Labetalol undergoes significant but variable first-pass metabolism when given by the oral route. In a study of 10 patients with histologically proven cirrhosis, exposure to oral labetalol was increased approximately three-fold compared with healthy controls. Inter-subject variability in both patients and controls was high (approximately 2.5-fold). Patients with hepatic impairment may require lower oral doses of labetalol (see section 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use).

**5.3 Preclinical safety data**

**Carcinogenicity, mutagenicity and teratogenicity**
There was no evidence of mutagenic potential from in vitro and in vivo tests.

Labetalol showed no evidence of carcinogenicity in long-term studies in mice and rats. No teratogenicity was observed in rats and rabbits at oral doses 6 and 4 times the maximum recommended human dose. Increased foetal resorptions were seen in both species at doses approximating the maximum recommended human dose. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the maximum recommended human dose revealed no evidence of drug-related harm to the foetus.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Glucose monohydrate;
Disodium edetate;
Water for injection;
Sodium hydroxide and hydrochloric acid (for pH adjustment).

### 6.2 Incompatibilities

Labetalol injection has been shown to be incompatible with Sodium Bicarbonate injection BP 4.2% w/v.

### 6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C, 30°C and 40°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Package of 5x20 ml (glass ampoule).

### 6.6 Special precautions for disposal and other handling

Labetalol should be diluted only with compatible I.V. infusion fluids under aseptic condition.

Labetalol injection is compatible with the following I.V. infusion fluids:

- 5% Dextrose BP.
- 0.18% Sodium Chloride and 4% Dextrose BP.
- 0.3% Potassium Chloride and 5% Dextrose BP.
- Compound Sodium Lactate BP (Ringer Lactate).
- 0.9% Sodium Chloride.

## 7 MARKETING AUTHORISATION HOLDER

S.A.L.F. S.p.A. Laboratorio Farmacologico
Via Marconi, 2
24069
Italy

## 8 MARKETING AUTHORISATION NUMBER

PA22760/001/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th August 2019/ Date of renewal: 10th December 2021

## 10 DATE OF REVISION OF THE TEXT

April 2022