1. NAME OF THE MEDICINAL PRODUCT

LABETALOL S.A.L.F. 5 MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 5 mg 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.
Clear, colorless solution free from visible particles in a 20ml glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension when rapid control of blood pressure is essential.

4.2 Posology and method of administration

Posology

LABETALOL S.A.L.F. 5 MG/ML is intended for intravenous use in hospitalized patients.

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 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 S.A.L.F. 5 MG/ML has been administered to patients with uncontrolled hypertension already receiving other hypotensive agents, including beta-blocking drugs, without adverse effects.

Populations

- **Adults:**

SEVERE HYPERTENSION

Bolus Injection:

If it is essential to reduce the blood pressure quickly, a dose of 50 mg should be given by intravenous injection (over a period of at least one minute) and, if necessary, repeated at five minute intervals until a satisfactory response occurs. The total dose should not exceed 200 mg. The maximum effect usually occurs within 5 minutes and the duration of action is usually about 6 hours but may be as long as 18 hours.

Intravenous Infusion:

A 1 mg/ml solution of labetalol should be used, i.e. the contents of two ampoules (200mg) diluted to 200 ml with Sodium Chloride and Dextrose Injection BP or 5% Dextrose Intravenous Infusion BP.

HYPERTENSION DUE TO OTHER CAUSES

Infuse at a rate of about 2 mg/min until a satisfactory response is obtained, then stop infusion. The effective dose is usually 50-200 mg but larger doses may be needed, especially in patients with phaeochromocytoma. The rate of infusion may be adjusted according to the response at the discretion of the physician.

- **Children:**

Safety and efficacy in children have not been established.

Method of administration

Patients must always be administered the medicinal product when lying on their back or left side.

Avoid moving the patient to an upright position within 3 hours after intravenous administration of labetalol, as severe postural hypotension may occur.

4.3 Contraindications

- Nonselective beta blockers must not be used in patients with asthma or a history of obstructive airway disease.
- LABETALOL S.A.L.F. 5 MG/ML is contraindicated in second or third degree heart block (unless a pacemaker is present), cardiogenic shock and other conditions associated with severe and prolonged hypotension or severe bradycardia.
- Uncompensated heart failure.
- Unstable/uncontrolled cardiac insufficiency.
- Sick sinus syndrome (including sino-atrial block) unless a pacemaker is present.
- Prinzmetal angina.
- Sinus node dysfunction.
- Labetalol S.A.L.F. 5 MG/ML is contraindicated for patients known to have hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatic disease

Caution must be observed in the presence of 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 has been reported and in some cases been fatal. Laboratory testing should be done at the first sign or symptom of hepatic dysfunction. If laboratory results show hepatic injury or the patient is jaundiced, labetalol therapy should be stopped and not resumed.

Particular caution must be observed when labetalol is used in patients with hepatic impairment, as such patients metabolise labetalol slower than patients without hepatic impairment.

Renal impairment

Caution must be observed when labetalol is used in patients with severe renal impairment (GFR = 15–29 ml/min/1.73 m^2).

Peripheral vascular disease

Labetalol should be used with caution in patients with peripheral vascular disease as their symptoms may deteriorate. Caution is advised for patients with peripheral arterial disease (Raynaud syndrome, intermittent claudication), as labetalol may aggravate symptoms. Alpha blockers can counteract the unwanted effect of beta blockers.

Symptomatic bradycardia

The dosage of labetalol should be reduced if the patient develops symptomatic bradycardia.

First degree atrioventricular block

Due to the negative effect of beta blockers on atrioventricular conduction time, labetalol should be administered with caution to patients with first degree atrioventricular block.

Diabetes mellitus

Caution must be observed in the presence of uncontrolled or difficult-to-control diabetes. As with other beta blockers, labetalol can mask the symptoms of hypoglycaemia (tachycardia and tremor) in diabetic patients. The hypoglycaemic effect of insulin and oral hypoglycaemic agents may be amplified by beta blockers.

Thyrotoxicosis

Beta blockers can mask the symptoms of *thyrotoxicosis,* however thyroid function is not affected.

Hypersensitivity to beta blockers

Risk of anaphylactic reaction: while taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may become more reactive to repeated challenges, regardless of whether these are accidental, diagnostic or therapeutic. Such patients might not respond to the usual doses of adrenaline used to treat allergic reactions.

Adrenaline

A reduced adrenaline dose should be used if patients receiving labetalol require treatment with adrenaline, as concurrent administration of labetalol and adrenaline may result in bradycardia and hypertension (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Labetalol can cause a paradoxical rise in blood pressure if there is a significantly elevated level of adrenaline in the blood, such as in phaeochromocytoma.

Skin rash and/or dry eyes

Skin rash and/or dry eyes have been reported in connection with the use of beta blockers. The reported incidence is small and in most cases the symptoms subsided once the treatment was discontinued. Gradual discontinuance of the drug should be considered if a reaction of this type cannot otherwise be explained.

Intraoperative Floppy Iris Syndrome

The development of intraoperative floppy iris syndrome (IFIS, a variation of small pupil syndrome) has been observed in connection with cataract surgery in some patients who were treated with, or previously treated with, tamsulosin. Isolated reports have also been received concerning other alpha-1 blockers; the risk of a drug class effect cannot be excluded. Since IFIS can involve an increase in complications in connection with the cataract surgery, the eye surgeon must be informed prior to the procedure of current or previous use of alpha-1 blockers.

Heart failure or impaired left ventricular function

Particular caution must be observed in patients with heart failure or impaired systolic left ventricular function. Labetalol is contraindicated in uncontrolled heart failure, but may be used with caution in symptom-free patients whose condition is well controlled. Heart failure is to be controlled with adequate therapy before using labetalol.

The use of beta blockers indicates a risk of the development or deterioration of heart failure or obstructive lung disease. In the case of heart failure, the heart muscle's contraction capacity must be maintained, and the failure must be compensated. Patients with reduced contraction capacity, especially the elderly, must be monitored regularly with regard to the development of heart failure.

It is strongly recommended that LABETALOL S.A.L.F 5 MG/ML therapy should not be discontinued abruptly, especially in patients with heart failure or angina pectoris (risk of aggravated angina, myocardial infarction and ventricular fibrillation).

Inhaled anaesthetics

Caution should be observed in cases of concurrent treatment with inhaled anaesthetics (see section 4.5 Interaction with other medicinal products and other forms of interaction). It is not necessary to discontinue labetalol therapy prior to anaesthesia however the patient should receive intravenous atropine prior to the administration of the anaesthetic. Labetalol can amplify the hypotensive effects of volatile anaesthetics.

Metabolic acidosis and pheochromocytoma

Caution should be observed in cases of metabolic acidosis and pheochromocytoma. Labetalol should only be administered to patients with pheochromocytoma once adequate alpha blockade has been achieved.

Calcium antagonists

Caution should be observed if labetalol is used concurrently with calcium antagonists, especially calcium channel antagonists, which negatively affect contraction capacity and AV conduction.

Caution should be observed in cases of concurrent administration of adrenaline, verapamil or class I antiarrhythmics (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

Sudden haemorrhage

During general anesthesia, labetalol may mask the compensatory physiological responses to sudden haemorrhage (tachycardia and vasoconstriction). Blood loss and the blood volume maintained must therefore be monitored closely.

Special warnings/precautions regarding excipients:

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, i.e. it is 'essentially sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

The hypotensive effect of labetalol can be reduced when used in combination with inhibitors of prostaglandin synthesis (NSAIDs). Dosage adjustments may therefore be required. Further interactions may occur with other blood pressure lowering agents.

Labetalol fluoresces in alkaline solution with an excitation wavelength of 334 nm and a fluorescence wavelength of 412 nm and can therefore interact with the analysis of certain fluorescent substances including catecholamines.

The presence of labetalol metabolites in the urine may indicate falsely elevated levels of urinary catecholamines, metadrenaline, normetadrenaline and vanillylmandelic acid (VMA) when measured by fluorometric or photometric methods. When patients with suspected pheochromocytoma who are treated with labetalol hydrochloride are screened, a specific method such as a high performance liquid chromatography with solid phase extraction should be used to determine catecholamines levels.

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

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

Caution should be observed if labetalol is used concurrently with Class I antiarrhythmic or calcium antagonists of the verapamil type.

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

Risk of pronounced bradycardia and hypotension in combination with calcium antagonists with a negative inotropic effect (e.g. verapamil, diltiazem). Particularly for patients with impaired ventricular function and/or conduction disturbances. When making the transition from a calcium antagonist to a beta blocker (or vice versa), new intravenous therapy must not be initiated until at least 48 hours have elapsed from the discontinuation of the previous therapy.

Concurrent treatment with dihydropyridine-derived calcium antagonists (e.g. nifedipine) can increase the risk of hypotension and cause heart failure in patients with latent cardiac insufficiency. The atrioventricular conduction time may be prolonged by the concurrent use of

digitalis glycosides and beta blockers. Labetalol can amplify the effect of digoxin in regards to the reduction of ventricular frequency.

Beta blockers, especially nonselective beta blockers, can increase the risk of hypoglycaemia in diabetic patients, mask the symptoms of hypoglycaemia (e.g. tachycardia and tremor) and delay the normalisation of blood sugar following insulin-induced hypoglycaemia. Dose adjustments of oral antidiabetics and insulin may be required.

Caution must be observed in connection with general anaesthesia in patients using beta blockers. Beta blockers reduce the risk of arrhythmias during anaesthesia but can cause a reduction in reflex tachycardia and increase the risk of hypotension during anaesthesia. The negative inotropic effect of the anaesthetic agent should be as small as possible. Cardiac function must be monitored closely; bradycardia due to vagal dominance should be corrected with the intravenous administration of 1–2 mg atropine (withdrawal prior to surgery: see section 4.2 Posology and method of administration).

When beta blockers and clonidine are discontinued in patients taking both agents, a gradual withdrawal of the beta blocker must be made several days prior to the withdrawal of clonidine. The purpose of this measure is to reduce the potentially recurrent hypertensive crisis resulting from the withdrawal of clonidine. Thus, when changing from clonidine to a beta blocker it is important to gradually withdraw clonidine and initiate beta blocker therapy several days after the withdrawal of clonidine.

Concurrent use of acetylcholinesterase inhibitors may increase the risk of bradycardia.

Concurrent treatment with alpha adrenergic agonists (e.g. phenylpropanolamine and adrenaline) can increase the risk of elevated blood pressure, while concurrent treatment with beta adrenergic agonists results in a mutual reduction of effect (antidote effect).

Concurrent use of ergotamine derivatives can increase the risk of vasospastic reactions in some patients.

Labetalol has been shown to increase the bioavailability of imipramine by over 50 %, due to the inhibition of its 2-hydroxylation. Concurrent treatment with labetalol and imipramine can increase the effect of imipramine. Concurrent use of tricyclic antidepressants can increase the incidence of tremor.

Labetalol can amplify the hypotensive effects of highly volatile anaesthetics.

Improved blood pressure lowering may be achieved with concurrent use of e.g. nitrates, antipsychotics (phenothiazine derivatives such as chlorpromazine) and other antipsychotics and antidepressants.

4.6 Fertility, pregnancy and lactation
Fertility
There is no information on the effect of labetalol on fertility.

Pregnancy
Based on experience of pregnancy in humans, labetalol is not expected to increase the risk of birth defects. Animal studies do not indicate teratogenicity. However, toxic effects on foetal development have been noted (see section 5.3). Depending on the pharmacological mechanism of action of alpha and beta-adrenoceptor blockade, and when these are used in late pregnancy, undesirable effects to the foetus and the neonate should be taken into consideration (bradycardia, hypotension, respiratory depression, hypoglycaemia), as labetalol crosses the placenta. Beta blockers can reduce the blood flow in the uterus.

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

Breastfeeding
Labetalol is excreted in small quantities in human milk (approximately 0.004 –0.07 % of the mother's dose). No undesirable effects have yet been reported. Caution must be observed when labetalol is administered to lactating women.

4.7 Effects on ability to drive and use machines
Not relevant.

4.8 Undesirable effects
Summary of the safety profile
The most common adverse reactions observed with labetalol for injection and gathered from post-marketing reports include: heart failure, postural hypotension, hypersensitivity, drug fever, elevated liver function tests, nasal congestion and erectile dysfunction.

Tabulated list of adverse reactions
The following convention has been used to classify the frequency:
Very common ≥ 1/10
Common ≥ 1/100 to <1/10
Uncommon ≥ 1/1,000 to <1/100
Rare ≥ 1/10,000 to <1/1,000
Very rare <1/10,000.

The adverse reactions marked with # are usually transient and occur during the first few weeks of treatment.

Organ system		Adverse reactions
Immune system disorders	Common	Hypersensitivity, drug fever
Cardiac disorders	Common	Heart failure
	Rare	Bradycardia
	Very rare	Heart block
Vascular disorders	Common	#Postural hypotension
	Very rare	Aggravated symptoms of Raynaud syndrome
Respiratory, thoracic and mediastinal disorders	Common	#Nasal congestion
	Uncommon	Bronchospasm
Hepatobiliary disorders	Common	Elevated liver function tests
	Very rare	Hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis
Reproductive system and breast disorders	Common	Erectile dysfunction

Description of selected adverse reactions:
Immune system disorders
Hypersensitivity reactions reported include rash, pruritus, dyspnoea and very rarely, drug fever or angioedema have been reported.

Vascular disorders
Pronounced postural hypotension can occur if patients are permitted to assume an upright position within 3 hours after receiving a labetalol injection.

Hepatobiliary disorders
Signs and symptoms of hepatic and biliary passage disturbances are usually reversible on discontinuation of the medicinal product.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il .

4.9 Overdose
Symptoms and signs
Significant cardiovascular effects can be expected, e.g. excessive, postural hypotension and occasional bradycardia. Renal failure with oliguria has been reported following massive overdose of oral labetalol. In one case, the use of dopamine to increase blood pressure may have aggravated the renal failure.

Treatment
Patients should be recumbent, with the legs in an elevated position.

Parenteral adrenergic/anticholinergic treatment should be administered as required, to improve circulation.

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

Continued management is to proceed according to the clinical indications or as recommended by the Poisons Information Centre, if available.

5. PHARMACOLOGICAL PROPERTIES

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

Mechanism of action
Labetalol lowers blood pressure by blocking alpha adrenoceptors on peripheral arterioles, thus reducing peripheral resistance; the concurrent betablockade protects the heart from the reflex sympathetic drive that would otherwise occur.

Pharmacodynamic effects
Cardiac output is not significantly reduced at rest or after moderate exertion. The increase in systolic blood pressure during exertion is reduced, but the corresponding changes in the diastolic pressure are essentially normal. All these effects would be expected to benefit hypertensive patients.

5.2 Pharmacokinetic properties
Pharmacokinetics
Chemically, labetalol consists of four stereoisomers with different pharmacodynamic effects.

Distribution
Labetalol is around 50% protein bound in the blood. Only negligible amounts of labetalol have passed the blood brain barrier. Labetalol passes the placental barrier and is excreted in breast milk.

Biotransformation
Labetalol is metabolised primarily 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 unmodified in the urine and bile. The half-life of labetalol in plasma is approximately 4 hours.

Special patient populations
- **Hepatic failure**
  Labetalol undergoes significant but varying first-pass metabolism when administered orally. In a study of 10 patients with histologically confirmed cirrhosis, the exposure for oral labetalol increased approximately threefold compared with the healthy control group. Individual variations in both patients and the control group were large (approximately 2.5 times). Patients with hepatic failure 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
- Carcinogenic, mutagenic and teratogenic effects
  No signs of mutagenic potential were seen in *in vitro* and *in vivo* examinations.

  Labetalol showed no signs of carcinogenicity in long-term studies of mice and rats.

  No teratogenicity was observed in rats and rabbits at oral doses of 6 and 4 times the maximum recommended human dose. Increased foetal resorptions were seen in both species at doses approaching the maximum recommended human dose. A teratology study performed with labetalol in rabbits with intravenous doses up to 1.7 times the maximum recommended human dose gave no evidence of drug-related foetal injury.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Glucose monohydrate, disodium edetate, sodium hydroxide/hydrochloric acid, water for injections.

6.2 Incompatibilities
LABETALOL S.A.L.F. 5 MG/ML must not be mixed with sodium bicarbonate solution for injection.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

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.

In case of dilution, the product is stable for 24 hours at 2-8°C or at 25°C, but from a microbial point of view, the product should be used immediately after dilution.

6.4 Special precautions for storage
Store below 25ºC. Store in the original package to protect the product from light.

6.5 Nature and contents of container
Colorless glass ampoule.

Package of 5 X 20 ml ampoules.

6.6 Special precautions for disposal and other handling
No special requirements.

LABETALOL S.A.L.F. 5 MG/ML is compatible with the following intravenous infusion solutions:
5% Dextrose BP,
0.18% Sodium Chloride and 4% Dextrose BP,
0.3% Potassium Chloride and 5% Dextrose BP,
Compound Sodium Lactate BP.

7. MANUFACTURER
S.A.L.F. S.p.A. Laboratorio Farmacologico,
Cenate Sotto (Bergamo), Italy.

8. MARKETING AUTHORISATION HOLDER
RAZ PHARMACEUTICS LTD.,
6 Hamatechet st., Kadima, Israel.

9. MARKETING AUTHORISATION NUMBER
165-81-35551-00
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