SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

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

Formulation and Strength

Injection containing 5mg/ml labetalol hydrochloride in a 20ml ampoule.
Solution for injection.
Clear, colorless solution free from visible particles.

Excipients

Glucose monohydrate, disodium edetate, sodium hydroxide/hydrochloric acid, water for injections.

Excipient with known effect: 1 ml contains 49.5 mg Glucose monohydrate.
This medicine contains less than 1 mmol sodium (23 mg) per ampoule, i.e. it is 'essentially sodium free'.

CLINICAL INFORMATION

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

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

Patients should always receive the drug whilst in the supine or left lateral position.

Raising the patient into the upright position within three hours of intravenous labetalol administration should be avoided since excessive postural hypotension may occur.

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.

Population

- **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.

Contraindications

- LABETALOL S.A.L.F. 5 MG/ML is contraindicated in second or third degree heart block, cardiogenic shock and other conditions associated with severe and prolonged hypotension or severe bradycardia.

- Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of obstructive airways disease.

- 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.

- When peripheral vasoconstriction suggests low cardiac output, the use of Labetalol S.A.L.F. 5 MG/ML to control hypertensive episodes following acute myocardial infarction is contraindicated.

Warnings and Precautions

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. Appropriate laboratory testing 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 to be used in patients with hepatic impairment as these patients metabolize labetalol more slowly than patients without hepatic impairment.

Labetalol should be used with caution in patients with peripheral vascular disease as their symptoms may be exacerbated.

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

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

As with other beta-adrenoceptor blocking drugs, labetalol may mask the symptoms of hypoglycemia in diabetic patients and thyrotoxicosis.

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.

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 *Interactions*).

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 such reaction is not otherwise explicable.

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.

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.

It is not necessary to discontinue labetalol therapy in patients requiring anesthesia, but the anesthetist must be informed and the patient should be given intravenous atropine prior to induction. Labetalol may enhance the hypotensive effects of halothane.

In patients with pheochromocytoma, labetalol may be administered only after adequate alpha-blockade is achieved.

During anesthesia 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.

Interactions

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

Labetalol fluoresces in alkaline solution at an excitation wavelength of 334 nm and a fluorescence wavelength of 412 nm 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 fluorometric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCL, a specific method, such as a high performance liquid chromatographic assay with 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.

Labetalol may enhance digoxin's effect of reducing ventricular rate.

Concomitant administration of labetalol with adrenaline may result in bradycardia and hypertension (see *Warnings and Precautions*).

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

Labetalol may enhance the hypotensive effects of halothane.

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.

In humans labetalol crosses the placental barrier and the possibility of the consequences of α and β-adrenoceptor blockade in the fetus 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. Intra-uterine and neonatal deaths have been reported 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.

Lactation

Labetalol is excreted in breast milk in small amounts (approximately 0.004% of the maternal dose). Adverse events of unknown causality (sudden death syndrome, diarrhea, hypoglycemia) have been reported very rarely in breast-fed neonates. Caution should be exercised when labetalol is administered to breast feeding women.

Adverse Reactions

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects.
The following convention has been utilized for the classification of frequency: Very common ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1,000 and <1/100, rare ≥1/10,000 and <1/1,000, very rare <1/10,000.

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

Immune system disorders
Common: Hypersensitivity
Hypersensitivity reactions reported include rash, pruritus, dyspnea and very rarely, drug fever or angioedema.

Cardiac disorders
Common: Congestive heart failure
Rare: Bradycardia
Very rare: Heart block

Vascular disorders
Common: #Postural hypotension
Very rare: Exacerbation of the symptoms of Raynaud's Syndrome
Pronounced postural hypotension may occur if patients are allowed to assume the upright position within three hours of receiving labetalol injection.

Respiratory, thoracic and mediastinal disorders
Uncommon: Bronchospasm
Common: #Nasal congestion

Hepatobiliary disorders
Common: Raised liver function tests
Very rare: Hepatitis, hepatocellular jaundice, cholestatic jaundice hepatic necrosis
The signs and symptoms of hepatobiliary disorders are usually reversible on withdrawal of the drug.

Reproductive system and breast disorders
Common: Erectile dysfunction

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

Overdosage

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.

Treatment

Patients should be laid supine with the legs raised.

Use a cardiac glycoside and a diuretic in cardiac failure; for bronchospasm, administer a beta-2-agonist per aerosol. Intravenous atropine 0.25 to 3 mg should be given to relieve bradycardia.

Intravenous noradrenaline 5 to 10 μg initially, repeated according to response, may be preferable to isoprenaline to improve the circulation. Alternatively, noradrenaline may be infused at a rate of 5 μg per minute until the response is satisfactory.

In severe overdose, intravenous glucagon may be preferred: an initial bolus dose of 5 to 10 mg in dextrose or saline should be followed by an intravenous infusion of 5 mg/hour or as sufficient to maintain cardiac output. Transvenous pacing may be required.

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.

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

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

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Labetalol lowers blood pressure by blocking peripheral arteriolar α-adrenoceptors, thus reducing peripheral resistance, and by concurrent β-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 diastolic pressure are essentially normal. All these effects would be expected to benefit hypertensive patients.

Pharmacokinetics

Distribution

About 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.

Metabolism

Labetalol is metabolized mainly through conjugation to inactive glucuronide metabolites.

Elimination

The glucuronide metabolites are excreted both in the urine and via the bile, into the faeces. The plasma half-life of labetalol is about four hours.

Special Patient Populations

- **Renal Impairment**

Labetalol does not adversely affect renal function and is particularly suitable for use in hypertensive patients with renal disease.

- **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 Dosage and Administration, Warnings and Precautions).

NON-CLINICAL INFORMATION

- **Carcinogenesis, Mutagenicity**

There was no evidence of mutagenic potential from *in vitro* and *in vivo* tests.
Labetalol showed no evidence of carcinogenicity in long-term studies performed in mice and rats.

PHARMACEUTICAL INFORMATION

Incompatibilities

LABETALOL S.A.L.F. 5 MG/ML has been shown to be incompatible with Sodium Bicarbonate Injection BP 4.2% W/V.

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.

Storage

Store below 25ºC. Store in the original package to protect the product from light.

Nature and Contents of Container

Colorless glass ampoule ,Package of 5 X 20 ml ampoules.

Use and Handling

LABETALOL S.A.L.F. 5 MG/ML is compatible with the following intravenous 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.

MARKETING AUTHORISATION NUMBER

165-81-35551-00

MARKETING AUTHORISATION HOLDER

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MANUFACTURER

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