אפריל 2022

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת רז רוקחות מבקשת להודיעכם על עדכון העלון לרופא של התכשיר:

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

בהודעה זו מצוינים רק הסעיפים בהם נעשו שינויים מהותיים בעלון לרופא.

התוספות סומנו בצבע כחול, החמרות סומנו בצהוב והמחיקות סומנו בצבע אדום עם קו מחיקה.

העלון המעודכן נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות:

www.health.gov.il וניתן לקבלו מודפס על ידי פנייה לבעל הרישום: רז רוקחות בע"מ, רחוב המתכת 6, א.ת. קדימה.

בברכה,

אריאל מימון

רוקחת ממונה

מרכיב פעיל וחוזק:

LABETALOL HYDROCHLORIDE 5 MG / 1 ML

התוויה מאושרת:

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

להלן העדכונים המהותיים שבוצעו בעלון לרופא:

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4.2 Posology and method of administration

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.
- ~~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 listed in section 6.1.

- ~~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.~~

4.4 Special warnings and precautions for useWarnings and Precautions

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. ~~Appropriate~~ laboratory testing should be done at the first sign or symptom of hepatic ~~liver~~ 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 suchpatients 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 m2).

Peripheral vascular disease

Labetalol should be used with caution in patients with peripheral vascular disease as their symptoms may deteriorate ~~be exacerbated~~. 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 atrio-ventricular 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.

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

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 ~~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).~~ 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.

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Heart failure or impaired left ventricular function

Particular caution must be observed in ~~Special care should be taken with~~ patients with ~~who suffer from~~ heart failure or impaired ~~poor left ventricular~~ 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 ~~should be~~ controlled with adequate ~~appropriate~~ 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).

~~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.~~

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.

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

4.5 Interaction with other medicinal products and other forms of interaction Interactions

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

Increased risk of myocardial depression in combination with class I antiarrhythmics (e.g. disopyramide and quinidine) and amiodarone (class II antiarrhythmic). ~~Labetalol may enhance the hypotensive effects of halothane.~~

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 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.

~~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.~~

Breastfeeding ~~Lactation~~

Labetalol is excreted in breast milk in small quantities in human milk ~~amounts~~ (approximately 0.004 –0.07 % of the mother's ~~maternal~~ dose). No undesirable effects have yet been reported ~~Adverse events of unknown causality (sudden death syndrome, diarrhea, hypoglycemia) have been reported very rarely in breast-fed neonates~~. Caution must be observed ~~should be exercised~~ when labetalol is administered to lactating ~~breast feeding~~ 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

~~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 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

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4.9 Overdose

Symptoms and signs

Significant cardiovascular effects can be expected, e.g. excessive, posturale-~~sensitive~~ 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. In one case, the use of dopamine to increase blood pressure may have aggravated the renal failure.

Treatment

Patients should be recumbent, ~~laid supine~~ with the legs in an elevated position ~~raised.~~

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

~~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 □g 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% 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.

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

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5.2 Pharmacokinetic properties

Pharmacokinetics

Chemically, labetalol consists of four stereoisomers with different pharmacodynamic effects.

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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.

5.3 Preclinical safety data

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.