



דצמבר 2021

רופא/ה רוקח/ת נכבד/ה,

חברת פאדאג'יס מבקשת ליידע אתכם על עדכון העלון לרופא של התכשיר:

טרנדייט זריקות / TRANDATE INJECTION

החומר הפעיל בתכשיר וחוזקו: Labetalol hydrochloride 5 mg/ml

התוויה הרשומה לתכשיר בישראל:

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

מהות העדכון:

עדכוני בטיחות ועדכוני נוסח בהתאם לעלון האסמכתא וכן התאמה לנוהל והנחיות משרד הבריאות.

העלון המעודכן לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות: <http://www.health.gov.il> וניתן לקבלו מודפס ע"י פניה לחברת פאדאג'יס ישראל סוכנויות בע"מ בטלפון: 03-5773700

בברכה,

פאדאג'יס ישראל סוכנויות בע"מ

4.3 Contraindications

[...]

- Labetalol injections and tablets are 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

[...]

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-term and long-term treatment. However, hepatic necrosis has been reported and in some cases been fatal.

[...]

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.

[...]

Diabetes mellitus

Caution must be observed in the presence of uncontrolled or difficult-to-control diabetes. As with other beta blockers beta-adrenoceptor blocking drugs, labetalol can may 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.

[...]

Adrenaline

[...]

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.

[...]

Heart failure or impaired 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 treatment 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 Trandate 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).

[...]

Labetalol can amplify ~~may enhance~~ the hypotensive effects of **volatile anaesthetics** ~~halothan~~.

Metabolic acidosis and pheochromocytoma

Caution should be observed in cases of metabolic acidosis and pheochromocytoma.

[...]

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** anaesthesia, labetalol may mask the compensatory physiological responses to ~~of~~ sudden haemorrhage (tachycardia and vasoconstriction).

[...]

4.5 Interaction with other medicinal products and other forms of interaction

The hypotensive effect of labetalol ~~can may~~ be reduced when used in combination with ~~inhibitors of prostaglandin synthetase synthesis 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).

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.

[...]

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.

[...]

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

Based on experience of pregnancy in humans, labetalol is not expected to increase the risk of birth defects.

[...]

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. Perinatal and neonatal distress (bradycardia, hypotension, respiratory depression, hypoglycaemia, hypothermia), has been rarely reported as 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. Beta blockers can reduce the blood flow in the uterus.

[...]

Breastfeeding

Labetalol is excreted in small quantities in human breast-milk in small amounts (around approximately 0.004–0.07 % of the mother's maternal dose). No undesirable effects. Adverse events of unknown causality (sudden death syndrome, diarrhoea, hypoglycaemia) have yet been reported very rarely in breast-fed neonates.

[...]

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.

[...]