TRANDATE™
Labetalol

QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mg/ml labetalol hydrochloride solution for injection in a 20 ml or a 5 ml ampoule.

PHARMACEUTICAL FORM

Solution for injection.

CLINICAL PARTICULARS

Indications

TRANDATE injection is indicated for:

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

Dosage and Administration

TRANDATE injection is intended for i.v. use in hospitalised patients. Patients should always receive the drug whilst in the supine or left lateral position. Raising the patient into the upright position within 3 h of i.v. *TRANDATE* 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.

TRANDATE injection has been administered to patients with uncontrolled hypertension already receiving other hypotensive agents, including beta-blocking drugs, without adverse effects.

Populations

• **Adults**

Interaction	**Dose**
Severe Hypertension	Bolus injection If it is essential to reduce the blood pressure quickly a dose of 50 mg should be given by i.v. injection (over a period of at least 1 min) and, if necessary, repeated at 5 min intervals until a satisfactory

	response occurs. The total dose should not exceed 200 mg. 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.
	<u>Intravenous infusion</u> A 1 mg/ml solution of TRANDATE should be used, i.e. the contents of two 20 ml ampoules or eight 5 ml ampoules (200 mg) diluted to 200 ml with Sodium Chloride and Dextrose Injection BP or 5% Dextrose Intravenous Infusion BP. The infusion rate should normally be about 120 – 160mg/h but may be adjusted according to the response at the discretion of the physician The effective dose is usually 50 to 200 mg but 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 min until a satisfactory response is obtained or a dosage of 160 mg/h is reached.
Achieving controlled hypotension during anaesthesia	To achieve controlled hypotension during anaesthesia, the recommended starting dose of labetalol injection is 10 to 20 mg intravenously depending on the age and condition of the patient. 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. The mean duration of hypotension following 20 to 25 mg of labetalol is 50 min.

• **Paediatric population**

Safety and efficacy in paediatric patients aged 0 to 18 years has not been established. No data are available.

Contraindications

TRANDATE injection 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.

Non-selective beta-blockers should not be used in patients with asthma or a history of obstructive airway disease.

Uncompensated heart failure

Unstable/uncontrolled heart insufficiency

Sick sinus syndrome (including sinus atrial block) unless pacemaker in situ

Sinus node dysfunction

Prinzmetal angina

TRANDATE injection is contraindicated for patients known to have hypersensitivity to the active substance or to any of the excipients listed.

Warnings and Precautions

Liver disease
Care should be taken in liver disease. There have been very rare reports of severe hepatocellular injury with *TRANDATE* 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 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, *TRANDATE* therapy should be stopped and not re-started.

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

Renal impairment
Caution is advised when labetalol is used in patients with severe renal impairment (GFR = 15-29 ml/min/1.73m2).

Peripheral vascular disease

TRANDATE 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 (Raynaud's syndrome, intermittent claudication) as labetalol may exacerbate their symptoms. However, it has also been reported that the alpha-block properties of labetalol may counteract the effect of pure beta-blockers on the exacerbation of peripheral vascular disease.

Symptomatic bradycardia

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

First-degree atrioventricular block

Given the negative effect of beta-adrenoceptor blocking drugs on atrioventricular conduction time, *TRANDATE* 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 medicinal products, *TRANDATE* 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.

Thyrotoxicosis

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

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 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.

Adrenaline

If patients receiving *TRANDATE* require adrenaline treatment, a reduced dosage of adrenaline should be used as concomitant administration of *TRANDATE* with adrenaline may result in bradycardia and hypertension (*see Interactions*).
Upon severe influence of adrenaline as in pheochromocytoma, labetalol may cause a paradoxical blood pressure elevation.

Intraoperative Floppy Iris Syndrome

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.

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 TRANDATE.
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 Trandate 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 Interactions). *TRANDATE* injection need not be discontinued prior to anaesthesia but patients should receive i.v. atropine prior to induction. TRANDATE may enhance the hypotensive effects of volatile anaesthetics.

Sudden haemorrhage
During anaesthesia, *TRANDATE* injection 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.

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 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.

Metabolic acidosis and pheochromocytoma
Care should be taken in cases of metabolic acidosis and pheochromocytoma. In patients with pheochromocytoma, *TRANDATE* may be administered only after 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 class-1 antiarrhythmics.

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

Interactions

The hypotensive effect of *TRANDATE* 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.

Concomitant treatment with calcium antagonists which are dihydropyridine derivates (e.g. nifedipine), may increase the risk of hypotension and may lead to heart failure in patients with latent cardiac insufficiency.

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 vaillylmandelic acid (VMA) when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with *TRANDATE*, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction should be employed in determining levels of catecholamines.

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

Digitalis glycosides in combination with beta blockers should not be used as they may increase the atrioventricular conduction time. *TRANDATE* may enhance digoxin's effect of reducing ventricular rate.

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

Risk of marked bradycardia and hypotension in combination with calcium antagonists with negative inotropic effect (e.g. verapamil, diltiazem), especially in patients with 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.

Beta blockers, especially non-selective beta blockers, may increase the risk of hypoglycemia in diabetic patients and mask the symptoms of hypoglycemia 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. An anaesthetic 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 with intravenous administration of atropine, 1-2 mg intravenously.

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 the beta blocker several days after clonidine has been withdrawn

Concomitant administration of labetalol with cholinesterase inhibitors may increase the risk of bradycardia.

Concomitant treatment with alpha 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 derivates 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 anti-depressants may increase the incidence of tremor.

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

TRANDATE injection may enhance the hypotensive effects of volatile anaesthetics.

Enhanced blood pressure reduction may occur in case of concomitant use of e.g. nitrates, antipsychotics (fentiazine derivates such as chloropromazine) and other antipsychotics, antidepressants.

Care should be taken if labetalol is used concomitantly with either Class I antiarrhythmic agents or calcium antagonists of the verapamil type (e.g. disopyramide, quinidine), as calcium antagonists such as verapamil and to a lesser extent diltiazem have a negative influence on contractility and atrio-ventricular conduction.

Pregnancy and Lactation

Fertility

There are no data on the effects of labetalol on fertility.

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 Non-Clinical Information). 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-blocker may reduce uterine blood flow.

TRANDATE should only be used during pregnancy if the benefits to Mother outweighs the potential risk.

Lactation

In humans, labetalol crosses the placental barrier and the possibility of the consequences of alpha- and beta-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. i.v. fluids and glucose) is usually prompt but with severe pre-eclampsia, particularly after prolonged i.v. *TRANDATE*, 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 TRANDATE and delaying delivery and against co- administration of hydralazine. Labetalol is excreted in breast milk in small amounts (approximately 0.004-0.07% of the maternal dose). Nipple Pain and Raynaud's phenomenon of the nipple have been reported. Caution should be exercised when labetalol is administered to breast feeding women.

Ability to perform tasks that require judgement, motor or cognitive skills

There is no information on the effect of TRANDATE injection on the ability to drive and use machines.

Adverse Reactions

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.

The following convention has been utilised for the classification of frequency: very common ≥1/10, common ≥1/100, <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

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

Body system		**Adverse effects**
Immune system	**Common**	Hypersensitivity, drug fever
Heart	**Common**	Congestive heart failure
	Rare	Bradycardia
	Very rare	Heart block
Blood vessel	**Common**	#Postural hypotension
	Very rare	Exacerbation of the symptoms 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
Hypersensitivity reactions reported include rash, pruritus, dyspnoea and very rarely, drug fever or 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
The signs and symptoms of hepatobiliary disorders are usually reversible on withdrawal of the medicinal product.

Overdose

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 *TRANDATE* 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 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Labetalol lowers blood pressure by blocking peripheral arteriolar alpha-adrenoceptors, thus reducing peripheral resistance, and by concurrent beta-blockade, protects the heart from reflex sympathetic drive that would otherwise occur. 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. In patients with angina pectoris with coexisting hypertension, the reduced peripheral resistance decreases myocardial afterload and oxygen demand.

All these effects would be expected to benefit hypertensive patients, including those with coexisting angina.

Pharmacokinetics

Absorption

Labetalol is rapidly absorbed from *TRANDATE* tablets in the gastrointestinal tract with peak plasma levels occurring 1 to 2 h after oral administration. There is a significant first-pass metabolism leading to a bioavailability of approximately 25%, but there is considerable variation.

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.

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.

Non-clinical information

Carcinogensis, mutagenesis and teratogenesis

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.

No teratogenicity was observed in rats and rabbits at oral doses 6 and 4 times the maximum recommended human dose, respectively. 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Injection:

Dilute hydrochloric acid or sodium hydroxide
Water for injection.

Incompatibilities

TRANDATE injection has been shown to be incompatible with sodium bicarbonate injection BP 4.2% W/V.

Shelf Life

The expiry date is indicated on the packaging.

Unused *TRANDATE* injection solution should be discarded 24 h after preparation.

Special Precautions for Storage

Store below 30^{o}C. Protect from light.

Nature and Contents of Container

TRANDATE injection is supplied in clear Type I glass ampoules, either 20 ml and 5 ml capacity.

Instructions for Use/Handling

TRANDATE 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.

Not all presentations are available in every country.

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