

NEW ZEALAND DATA SHEET

TRANDATE



1. Product Name

Trandate, 5 mg/mL, solution for injection.

2. Qualitative and Quantitative Composition

Each ampoule contains 100 mg of labetalol hydrochloride

3. Pharmaceutical Form

Solution for injection. 20 mL glass ampoules each containing 100 mg (5 mg/mL) labetalol hydrochloride in an aqueous colourless solution.

4. Clinical Particulars

4.1 *Therapeutic indications*

Severe hypertension when rapid control of blood pressure is essential.

Anaesthesia when a hypotensive technique is indicated.

Hypertensive episodes following acute myocardial infarction.

4.2 *Dose and method of administration*

TRANDATE Injection is intended for intravenous use in hospitalised patients.

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

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

For instructions on the dilution of this medicine before administration, see section 6.6.

Adults

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 TRANDATE should be used, i.e. the contents of two ampoules (200 mg) diluted to 200 mL with Sodium Chloride and Dextrose Injection BP or 5% Dextrose Intravenous Infusion BP.

Hypertension in pregnancy - Infusion should be started at 20 mg/hour, then doubled every 30 minutes until a satisfactory response is obtained or a dosage of 160 mg/hour is reached. Occasionally higher doses may be necessary.

Hypertensive episodes following acute myocardial infarction - Infusion should be started at 15 mg/hour and gradually increased to a maximum of 120 mg/hour depending on the control of blood pressure.

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.

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 1-2 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 β -blocking drugs, without adverse effects.

Hypotensive anaesthesia - Induction should be with standard agents (e.g. sodium thiopentone) and anaesthesia maintained with nitrous oxide and oxygen with or without halothane. The recommended starting dose of TRANDATE Injection is 10-20 mg intravenously depending on the age and condition of the patient. Patients for whom halothane is contraindicated usually require a higher initial dose of TRANDATE (25-30 mg). If satisfactory hypotension is not achieved after five minutes, increments of 5-10 mg should be given until the desired level of blood pressure is attained.

Halothane and TRANDATE act synergistically therefore the halothane concentration should not exceed 1-1.5% as profound falls in blood pressure may be precipitated.

Following TRANDATE Injection the blood pressure can be quickly and easily adjusted by altering the halothane concentration and/or adjusting table tilt. The mean duration of hypotension following 20- 25 mg of TRANDATE is fifty minutes.

Hypotension induced by TRANDATE Injection is readily reversed by atropine 0.6 mg and discontinuation of halothane.

Tubocurarine and pancuronium may be used when assisted or controlled ventilation is required. IPPV may further increase the hypotension resulting from TRANDATE Injection and/or halothane.

Special populations

Paediatric

Safety and efficacy in children have not been established.

4.3 Contraindications

TRANDATE Injection is contraindicated in second or third degree heart block, cardiogenic shock and other conditions associated with severe and prolonged hypotension or severe bradycardia.

When peripheral vasoconstriction suggests low cardiac output, the use of TRANDATE Injection to control hypertensive episodes following acute myocardial infarction is contraindicated.

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

Labetalol is contraindicated for patients known to have hypersensitivity to the medicine.

4.4 Special warnings and precautions for use

There have been 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.

TRANDATE 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 TRANDATE should be reduced.

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.

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.

TRANDATE Injection need not be discontinued prior to anaesthesia but patients should receive intravenous atropine prior to induction.

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

During anaesthesia TRANDATE 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.

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

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

Risk of anaphylactic reaction: While taking β -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 adrenaline (epinephrine) used to treat allergic reaction.

If patients receiving labetalol require adrenaline (epinephrine) treatment, a reduced dosage of adrenaline (epinephrine) should be used as concomitant administration of labetalol with adrenaline (epinephrine) may result in bradycardia and hypertension (see section 4.5).

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.

4.5 Interaction with other medicines and other forms of interaction

TRANDATE may enhance the hypotensive effects of halothane.

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

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

TRANDATE 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 of urinary catecholamines, metanephrine, normetanephrine, and vanillylmandelic acid (VMA) when measured by fluorimetric 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.

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

Concomitant administration of labetalol with adrenaline may result in bradycardia and hypertension (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Although no teratogenic effects have been demonstrated in animals, TRANDATE 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 foetus 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 medicines (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.

Breast-feeding

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

Fertility

No data available.

4.7 Effects on ability to drive and use machines

No data available

4.8 Undesirable effects

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 utilised for the classification of frequency: Very common $\geq 1/10$, common $\geq 1/100$ and $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10000$ and $< 1/1000$, very rare $< 1/10000$.

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, dyspnoea 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 TRANDATE injection.

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

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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Profound cardiovascular effects are to be expected, e.g. excessive, posture-sensitive hypotension and sometimes bradycardia. Patients should be laid supine with the legs raised. Use a cardiac glycoside and a diuretic in cardiac failure; for bronchospasm, administer a β 2-agonist per aerosol. Intravenous atropine 0.25 to 3 mg should be given to relieve bradycardia. Intravenous noradrenaline (norepinephrine) 5 to 10 micrograms initially, repeated according to response, may be preferable to

isoprenaline to improve the circulation. Alternatively, noradrenaline (norepinephrine) may be infused at a rate of 5 micrograms 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 clinically indicated or as recommended by the national poison centre.. For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 *Pharmacodynamic properties*

Pharmacotherapeutic group: alpha and beta blocking agents, ATC code: C07AG01

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. 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.

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

5.2 *Pharmacokinetic properties*

The plasma half-life of labetalol is about four hours. About 50% of labetalol in the blood is protein bound. Labetalol is metabolised mainly through conjugation to inactive glucuronide metabolites. These are excreted both in the urine and via the bile, into the faeces. Only negligible amounts of labetalol cross the blood brain barrier in animal studies. Labetalol crosses the placental barrier and is secreted in breast milk.

5.3 *Preclinical safety data*

Mutagenicity:-

There was no evidence of mutagenic potential from *in vitro* and *in vivo* tests.

Carcinogenicity:-

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

6. Pharmaceutical Particulars

6.1 *List of excipients*

TRANDATE injection also contains:

- Dilute hydrochloric acid
- Sodium hydroxide,
- Water for Injections.

6.2 Incompatibilities

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

TRANDATE injection must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

2 years

Unused admixtures should be discarded 24 hours after preparation.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

Clear Type I glass ampoules, 20 mL capacity. Boxes of 5 ampoules.

6.6 Special precautions for disposal (and other handling)

Instructions for use

TRANDATE Injection 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.

Dilution with Normal Saline

There are two methods for dilution of TRANDATE Injection with normal saline (0.9% sodium chloride):

- a. Add 40 mL (2 ampoules) of TRANDATE Injection to 160 mL of diluting fluid. The resultant 200 mL of solution contains 200 mg labetalol hydrochloride 1 mg/mL. The diluted solution should be administered at a rate of 2 mL/min to deliver 2 mg/min.
- b. Add 40 mL of TRANDATE Injection to 250 mL of diluting fluid. The resultant 290 mL of solution contains 200 mg labetalol hydrochloride, approximately 2 mg/3mL. The diluted solution should be administered at a rate of 3 mL/min to deliver 2 mg/min approximately.

The rate of infusion of diluted solution may be adjusted according to blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion the diluted solution can be infused using a controlled administration mechanism, e.g. graduated burette or mechanically driven infusion pump.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
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AUCKLAND
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9. Date of First Approval

15 January 2009

10. Date of Revision of the Text

06 January 2021 **Summary table of changes**

Section	Summary of new information
All sections	To Mylan format and editorial corrections
5.1	Addition of pharmacotherapeutic group and ATC code
8	Change in sponsor