**1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE **

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TRANDATE INJECTION 5 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of TRANDATE INJECTION contains 5 mg of labetalol hydrochloride.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

TRANDATE INJECTION is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 controlled hypotension during anaesthesia.

4.2 Posology and method of administration

Posology

Adults

TRANDATE INJECTION is intended for intravenous use in hospitalised patients.

The plasma concentrations achieved after intravenous doses of TRANDATE INJECTION in severe hypertension are substantially greater than those following oral administration of the medicine.

Patients should therefore always receive TRANDATE INJECTION whilst in the supine position.

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

The blood pressure and heart rate should be monitored after injection and during infusion.

It is desirable to monitor the BP 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 IV. Respiratory function should be observed particularly in patients with any known impairment.

Once the BP has been adequately reduced by bolus injection or infusion, maintenance therapy with TRANDATE tablets should be substituted with a starting dose of 100 mg twice daily.

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

Severe hypertension (Adults)

Bolus injection:

If it is essential to reduce the blood pressure quickly, as, for example, in hypertensive encephalopathy, 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.

Intravenous infusion

The resultant infusion solution contains 1 mg/ml of TRANDATE INJECTION. An intravenous infusion of a solution made by diluting the contents of two 20 ml ampoules or eight 5 ml ampoules (200 mg) to 200 ml with sodium chloride and dextrose injection BP is given. It should be administered using a volume-controlled infusion pump to facilitate accurate dosage.

Hypertension due to other causes

The rate of infusion of TRANDATE INJECTION should be about 2 mg (2 ml of infusion solution) per minute until a satisfactory response is obtained; the infusion should then be stopped.

The effective dose is usually in the range of 50 to 200 mg depending on the severity of the hypertension. For most patients, it is unnecessary to administer more than 200 mg but doses up to 300 mg may be required, especially in patients with phaeochromocytoma. The rate of infusion may be adjusted according to the response, at the discretion of the medical practitioner.

Abrupt withdrawal of clonidine or beta-blocking medicines is undesirable. For long-term control of hypertension following the use of labetalol injection, oral therapy with labetalol tablets should start at 100 mg twice daily.

Severe hypertension of pregnancy

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/hour. The dose may be doubled every 30 minutes until a satisfactory response is obtained or a dosage of 160 mg/hour is reached.

Hypotensive anaesthesia

In hypotensive anaesthesia, induction should be with standard medicines (e.g. sodium thiopentone) and anaesthesia maintained with halogenated inhalation anaesthetics. The recommended starting dose of TRANDATE INJECTION is 10 to 20 mg intravenously, depending on the age and condition of the patient. If satisfactory blood pressure reduction is not achieved after five minutes, 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 TRANDATE INJECTION is fifty minutes.

Paediatric population

The safety and efficacy of TRANDATE INJECTION in paediatric patients aged 0 to 18 years have not been established. No data is available.

Method of administration

Intravenous.

An alternative method of administering TRANDATE INJECTION is intravenous infusion of a solution made by diluting the contents of two ampoules (200 mg) to 200 ml with Sodium Chloride and Dextrose Injection BP or 5 % Dextrose Intravenous Infusion BP. The resultant infusion solution contains 1 mg/ml of labetalol hydrochloride.

Precautions to be taken before handling or administering the TRANDATE INJECTION:

Patients should always receive the medicine whilst in the supine or left lateral position. Raising the patient into the upright position within 3 h of i.v. 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. TRANDATE INJECTION has been administered to patients with uncontrolled hypertension already receiving other hypotensive medicines, including beta-blocking medicines, without adverse effects.

4.3 Contraindications

TRANDATE INJECTION is contraindicated in:

- Patients with hypersensitivity to labetalol or any of the excipients in TRANDATE INJECTION. (see section 6.1).
- Non-selective beta-blockers should not be used in patients with asthma, or a history of obstructive airways disease.
- 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.
- Uncompensated heart failure.
- Unstable/uncontrolled heart insufficiency.
- Sick sinus syndrome (including sinus atrial block) unless pacemaker in situ.
- Prinz metal angina.
- Sinus node dysfunction.
- Women who are breastfeeding their infants (see section 4.6).

4.4. Special warnings and precautions for use

Hepatobiliary disorders

Care should be taken in liver disease. There have been reports of severe hepatocellular injury with TRANDATE INJECTION therapy, including fatal liver toxicity. The hepatic injury is usually reversible on stopping treatment 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. Laboratory evidence of liver injury or the patient is jaundiced, TRANDATE INJECTION therapy should be stopped immediately and not restarted.

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

Peripheral vascular disease

TRANDATE INJECTION should be used with caution in patients with peripheral vascular disease as their symptoms may be exacerbated. Caution is advised in patients with peripheral arteriolar disease (Raynaud's syndrome, claudication intermittens) as TRANDATE INJECTION may exacerbate their symptoms. Alpha-block may counter the unfortunate effect of beta-blockers such as TRANDATE INJECTION.

Symptomatic bradycardia

If the patient develops symptomatic bradycardia, the dosage of TRANDATE INJECTION should be reduced, or should be stopped (see section 4.3).

First-degree atrio ventricular block

Given the negative effect of beta-adrenoceptor blocking medicines on atrioventricular conduction time, TRANDATE INJECTION should be administered with caution to patients with digoxin-resistant heart failure 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, as contained in TRANDATE INJECTION.

Diabetes mellitus

Care should be taken in case of uncontrolled or difficult-to-control diabetes mellitus.

As with other beta-adrenoceptor blocking medicines, TRANDATE INJECTION may mask the symptoms of hypoglycaemia (tachycardia and tremor) in diabetic patients. The hypoglycaemic effect of insulin and oral hypoglycaemic medicines may be enhanced by beta blockers such as TRANDATE INJECTION. This statement is based on the fact that a slight increase in blood sugar level occurs following the administration of TRANDATE INJECTION, and the possibility of interactions with TRANDATE INJECTION and insulin or oral anti-diabetic medicines (see section 4.5).

Thyrotoxicosis

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

Hypersensitivity to beta blockers

Risk of anaphylactic reaction: While receiving TRANDATE INJECTION, 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 (adrenaline) used to treat allergic reactions.

Adrenaline

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

Skin rashes and/or dry eyes

There have been common reports of skin rashes and/or dry eyes associated with the use of TRANDATE INJECTION. Gradual discontinuance of TRANDATE INJECTION should be considered if any such reaction is not otherwise explicable.

Inhalation anaesthetics

Care should be taken with concomitant treatment with inhalation anaesthetics (see section 4.5).

TRANDATE INJECTION may enhance the hypotensive effects of volatile anaesthetics.

Sudden haemorrhage

During anaesthesia TRANDATE INJECTION may mask the compensatory physiological responses to sudden haemorrhage (tachycardia and vasoconstriction). Close attention must therefore be paid to blood loss and the blood volume maintained.

Renal impairment

Caution is advised when TRANDATE INJECTION is used in patients with severe renal impairment (GFR = 15 to 29 ml/min/1,73m^2).

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.

Cardiovascular disorders

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.

TRANDATE INJECTION is contraindicated in uncontrolled heart failure but may be used with caution in patients who are well managed and free of symptoms (see section 4.3). Heart failure should be controlled with appropriate therapy before use of TRANDATE INJECTION.

Use of beta blockers such as TRANDATE INJECTION 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 INJECTION abruptly especially in patients with heart failure and patients with angina pectoris (risk of exacerbation of angina, myocardial infarction, and ventricular fibrillation).

Metabolic acidosis and phaeochromocytoma

Care should be taken in cases of metabolic acidosis and phaeochromocytoma. In patients with phaeochromocytoma, TRANDATE INJECTION may be administered only after adequate alpha-blockade is achieved.

Calcium antagonists

Care should be taken if TRANDATE INJECTION is used concomitantly with calcium antagonists, particularly the "calcium entry blockers", which influence contractility and AV conduction negatively (see section 4.5).

Bronchospasm

Caution must be observed if TRANDATE INJECTION is used to treat asthmatic patients or individuals prone to bronchospasm. Any resultant bronchospasm may be controlled by an inhaled beta agonist; the required dose may be greater than the normal anti-asthmatic dose. If further treatment is required, intravenous atropine 1 mg may be given.

Beta blockers such as TRANDATE INJECTION have negative inotropic effect but does not affect the positive inotropic effect of digitalis.

Concurrent use of TRANDATE INJECTION may result in an increased plasma concentration of the following medicines: hypoglycaemic medicines, phenothiazine's and various anti-dysrhythmic medicines. Such interactions can have life-threatening consequences (see section 4.5).

Caution should be taken to prevent occasional exaggerated hypotensive response, particularly in the presence of hypovolaemia.

Paediatric population

Safety and efficacy in children has not been established.

4.5 Interaction with other medicines and other forms of interaction

Non-steroidal anti-inflammatory drugs

The hypotensive effect of TRANDATE INJECTION may be reduced when it is used in combination with prostaglandin synthetase inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs). Dosage adjustments may therefore be necessary. Additive synergism may occur with other antihypertensive medicines.

Adrenaline

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

Antidysrhythmic medicines

Care should be taken if TRANDATE INJECTION is used concomitantly with either Class I antidysrhythmic medicines (e.g. disopyramide, quinidine) or calcium antagonists of the verapamil type.

Increased risk of myocardial depression in combination with class I antidysrhythmics (e.g. disopyramide and quinidine) and amiodarone (class II antidysrhythmic).

Phenothiazines

Concomitant use of phenothiazines medicines may increase the blood pressure-lowering effect of TRANDATE INJECTION.

Calcium antagonists

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 cardial insufficiency (see section 4.4).

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.

Digitalis

Digitalis glycosides in combination with beta blockers may increase the atrioventricular conduction time. TRANDATE INJECTION may enhance digoxin's effect of reducing ventricular rate.

Cholinesterase inhibitors

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

Ergotamine derivatives

Concomitant use of ergotamine derivates may increase the risk of vasospastic reactions in some patients.

Anaesthetic medicines

Care should be taken at general anaesthesia of patients using beta blockers such as TRANDATE INJECTION. Beta blockers reduce the risk of dysrhythmias during anaesthesia but may lead to reduction of the reflectoric tachycardia and increase the risk of hypotension during anaesthesia. An anaesthetic medicine 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 to 2 mg intravenously (withdrawal prior to surgery, see section 4.2).
TRANDATE INJECTION may enhance the hypotensive effects of volatile anaesthetics.

Alpha and beta stimulating adrenergics

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).

Imipramine

TRANDATE INJECTION has been shown to increase the bioavailability of imipramine by more than 50 % through the inhibition of its 2- hydroxylation. TRANDATE INJECTION in combination with imipramine may increase the effect of imipramine and concomitant use of tricyclic antidepressants. Concomitant use of tricyclic antidepressants may increase the incidence of tremor.

Clonidine withdrawal

For withdrawal in patients using both TRANDATE INJECTION and clonidine, gradual discontinuation of TRANDATE INJECTION 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 TRANDATE INJECTION it is important to discontinue clonidine gradually and start treatment with TRANDATE INJECTION several days after clonidine has been withdrawn.

Insulin and oral antidiabetic medicine

TRANDATE INJECTION with insulin and oral antidiabetic medicine may impair glycaemic control. Beta blockers, especially non-selective beta blockers, may increase the risk of hyperglycaemia in diabetic patients secondary to a deterioration in carbohydrate metabolism and peripheral insulin resistance. Beta-adrenergic blocking medicines, such as TRANDATE INJECTION, may impair the body's response to hypoglycaemia and may mask the manifestation of signs of hypoglycaemia, such as tachycardia, blood pressure and tremor, and delay the normalisation of blood sugar after insulin-induced hypoglycaemia, especially non-selective beta blockers (see section 4.4). Dose adjustments of oral antidiabetic medicines and insulin may be necessary.

Interference with drug assay

TRANDATE INJECTION 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 TRANDATE INJECTION metabolites in the urine may result in falsely elevated levels or 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 TRANDATE INJECTION hydrochloride, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction should be employed in determining levels of catecholamines.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Based on experience during human pregnancy TRANDATE INJECTION is not expected to increase the risk of congenital malformations.

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 TRANDATE INJECTION crosses the placental barrier (see section 5).

Beta-blockers such as TRANDATE INJECTION may reduce uterine blood flow.

Breastfeeding

Safety in breastfeeding has not been established.

TRANDATE INJECTION is excreted in breast milk in small amounts (approximately 0,004 to 0,07 % of the maternal dose). Adverse events such as sudden death syndrome, diarrhoea and hypoglycaemia have been reported in breastfed neonates. Nipple pain and Raynaud's phenomenon of the nipple have been reported (see section 4.8).

Mothers breastfeeding their infants should not be treated with TRANDATE INJECTION (see section 4.3).

Fertility

There are no data on the effects of TRANDATE INJECTION on fertility.

4.7 Effects on ability to drive and use machines

TRANDATE INJECTION has no or negligible influence on ability to drive and use machines. Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that TRANDATE INJECTION does not adversely affect their ability to do so safely (see section 4.4 and/or 4.8).

4.8 Undesirable effects

a) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Immune system disorders	Hypersensitivity including rash; pruritus; dyspnoea	Drug fever; angioedema	
Cardiac disorders	Congestive heart failure	Bradycardia; heart block	
Vascular disorders	#Postural hypotension; confusion; disorientation if patients are allowed to assume the upright position within three hours of receiving TRANDATE INJECTION	Exacerbation of the symptoms of Raynaud's syndrome	
Respiratory, thoracic and mediastinal disorders	#Nasal congestion	Bronchospasm	
Hepato-biliary disorders	Raised liver function tests	Hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis	
Reproductive system and breast disorders	Erectile dysfunction		* Nipple pain, Raynaud's phenomenon of the nipple

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

**Post marketing surveillance report*

b) Description of selected adverse reactions

Immune system disorders

Hypersensitivity reactions reported include rash (including reversible lichenoid rash), pruritus, dyspnoea and very rarely drug fever or angioedema.

Vascular disorders

Postural hypotension is more common at very high doses or if the initial dose is too high or doses are increased too rapidly.

Hepatobiliary disorders

The signs and symptoms of hepatobiliary disorders are usually reversible on withdrawal of TRANDATE INJECTION.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting From”. Found online under SAHPRA’s publications:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ +27 (0)11 239-6200

4.9 Overdose

Symptoms

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. Overdosage with TRANDATE INJECTION causes excessive hypotension, which is posture dependent, and excessive bradycardia.

Treatment

Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain.

The use of dopamine to increase the blood pressure may aggravate renal failure.

Haemodialysis removes less than 1 % TRANDATE INJECTION hydrochloride from the circulation.

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

Atropine 1 to 2 mg should be given intravenously to relieve bradycardia. Massive overdosage with TRANDATE INJECTION in man has not been reported, but profound cardiovascular effects are to be expected.

If further measures are required to obtain adequate circulatory pressure, vasopressors may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Vascular medicines, vasodilators, other hypotensives.

Pharmacotherapeutic group : Alpha and beta blocking agents

ATC code: C07AG01

Mechanism of action

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. All these effects would be expected to benefit hypertensive patients.

5.2 Pharmacokinetic properties

Intravenous labetalol hydrochloride reduces blood pressure without producing tachycardia or increasing plasma renin levels.

Distribution

About 50 % of labetalol in the blood is protein bound.

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.

Special populations

Hepatic impairment

Labetalol undergoes significant but variable first-pass metabolism when given by the oral route.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dilute hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection.

6.2 Incompatibilities

TRANDATE INJECTION has been shown to be incompatible with sodium bicarbonate injection BP.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C and protect from light.

Keep in original packaging until required for use.

6.5 Nature and contents of container

1 x 20 ml clear Type 1 glass ampoule. 5 ampoules are packed in an outer cardboard carton together with a leaflet.

Not all packs or pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

J/7.1.3/54

9. DATE OF FIRST AUTHORISATION

19 October 1976

10. DATE OF REVISION OF TEXT

25 April 2024

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