Final Approved Professional Information (PI)

for Medicines for Human Use

Prodorol 10/40 mg (Tablets)

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PRODOROL 10 mg tablets

PRODOROL 40 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PRODOROL 10 mg tablet contains 10 mg of propranolol hydrochloride.

Contains tartrazine.

Each PRODOROL 40 mg tablet contains 40 mg of propranolol hydrochloride.

Contains tartrazine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

PRODOROL 10 mg tablets: Round, biconvex pink scored tablets, 6,4 mm in diameter

PRODOROL 40 mg tablets: Round, biconvex pink scored tablets, 8,7 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Cardiac arrhythmias, especially supraventricular arrhythmias
- Treatment of hypertension

- Thyrotoxicosis
- Phaeochromocytoma
- Treatment of angina pectoris
- Control of anxiety-induced tachycardia and tremor.

4.2 Posology and method of administration

Posology

PRODOROL tablets should preferably be taken before meals. Dosage is largely determined by the response of the patient. In most conditions, treatment should begin with a small dose which should be gradually increased. The most usual doses are 20 mg to 40 mg three or four times a day. The dose may be increased up to 320 mg daily in the treatment of hypertension.

In phaeochromocytoma, 60 mg daily should be given for 3 days pre-operatively.

The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction, as adverse effects are more common in these patients.

If symptoms of weakness or faintness occur, treatment should be withdrawn temporarily and started again at a lower dose which may be increased very slowly.

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.

4.3 Contraindications

PRODOROL is contraindicated in patients with any of the following:

- Hypersensitivity to propranolol or to any of the excipients listed in section 6.1
- Bronchial asthma or bronchospasm
- Metabolic acidosis (e.g. in diabetes)
- Atrioventricular block

- Marked bradycardia (less than 50 beats per minute)
- Heart failure refractory to digitalis
- Uraemia
- Pregnancy and lactation
- Hypoglycaemia
- Raynaud's phenomenon
- Patients suffering from peripheral vascular disease
- Untreated phaeochromocytoma.

Particular caution should be exercised with patients suffering from the following: bronchitis, chronic respiratory diseases and second and third degree heart block.

In the pre-operative period it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or of hypertension.

A patient's normal tachycardic response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.

4.4 Special warnings and precautions for use

Bronchospasm may occur, particular in susceptible individuals.

PRODOROL contains tartrazine which may cause allergic type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of tartrazine sensitivity in the general population is currently thought to be low it is frequently seen in patients who also have aspirin sensitivity.

Digitilisation of patients receiving long-term beta-blocker therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in the situation.

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.

Special care should be taken with patients whose cardiac reserve is poor. PRODOROL should be avoided in overt heart failure; however, it may be used in patients whose signs of failure have been controlled.

PRODOROL should not be used in combination with calcium channel blockers with negative inotropic effects (e.g. verapamil, diltiazem), as it can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure (see section 4.5).

Concomitant therapy with dihydropyridine calcium channel blockers, e.g., nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Although contraindicated in severe peripheral circulatory disturbances, PRODOROL may also aggravate less severe forms. Therefore, PRODOROL should be used with great caution in conditions such as

Raynaud's disease/syndrome or intermittent claudication (see section 4.3).

Caution must be exercised if PRODOROL is given to patients with first degree heart block.

PRODOROL may block/modify the signs and symptoms of the hypoglycaemia (especially tachycardia). PRODOROL

occasionally causes hypoglycaemia, even in non-diabetic patients, e.g. neonates, infants, children, elderly patients, patients on haemodialysis or patients suffering from chronic liver disease and patients suffering from overdose.

Caution must be exercised in the concurrent use of PRODOROL and hypoglycaemic therapy in diabetic patients. PRODOROL may prolong the hypoglycaemic response to insulin (see section 4.3).

Heart failure due to thyrotoxicosis often responds to PRODOROL alone, but if other adverse factors co-exist myocardial contractility must be maintained and signs of failure controlled with digitalis and

diuretics. PRODOROL may mask the important signs of thyrotoxicosis and hyperthyroidism.

PRODOROL may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens.

Particular caution is necessary, when PRODOROL tablets

are used in patients with a history of anaphylaxis.

In patients with ischaemic heart disease, treatment should not be

discontinued abruptly.

Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported in patients given PRODOROL

Psoriasis may be aggravated with the use of PRODOROL.

Abrupt withdrawal of PRODOROL is to be avoided. The dosage should be withdrawn gradually over a period of 7 to 14 days. Patients should be followed during withdrawal especially those with ischaemic heart disease.

4.5 Interaction with other medicines and other forms of interaction

It can be dangerous to administer PRODOROL concomitantly with phenothiazines, hypoglycaemic agents, and the following medicines. Such interactions can have life-threatening consequences.

Adrenaline and noradrenaline:

The effects of PRODOROL are diminished by beta-adrenergic stimulating agents; the hypotensive effects of PRODOROL may be dangerously reversed and the peripheral vasoconstrictor effects enhanced by alpha-adrenergic stimulating agents such as noradrenaline or those mixed with alpha- and beta-adrenergic stimulating properties such as adrenaline.

Care should be taken in the parenteral administration of preparations containing adrenaline (epinephrine) to patients taking beta-adrenoceptor blocking drugs such as PRODOROL, in rare cases, vasoconstriction, hypertension and bradycardia may result.

Anaesthetics:

The effects of lignocaine may be enhanced by PRODOROL.

Care should be taken when using anaesthetic medicines with PRODOROL. The anaesthetist should be informed and the choice of anaesthetic should be the medicine with as little negative inotropic activity as possible.

Use of betablockers, such as PRODOROL, with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of

hypotension. Anaesthetic medicines causing myocardial depression are best avoided.

Anti-arrhythmics:

Caution must be exercised in co-prescribing PRODOROL with Class I anti-arrhythmic agents such as disopyramide, quinidine, procainamide, flecainide and amiodarone may have potentiating effects on arterial conduction time and induce negative inotropic effect. The effects of quinidine and procainamide may be enhanced by PRODOROL.

Combined use of PRODOROL and calcium channel blockers with negative inotropic effects *e.g.* verapamil, diltiazem can lead to prolongation of SA and AV conduction particularly in patients with impaired ventricular function or conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. PRODOROL should not be used with verapamil and neither medicine should be administered within several days of discontinuing the other.

Adrenergic neurone blocking medicines:

Digitalis glycosides used in association with PRODOROL may increase AV conduction time.

The effects of PRODOROL may be enhanced by adrenergic neurone blocking medicines such as guanethidine, bethanidine or reserpine and the hypotensive effects by diuretics.

PRODOROL may enhance some of the cardiac effects of digitalis and diminish others.

Anticoagulants:

PRODOROL may cause a reduction in clearance and an increase in plasma concentrations of warfarin.

Antidiabetic medicines:

PRODOROL modifies the tachycardia of hypoglycaemia; caution should therefore be exercised in the concomitant use of PRODOROL and hypoglycaemic therapy in diabetic patients. PRODOROL may prolong the hypoglycaemic response to insulin.

Antihypertensives:

Caution should be used when transferring a patient from clonidine onto PRODOROL, as this may result in a hypertensive crisis.

If PRODOROL and clonidine are given concurrently, then clonidine should not be discontinued until several days after the withdrawal of PRODOROL as severe rebound hypertension may occur.

Concomitant use of moxonidine and PRODOROL may result in an enhanced hypotensive effect. The steps for moxonidine withdrawal/introduction should be the same as for clonidine. Hypotensive effect may be enhanced when PRODOROL is taken with diuretics, methyldopa or levodopa.

Prazosin or other alpha-adrenoreceptor blockers may potentiate postural hypotension, tachycardia and palpitations.

Antimigraine medicines:

Caution is necessary if ergotamine, dihydroergotamine or related medicines are given in combination with PRODOROL since vasospastic reactions have been reported in a few patients. Simultaneous administration of rizatriptan and PRODOROL can cause an increased rizatriptan AUC and Cmax by approximately 70-80%. Administration should be separated by 2 hours.

Barbiturates:

The metabolism of PRODOROL may be increased by potent liver enzyme inducer barbiturates.

Chlorpromazine:

Concomitant administration of PRODOROL and chlorpromazine may result in an increase in plasma levels of both medicines. This may lead to an enhanced antipsychotic effect for chlorpromazine and an increased antihypertensive effect for PRODOROL.

Cimetidine:

Concomitant use of cimetidine will increase, whereas alcohol will decrease the plasma levels of PRODOROL.

Hydralazine:

Concomitant use of hydralazine will increase, whereas alcohol will decrease the plasma levels of PRODOROL.

Imipramine:

PRODOROL may cause plasma concentrations of imipramine to increase.

Monamine-oxidase Inhibitors:

The hypotensive effects of beta-blockers, such as PRODOROL may be enhanced by MAOIs.

Non-steroidal anti-inflammatory drugs (NSAIDs):

Concomitant use of prostaglandin synthetase inhibiting drugs e.g., ibuprofen and indomethacin, may decrease the hypotensive effects of PRODOROL. This may be particularly significant in patients with poorly controlled hypertension.

Rifampicin:

The metabolism of PRODOROL may be increased by potent liver enzyme inducer rifampicin.

Selective Serotonin Re-uptake Inhibitors (SSRIs):

Fluvoxamine inhibits oxidative metabolism and increases plasma concentrations of PRODOROL. This may result in severe bradycardia.

Theophylline:

PRODOROL reduces the clearance and consequentially increases the plasma concentration of theophylline.

Tobacco:

Smoking tobacco may oppose the effects of beta blockers, such as PRODOROL in the treatment of angina or hypotension. Patients should be encouraged to stop smoking, however if the patient continues to smoke, the dosage of PRODOROL may need to be increased.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. PRODOROL is contraindicated for use during pregnancy (see section 4.3).

Administration of PRODOROL to pregnant mothers shortly before giving birth or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic.

Breastfeeding

Breastfeeding is not recommended following administration of PRODOROL.

4.7 Effects on ability to drive and use machines

The use of PRODOROL is unlikely to result in any significant impairment of the ability of patients to drive or operate machinery. However, patients should be warned that visual disturbances, hallucinations, mental confusion, dizziness, drowsiness or fatigue may occur and they should not drive or operate machinery if they feel affected.

4.8 Undesirable effects

The frequency of adverse reactions reported with PRODOROL are summarised in Table 1 as per the MedDRA system organ classification (SOC).

Table 1: Tabulated list of adverse reactions		
System Organ Class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	Thrombocytopenia	Less frequent
	Agranulocytosis	Unknown
Endocrine disorders	Masking signs of thyrotoxicosis	Unknown
Metabolic and nutritional disorders	Hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported. Changes in lipid metabolism (changes in blood concentrations of triglycerides and cholesterol)	Unknown
Psychiatric disorders	Sleep disturbances, nightmares	Frequent
	Depression, confusion	Unknown
Nervous system disorders	Hallucinations, psychoses, mood changes, confusion, memory loss, dizziness, paraesthesia, isolated reports of myasthenia gravis like syndrome or exacerbation of	Less frequent

	myasthenia gravis have been reported.	
	Headache, seizure linked to hypoglycaemia	Unknown
Eye disorders	Visual disturbances, dry eyes	Less frequent
	Conjunctivitis	Unknown
Cardiac disorders	Bradycardia	Frequent
	Heart failure deterioration, precipitation of heart block, postural hypotension which may be associated with syncope	Less frequent
	Worsening of attacks of angina pectoris Congestive cardiac failure	Unknown
Vascular disorders	Cold extremities, Raynaud's syndrome	Frequent
	Exacerbation of intermittent claudication	Less frequent
	Peripheral vascular disease, peripheral gangrene. This is more common in patients with renal decompensation	Unknown
Respiratory, thoracic and mediastinal disorders	Bronchospasm may occur in patients with asthma, bronchitis and other chronic pulmonary diseases.	Less frequent

	Dyspnoea	Unknown
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Less frequent
	Constipation, dry mouth	Unknown
Skin and subcutaneous tissues disorders	Alopecia, purpura, psoriasiform skin reactions, exacerbation of psoriasis, rash	Less frequent
Musculoskeletal and connective tissue disorders	Arthralgia Muscle weakness	Unknown
Renal and urinary disorders	Reduced renal blood flow and GFR (glomerular filtration rate)	Unknown
Reproductive system and breast disorders	Sexual dysfunction	Unknown
General disorders and administration site conditions	Fatigue and/or lassitude (often transient)	Frequent
Investigations	An increase in ANA (antinuclear antibodies) has been observed with many beta blockers, however the clinical relevance of this is not clear.	Less frequent

4.9 Overdose

Excessive bradycardia, severe hypotension, bronchospasm and heart failure may be produced in certain individuals.

Patients with mild overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly. Gastric lavage should be performed within 4 hours of suspected overdose. Activated charcoal is necessary in severe overdose.

Atropine may be used to treat bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine or isoprenaline may be used for the management of hypotension. Large doses of isoprenaline may be required to counteract the beta-blockade.

Transvenous cardiac pacing may be required for severe bradycardia.

Bronchospasm should be treated by the intravenous injection of aminophylline or by the inhalation or intravenous injection of a selective beta-2-stimulant.

Further treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 5.2 Adrenolytics (sympatholytics).

Pharmacotherapeutic group: beta blocking agents, non-selective.

ATC code: C07A A05

Mechanism of action

PRODOROL is a non-selective beta-adrenergic blocking agent and reduces cardiac activity by diminishing or preventing beta-adrenergic stimulation. It reduces the rate of contraction and the cardiac output and prolongs A-V conduction time. In response to the inhibition of the beta-adrenergic-receptors, the cardiac oxygen requirement diminishes.

The blood pressure in hypertensive patients is also reduced.

5.2 Pharmacokinetic properties

Absorption

Propranolol is almost completely absorbed from the gastrointestinal tract, but it is subject to considerable first-pass metabolism.

Distribution

Peak plasma concentrations occur about 1 to 2 hours after dosing in fasting patients. Propranolol is widely and rapidly distributed throughout the body with highest levels occurring in the lungs, liver, kidney, brain and heart. Propranolol is highly protein bound (80 to 95 %).

Biotransformation and Elimination

Propranolol is metabolised in the liver, the metabolites being excreted in the urine together with only small amounts of unchanged Propranolol; at least one of its metabolites is considered to be biologically active.

The biological half-life of propranolol is longer than would be anticipated from its plasma half-life of about 3-6 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets contain: guava deep, ludipress, magnesium stearate and purified water.

6.2 Incompatibilities

None known.

6.3 Shelf life

Securitainer: 36 months from the date of manufacture.

Patient ready packs: 15 months from the date of manufacture.

6.4 Special precautions for storage

Store in a well closed container at or below 25°C.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

White, round, polypropylene securitainers with white LDPE caps containing 50, 250, 500 and 1000 tablets.

White LDPE patient ready packs of different pack sizes.

Not all pack sizes and types may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) ltd

Cnr Birch Road & Bluegum Avenue

Anchorville

Lenasia, 1827

South Africa

8. REGISTRATION NUMBER(S)

PRODOROL 10 mg: X/5.2/315

PRODOROL 40 mg: X/5.2/316

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

28 January 1991

10. DATE OF REVISION OF THE TEXT

29 March 2021