PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1 NAME OF THE MEDICINE

INDERAL® 10, INDERAL® 40, Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

INDERAL 10: Each tablet contains 10 mg propranolol hydrochloride

INDERAL 40: Each tablet contains 40 mg propranolol hydrochloride

Contains sugar: lactose monohydrate

INDERAL 10: each tablet contains 79 mg lactose monohydrate.

INDERAL 40: each tablet contains 147,4 mg lactose monohydrate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

INDERAL 10:

Pink, round, biconvex, film-coated tablets, intagliated on one face with 10 and scored on the reverse face.

INDERAL 40:

Pink, round, biconvex, film-coated tablets, intagliated on one face with 40 and scored on the reverse face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- INDERAL is indicated to reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable.
- Treatment of angina pectoris.
- Control of essential and renal hypertension.
- Control of essential and senile tremor and the management of Parkinsonian tremor.
- Control of anxiety related autonomic symptoms and anxiety tachycardia.

- Cardiac dysrhythmias, especially supra-ventricular tachydysrhythmias; dysrhythmias triggered by sympathetic overstimulation.
- An adjunct in the management of hyperthyroidism and thyrotoxic crisis.
- Management of hypertrophic obstructive cardiomyopathy.
- Management of phaeochromocytoma (INDERAL should only be started in the presence of effective alpha blockade).
- Prophylaxis of migraine.

4.2 Posology and method of administration

Since the half-life of INDERAL may be increased in patients with significant hepatic or renal impairment, care should be taken when starting treatment and selecting the initial dose.

Adults:

Oral dosage:

INDERAL tablets should preferably be taken before food.

In angina, hypertension, anxiety and essential tremor, the standard starting dose is 40 mg 2 or 3 times daily increasing by the same amount at weekly intervals according to patient response. An adequate response in anxiety and essential tremor is usually seen in the range 80-160 mg/day and in angina and hypertension 120-320 mg/day.

In hypertension, further reduction of blood pressure is obtained when diuretic and/or other anti- hypertensive therapy is given in addition to INDERAL.

In cardiac dysrhythmias (especially supra-ventricular tachydysrhythmias; dysrhythmias triggered by sympathetic overstimulation), anxiety tachycardia, hypertrophic obstructive cardiomyopathy and hyperthyroidism and for the prophylaxis of migraine, most patients respond within the dosage range of 10-40 mg 3 or 4 times a day.

Myocardial infarction:

The recommended daily dosage is 180-240 mg per day in 3 divided doses. Therapy should begin between days 5 and 21 after myocardial infarction. The effectiveness and safety of daily dosages greater than 240 mg

for prevention of cardiac mortality have not been established. However, higher dosages may be needed to effectively treat co-existing diseases such as angina or hypertension.

In a phaechromocytoma (used only in conjunction with an alpha-receptor blocking medicine) pre-operatively: 60 mg daily for 3 days is recommended-malignant cases (non-operable): 30 mg daily.

Elderly:

Evidence concerning the relation between blood levels and age is conflicting. With regard to the elderly, the optimum dose should be individually determined according to clinical response.

4.3 Contraindications

INDERAL must not be given to patients with bronchospasm or asthma or to those with a history of obstructive airways disease. (For information on the treatment of bronchospasm, see section 4.9).

INDERAL should not be used:

- In patients with a known hypersensitivity to propranolol or to any of the ingredients.
- In patients with bradycardia.
- In patients with cardiogenic shock.
- In the presence of hypotension.
- In patients with metabolic acidosis (e.g. in diabetes).
- After prolonged fasting.
- In patients with severe peripheral arterial circulatory disturbances.
- In the presence of second or third degree heart block.
- In patients with Sick Sinus Syndrome.
- In patients with phaeochromocytoma uncontrolled by α-blockade.
- In patients with uncontrolled heart failure, because of its negative inotropic effect.
- In patients with Prinzmetal's angina.

INDERAL must not be used in patients prone to hypoglycaemia, i.e. patients after prolonged fasting or patients with restricted counter- regulatory reserves.

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

period. A patient's normal tachycardiac response to hypovolaemia or blood loss may be obscured during or after surgery by beta-blocker therapy such as INDERAL. Particular caution should be taken in this regard.

INDERAL is contraindicated during pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Special care should be taken with patients whose cardiac reserve is poor. INDERAL should be avoided in cardiac failure, unless or until signs of failure are controlled with digoxin or diuretics.

Although contraindicated in severe peripheral arterial circulatory disturbances, INDERAL may also aggravate less severe peripheral arterial circulatory disturbances and severe peripheral vascular disease and even peripheral gangrene may be precipitated.

Due to its negative effect on conduction, INDERAL should only be given with caution to patients with first degree heart block.

INDERAL may block/modify the signs and symptoms of hypoglycaemia (especially tachycardia). INDERAL 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. Severe hypoglycaemia associated with INDERAL has occurred, presenting with seizures and/or coma. Caution must be exercised in the concurrent use of INDERAL and hypoglycaemic therapy in diabetic patients. INDERAL may prolong the hypoglycaemic response to insulin. INDERAL may mask the signs of hyperthyroidism.

One of the pharmacological actions of INDERAL is to reduce the heart rate. Bradycardia (usually less than 50-55 beats/minute) indicates that dosage should not be further increased.

While taking INDERAL, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge. Such patients may be unresponsive to the usual dose of adrenaline (epinephrine) used to treat the allergic reactions.

In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop. There have been reports suggesting that treatment with propranolol may increase the risk of developing hepatic encephalopathy.

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

INDERAL should be used with caution in patients with decompensated cirrhosis.

Impotence has been reported following INDERAL administration.

Heart failure following myocardial infarction must have been controlled before treatment with INDERAL is started.

Simultaneous administration of INDERAL and rizatriptan can cause an increased exposure to rizatriptan (see section 4.3).

Administration of INDERAL during infusion of lidocaine (lignocaine) may increase the plasma concentration of lidocaine (lignocaine) by approximately 30 %. Patients already receiving INDERAL tend to have higher lidocaine (lignocaine) levels than controls. The combination of INDERAL and lidocaine (lignocaine) (given intravenously) should be avoided.

Lactose:
Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose-malabsorption or fructose intolerance should not take INDERAL.

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

INDERAL masks the symptoms of hypoglycaemia. Caution should be exercised in the concurrent use of INDERAL and hypoglycaemic therapy in diabetic patients. INDERAL may prolong the hypoglycaemic response to insulin.

Simultaneous administration of rizatriptan and INDERAL can cause an increased rizatriptan AUC and C_{max} by approximately 70-80 %. The increased rizatriptan exposure is presumed to be caused by the inhibition of first-passage metabolism of rizatriptan through inhibition of monoamine oxidase-A. If both medicines are to be used, a rizatriptan dose of 5 mg has been recommended.

It can be dangerous to administer INDERAL concomitantly with the following medicines: hypoglycaemic medicines, phenothiazines, Class I antidysrhythmic medicines such as disopyramide and amiodarone. Class I antidysrhythmic medicines may have a potentiating effect on atrial conduction time and induce negative inotropic effect.

N.B. Such medicine interactions can have life-threatening consequences.

Digitalis glycosides in association with INDERAL may increase atrioventricular conduction time leading to heart block.

Combined use of INDERAL and calcium channel blockers with negative inotropic effects e.g. verapamil and diltiazem, 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.

Concomitant therapy with dihydropyridine calcium channel blockers e.g. nifedipine, may increase the risk of hypotension. In patients with latent cardiac insufficiency, treatment with INDERAL may lead to cardiac failure.

Concomitant use of sympathomimetic medicines e.g. adrenalin (epinephrine), may counteract the effect of INDERAL. Care should be taken in the parenteral administration of preparations containing epinephrine (adrenaline) to patients taking INDERAL as vasoconstriction, hypertension and bradycardia may result. Administration of INDERAL during infusion of lidocaine (lignocaine) may increase the plasma concentration of lidocaine (lignocaine) by approximately 30 %. Patients already receiving INDERAL tend to have higher

lidocaine (lignocaine) levels than controls. The combination of INDERAL and lidocaine (lignocaine) (given intravenously) should be avoided.

Concomitant use of cimetidine or hydralazine will increase plasma levels of propranolol, and concomitant use of alcohol may increase the plasma levels of propranolol.

INDERAL may exacerbate the rebound hypertension which may follow the withdrawal of clonidine. If the 2 medicines are co-administered, INDERAL should be withdrawn several days before discontinuing clonidine. If replacing clonidine by INDERAL therapy, the introduction of INDERAL should be delayed for several days after clonidine administration has stopped.

Care should be taken when using INDERAL with ergotamine, dihydroergotamine or related compounds, since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting medicines e.g. ibuprofen and indomethacin or other NSAIDs may reduce the antihypertensive effect of INDERAL.

The concomitant administration of INDERAL 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 INDERAL.

Care should be taken when using anaesthetic medicines in patients taking INDERAL. The anaesthetist should be informed and the choice of the anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers including INDERAL with anaesthetic medicines may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic medicines causing myocardial depression are best avoided.

Pharmacokinetic studies have shown that the following medicines may interact with INDERAL due to effects on enzyme systems in the liver which metabolise propranolol and these medicines: quinidine, propafenone, rifampicin, theophylline, warfarin and dihydropyridine calcium channel blockers such as nifedipine, nisoldipine, nicardipine, isradipine and lacidipine. Owing to the fact that blood concentrations of either medicine may be affected, dosage adjustments may be needed according to clinical judgement (see also the interaction above concerning the concomitant therapy with dihydropyridine calcium channel blockers).

4.6 Fertility, pregnancy and lactation

INDERAL should not be given during pregnancy. Beta-blockers reduce placental perfusion, which may result in intra-uterine foetal death, immature or premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia in the neonate and bradycardia in the foetus) may occur. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period.

Propranolol is highly lipophilic and passes into breast milk. Therefore, breastfeeding is a contraindication for the use of INDERAL (see section 4.3)

4.7 Effects on ability to drive and use machines

INDERAL may have an effect on the ability to drive or operate machinery and caution must therefore be taken.

4.8 Undesirable effects

The following adverse reactions have been identified. Their frequency is presented in Table 1 Frequency of Adverse Reactions using CIOMS III frequency classification and then listed by MedDRA SOC and at the preferred level or lower level term. Frequencies of occurrence of undesirable effects are defined as: common (≥ 1% to < 10 %); uncommon (≥ 0,1 % to < 1 %); rare (≥ 0,01 % to < 0,1 %); very rare (<0,01 %); not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Reaction**
Blood and lymphatic system disorders	Rare	Thrombocytopenia
Metabolism and nutrition disorders	Very rare	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.
Psychiatric disorders	Common	Nightmares
	Rare	Hallucinations, psychosis, mood changes, depression, confusion

Nervous system disorders	Common	Sleep disturbance
	Rare	Paraesthesia, dizziness
	Very rare	Myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.
Eye disorders	Rare	Dry eyes, visual disturbances
Cardiac disorders	Common	Bradycardia
	Rare	Cardiac failure aggravated, heart block, congestive cardiac failure
Vascular disorders	Common	Cold extremities, Raynaud's phenomenon
	Rare	Postural hypotension which may be associated with syncope, intermittent claudication
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome.
Gastrointestinal disorders	Uncommon	Nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Rare	Purpura, alopecia, rash, psoriasiform skin reactions, exacerbation of psoriasis
Reproductive system and breast disorders	Not known	Impotence
General disorders and administration site conditions	Common	Fatigue and/or lassitude (often transient)
Investigations	Very rare	Antinuclear antibody increased

In the event of intolerance to INDERAL manifested as bradycardia and hypotension, the medicine should be withdrawn and if necessary, treatment instituted as stated below (see section 4.9).

Note: Adverse reactions are more common in elderly patients and in patients with renal impairment.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Propranolol is known to cause severe toxicity when used in overdose. Patients should be informed of the signs of overdose and advised to seek urgent medical assistance if an overdose of propranolol has been taken.

Clinical features:

Cardiac:

Bradycardia, hypotension, and cardiogenic shock may develop. QRS complex prolongation, ventricular tachycardia, first to third degree AV block, ventricular fibrillation or asystole may also occur. Development of cardiovascular complications is more likely if other cardioactive drugs, especially calcium channel blockers, digoxin, cyclic antidepressants or neuroleptics have also been ingested.

CNS:

Drowsiness, seizures, and in severe cases coma may occur.

Other features:

Bronchospasm, hyperkalaemia and occasionally CNS-mediated respiratory depression may occur.

Management:

General treatment should include close supervision, treatment in an intensive care ward, activated charcoal if within one hour of overdose and a laxative to prevent absorption of any medicine still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1-2 mg intravenously and/ or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2,5-10 micrograms/kg/minute by intravenous infusion may be given, although larger doses may be required.

Bronchospasm can usually be reversed by beta-2-agonist bronchodilators such as salbutamol.

Large doses of the beta-2-agonist bronchodilator may be required to overcome the beta-blockade produced by propranolol and the dose should be titrated according to the clinical response; both intravenous and inhalational administration should be considered. The use of intravenous aminophylline and/or the use of ipratropium (given by nebuliser), may also be considered.

Glucagon (1-2 mg given intravenously) has also been reported to produce a bronchodilator effect in asthmatic patients. Oxygen or artificial ventilation may be required in severe cases.

Heart failure must be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 5.2 Adrenolytics (Sympatholytics)

Pharmacotherapeutic group: Beta blocking agents, non-selective, ATC code: C07AA05.

Propranolol is a competitive antagonist at both the beta-1- and beta-2- adrenoceptors. It has no agonist activity at the beta-adrenoceptor.

5.2 Pharmacokinetic properties

Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1-2 hours after dosing in fasting patients.

The liver removes up to 90 % of an oral dose with an elimination half- life of 3-6 hours. 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 (80-95 %).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carboxymethylcellulose

Carmine (E120)

Gelatin (E441)

Glycerol (E422)

Lactose

Light magnesium carbonate (E504)

Magnesium stearate

Methylhydroxypropylcellulose (E464)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

INDERAL 10:

Store at or below 25 °C. Protect from light and moisture.

INDERAL 40:

Store at or below 30 °C. Protect from light and moisture.

Keep out of reach of children.

6.5 Nature and contents of container

INDERAL 10 is presented in PVC-PVDC/Aluminium blister of 50 tablets in a pack.

INDERAL 40 is presented in HDPE containers of 50 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

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South Africa

8 REGISTRATION NUMBERS

INDERAL 10: G/5.2/2863

INDERAL 40: G2864 (Act 101/1965)

9 DATE OF FIRST AUTHORISATION

INDERAL 10: 16 January 1989

10 DATE OF REVISION OF THE TEXT

01 March 2022