Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Inderal 10mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains propranolol hydrochloride 10mg.

Excipient(s) with known effect:
Each tablet also contains lactose monohydrate 79mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet (Tablet)

Pink round bi-convex film coated tablets impressed with the legend 'Inderal 10' on one face. The impressions are highlighted in white.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

i. Control of essential and renal hypertension.
ii. Management of angina pectoris.
iii. Long term prophylaxis after recovery from acute myocardial infarction.
iv. Control of most forms of cardiac arrhythmia.
v. Prophylaxis of migraine
vi. Management of essential tremor
vii. Control of anxiety and anxiety tachycardia
viii. Prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices
ix. Adjunctive management of thyrotoxicosis.
x. Management of phaeochromocytoma ('Inderal' should only be started in the presence of effective alpha blockade).

4.2 Posology and method of administration

Since the half-life may be increased in patients with significant hepatic or renal impairment, caution must be exercised when starting treatment and selecting the initial dose.

Posology

Adults:

Hypertension:

A starting dose of 80mg twice a day may be increased at weekly intervals according to response. The usual dosage range is 160-320mg per day. With concurrent diuretic or other antihypertensive drugs a further reduction of blood pressure is obtained.

Angina, anxiety, migraine and essential tremor:

A starting dose of 40mg two or three times daily may be increased by the same amount at weekly intervals according to patient response. The usual dose range in angina is 80-320mg/day.

An adequate response in anxiety, migraine and essential tremor is usually seen in the range 80-160 mg/day and in angina in the range 120-240 mg/day.

Arrhythmias, anxiety tachycardia and thyrotoxicosis:

A dosage range of 10-40 mg three or four times a day usually achieves the required response.

Post-myocardial infarction:

Treatment should start between days 5 and 21 after myocardial infarction, with an initial dose of 40mg four times a day for 2 or 3 days. In order to improve compliance the total daily dosage may thereafter be given as 80mg twice a day with later transfer if desired to the 160mg long-acting dose form.

Portal hypertension/oesophageal varices:

Dosage should be titrated to achieve approximately a 25% reduction in resting heart rate. Dosing should begin with 40mg twice daily increasing to 80mg twice daily depending on heart rate response. If necessary the dose may be increased incrementally to a maximum of 160mg twice daily.

Phaeochromocytoma:

(Inderal is to be used only in the presence of effective alpha-blockade).

Pre-operative:

60mg daily for three days is recommended.

Non-operable malignant cases:
30 mg daily.

Summary Table of Inderal Dosage - Adults (in divided daily doses)

	Min./Day	Max/Day
Hypertension	160mg	320mg
Angina pectoris	80mg	320mg
Arrhythmias	30mg	160mg
Migraine	80mg	160mg
Tremor	40mg	160mg
Anxiety	80mg	160mg
Anxiety Tachycardia	30mg	160mg
Portal hypertension/Oesophageal varices	80mg	320mg
Thyrotoxicosis	30mg	160mg
Phaeochromocytoma	60mg (pre op)	60mg
	30mg (maintenance)	30mg
Post-infarction	160mg	160mg

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

Paediatric population
Arrhythmias
Dosage should be individually determined and the following is only a guide.
0.25–0.5 mg/kg three to four times daily, adjusted according to response. Maximum 1 mg/kg four times daily, total daily dose not to exceed 160 mg daily.

Method of administration
For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Inderal must not be used if there is a history of bronchial asthma or bronchospasm.

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

Inderal as with other beta-blockers must not be used in patients with any of the following: known hypersensitivity to the substance; bradycardia, cardiogenic shock; hypotension; metabolic acidosis; after prolonged fasting; severe peripheral arterial circulatory disturbances; second or third degree heart block; sick sinus syndrome; untreated phaeochromocytoma; uncontrolled heart failure or digitalis/diuretic refractory; 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. Patients with restricted counter-regulatory reserves may have reduced autonomic and hormonal responses to hypoglycaemia which includes glycogenolysis, gluconeogenesis and /or impaired modulation of insulin secretion. Patients at risk for an inadequate response to hypoglycaemia includes individuals with malnutrition, prolonged fasting, starvation, chronic liver disease, diabetes and concomitant use of drugs which block the full response to catecholamines.

4.4 Special warnings and precautions for use

Inderal as with other beta blockers:
–although contra-indicated in uncontrolled heart failure, may be used in patients whose signs of heart failure have been controlled. Caution must be exercised inpatients whose cardiac reserve is poor. Beta-adrenoreceptor blocking drugs should be avoided in overt heart failure.

–Inderal should only be used with caution in patients with controlled congestive cardiac failure or with a family history of asthma. Evidence of development of either condition should be regarded as a signal to discontinue therapy.

–although contra-indicated in severe peripheral arterial circulatory disturbances (see Section 4.3), may also aggravate less severe peripheral arterial circulatory disturbances.

–due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.

–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 rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of Inderal and hypoglycaemic therapy in diabetic patients. Inderal may prolong the hypoglycaemic response to insulin.

–may mask the signs of thyrotoxicosis.

–will reduce heart rate, as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate, the dose may be reduced.

– should not be discontinued abruptly in patients suffering from ischaemic heart disease. Either the equivalent dosage of another beta-blocker may be substituted or the withdrawal of Inderal should be gradual.

–Sudden withdrawal of beta-adrenoceptor blocking agents in patients with ischaemic heart disease may result in the appearance of anginal attacks of increased frequency or severity of deterioration in cardiac state.

–May cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

Hypertension
The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic pressure with impairment of autoregulatory mechanisms.

Hepatic and Renal Impairment
Inderal must be used with caution in patients with decompensated cirrhosis.

In patients with significant hepatic or renal impairment care should be taken when starting treatment and selecting the initial dose.

When this agent is administered to patients in renal failure, the interval between doses may need to be increased or the dosage reduced to avoid accumulation of drug.

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.

Anaesthetic agents
Caution must be exercised when using anaesthetic agents with Inderal. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible.

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Inderal modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of Inderal and hypoglycaemic therapy in diabetic patients. Inderal may prolong the hypoglycaemic response to insulin (see Section 4.3 and 4.4).

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

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Inderal should be used with great caution in patients who are receiving concomitant myocardial depressants such as chloroform, ether or related anaesthetics, anti-arrythmic agents such as quinidine, lidocaine, procainamide which accentuate depressant effects.

Neurone blocking agents such as guanethidine, reserpine, diuretics and other antihypertensive agents, including the vasodilator group, will have an additive effect on the antihypertensive action of the drug.
Digitalis glycosides in association with beta-blockers may increase atrioventricular conduction time.

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects (e.g. verapamil, 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. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

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

Concomitant use of sympathomimetic agents e.g. adrenaline, may counteract the effect of beta-blockers. Caution must be exercised in the parenteral administration of preparations containing adrenaline to patients taking beta-blockers as, in rare cases, vasoconstriction, hypertension and bradycardia may result. Care should also be taken with preparations such as isoprenaline and noradrenaline.

Administration of Inderal during infusion of lidocaine may increase the plasma concentration of lidocaine by approximately 30%. Patients already receiving Inderal tend to have higher lidocaine levels than controls. The combination 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.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Caution must be exercised if ergotamine, dihydroergotamine or related compounds are given in combination with Inderal since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting drugs e.g. ibuprofen and indometacin, may decrease the hypotensive effects of Inderal.

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

Caution must be exercised when using anaesthetic agents with Inderal. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Pharmacokinetic studies have shown that the following agents may interact with propranolol due to effects on enzyme systems in the liver which metabolise

propranolol and these agents: quinidine, propafenone, rifampicin, theophylline, warfarin, thioridazine and dihydropyridine calcium channel blockers such as nifedipine, nisoldipine, nicardipine, isradipine and lacidipine. Owing to the fact that blood concentrations of either agent 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

Pregnancy
As with all drugs Inderal should not be given during pregnancy unless its use is essential. There is no evidence of teratogenicity with Inderal. However beta-blockers reduce placental perfusion, which may result in intra-uterine foetal death, immature and 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.

Breast-feeding
Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast-feeding is therefore not recommended following administration of these compounds.

4.7 Effects on ability to drive and use machines

Inderal Tablets has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Inderal is usually well tolerated. In clinical studies the possible adverse reactions reported are usually attributable to the pharmacological actions of propranolol.

Tabulated list of adverse reactions
The following definitions apply to the incidence of undesirable effects. Frequencies are defined as: Very Common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000) and Not Known (cannot be estimated from the available data).

Blood and lymphatic system disorders	Rare	Thrombocytopenia

Endocrine disorders	Not Known	Hypoglycaemia in neonates, infants, children, elderly patients, patients on hemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported, seizure linked to hypoglycaemia
Nervous system disorders	Common	Sleep disturbances, nightmares
	Rare	Paraesthesia
	Rare	Hallucinations, psychoses, mood changes, confusion
	Very rare	Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported
Eye disorders	Rare	Dry eyes, visual disturbances
Cardiac disorders	Common	Bradycardia, cold extremities, Raynaud's phenomenon
	Rare	Heart failure deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome
Gastrointestinal disorders	Uncommon	Gastrointestinal disturbance, such as nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Rare	Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes
General disorders and administration site conditions	Common	Fatigue and/or lassitude (often transient)
	Rare	Dizziness.
Investigations	Very rare	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions. Cessation of therapy with a beta-blocker should be gradual. In the rare event of intolerance, manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment for overdosage instituted.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastronintestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1-2mg intravenously. If necessary this may be followed by a bolus dose of glucagon 10mg intravenously. If required this may be repeated or followed by an intravenous infusion of glucagon 1-10mg/hour depending on response. If no response to glucagon occurs, or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. (Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency). It is likely that this dose would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine or isoprenaline should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: Beta blocking agents, non-selective. C07A A05.

Inderal is a competitive antagonist at both the beta-$_1$ and beta-$_2$ adrenoceptors. It has no agonist activity at the beta-adrenoceptor, but has membrane stabilising activity at concentrations exceeding 1-3mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta-adrenoceptor blockade has been demonstrated in man by a parallel shift to the right in the dose-heart rate response curve to beta agonists such as isoprenaline.

Propranolol, as with other beta-blockers, has negative inotropic effects, and is therefore contra-indicated in uncontrolled heart failure.

Inderal is a racemic mixture and the active form is the S(-) isomer, of propranolol. With the exception of inhibition of the conversion of thyroxine to triiodothyronine it is unlikely that any additional ancillary properties possessed by R (+) propranolol, in comparison with the racemic mixture will give rise to different therapeutic effects.

Inderal is effective and well-tolerated in most ethnic populations, although the response may be less in black patients.

5.2 Pharmacokinetic properties

Following intravenous administration the plasma half-life of propranolol is about 2 hours and the ratio of metabolites to parent drug in the blood is lower than after oral administration. In particular 4-hydroxypropranolol is not present after intravenous administration. 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 to 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%).

5.3 Preclinical safety data

Propranolol is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Prescribing Information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Carmellose calcium
Gelatin
Magnesium stearate

Coating:
Hypromellose
Glycerol (E422)
Titanium dioxide (E171)
Carmine (E120)

Highlighting and coating:
Hypromellose
Glycerol (E422)
Light Magnesium carbonate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30ºC. In order to protect from light and moisture, store in the original package.

6.5 Nature and contents of container

White HDPE bottle (100 tablets).

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1019/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979

Date of last renewal: 12 October 2008

10 DATE OF REVISION OF THE TEXT

January 2019