Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Inderal LA Prolonged-release Capsules 160mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Propranolol hydrochloride 160 mg

For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release Capsules, Hard

Product imported from the UK:
Hard gelatin capsules, consisting of an opaque pale lavender cap and a clear pink body. They are printed in white ink with 'INDERAL LA'. The capsules contain white to pale cream coloured spheroids.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

i) Control of hypertension.
ii) Management of Angina Pectoris.
iii) Prophylaxis of migraine.
iv) Management of essential tremor.
v) Control of anxiety.
vi) Prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices.
vii) Adjunctive management of thyrotoxicosis.
viii) Long-term prophylaxis after recovery from acute myocardial infarction.

4.2 Posology and method of administration

For oral use. The capsule must not be chewed, but swallowed whole to ensure a prolonged release action.

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

Adults
Hypertension:
The usual starting dose is one 160mg Inderal LA capsule daily, taken either morning or evening. An adequate response is seen in most patients at this dosage. If necessary, it can be increased in 80mg Half Inderal LA increments until adequate response is achieved. A further reduction in BP can be attained if a diuretic or other antihypertensive agent is given in addition to Inderal LA and Half-Inderal LA.

One Half-Inderal LA capsule 80mg daily is unlikely on its own to be sufficient to treat hypertension but it may be used as a starting dose in appropriate patients (e.g. the elderly) or to provide a convenient method of gradual dose alteration.

Angina, anxiety, essential tremor, thyrotoxicosis and the prophylaxis of migraine:
One Half-Inderal LA capsule 80mg daily taken either morning or evening may be sufficient to provide adequate control in many patients. If necessary, the dose may be increased to one 160mg Inderal LA capsule per day and an additional Half-Inderal LA increment may be given.

Patients who are already established on equivalent daily doses of Inderal tablets should be transferred to the equivalent doses of 80mg Half-Inderal LA capsule 80mg or 160mg Inderal LA capsule taken either morning or evening.

Portal hypertension/Oesophageal varices:
Dosage should be titrated to achieve approximately a 25% reduction in resting heart rate. Dosing should begin with one Half-Inderal LA capsule 80mg daily, increasing to one 160mg Inderal LA capsule daily depending on heart rate response. Further 80mg Half-Inderal LA increment may be added up to a maximum dose of 320mg daily.

Post Myocardial Infarction:
Treatment should start between days 5 and 21 after myocardial infarction with an initial dose of one Inderal 40mg tablet four times a day for 2 or 3 days. In order to achieve maximum compliance the total daily dosage of 160mg Inderal may be given thereafter as a single Inderal LA capsule or two Half-Inderal LA capsules 80mg.

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

Children:
Inderal LA and Half-Inderal LA are not recommended for use in children.

4.3 Contraindications

Inderal LA and Half-Inderal LA 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 inhalation 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 LA and Half-Inderal LA as with other beta-blockers must not be used in patients with any of the following:

- 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.

Known hypersensitivity to the active substance or any of the excipients.

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 LA and Half-Inderal LA, as with other beta-blockers:

- Although contra-indicated in uncontrolled heart failure (see *Section 4.3, Contraindications*), may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

- Should be used with caution in patients with controlled congestive cardiac failure. Evidence of development of the condition should be regarded as a signal to discontinue therapy.

- Patients with a family or personal history of asthma are at risk of suffering attacks of refractory asthma.

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

- 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. 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 given to patients with uncontrolled or incipient cardiac decompensation.

- 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 LA/Half-Inderal LA should be gradual. This can be achieved by first substituting the daily Inderal LA dose by the equivalent in Half-Inderal LA capsules and then gradually reducing the number of capsules.

- 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 dose of adrenaline used to treat the allergic reactions.

Inderal LA must be used with caution in patients with decompensated cirrhosis.
Since the half life may be increased 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.

4.5 Interaction with other medicinal products and other forms of interaction

If Inderal LA or Half-Inderal LA is administered in conjunction with other antihypertensives an adjustment of dosage may be required.

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

Adjustment of dosage of hypoglycaemic agents may be necessary if Inderal LA is given to patients with uncontrolled or 'brittle' diabetes mellitus.

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

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.

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 blockers e.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 effects 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.

Adrenergic neurone blocking agents (such as guanethidine and reserpine), diuretics and other antihypertensive agents, including the vasodilator group will have an additive effect on the antihypertensive action of the drug.

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

Concomitant use of cimetidine 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 clonidine administration has stopped. If replacing clonidine by beta-blocker therapy the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped (see also prescribing information for clonidine).

Caution must be exercised if ergotamine, dihydroergotamine or related compounds are given in combination with propranolol 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 propranolol.

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

Caution must be exercised when using anaesthetic agents with Inderal LA/Half Inderal LA. 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 LA 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.

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

4.7 Effects on ability to drive and use machines

Use is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Inderal LA/Half-Inderal LA are usually well tolerated. In clinical studies the adverse reactions reported are usually attributable to the pharmacological actions of propranolol.

The following possible adverse reactions, listed by frequency and body system have been reported:-

Common (1-9.9%)

General:	Fatigue and/or lassitude (often transient)
Cardiovascular:	Bradycardia, cold extremities, Raynaud's phenomenon
CNS:	Sleep disturbances, nightmares

Uncommon (0.1-0.9%)

GI:	Gastrointestinal disturbance, such as nausea, vomiting, diarrhoea.

Rare (0.01-0.09%)

General:	Dizziness.
Blood:	Thrombocytopenia.
Cardiovascular:	Heart failure deterioration, precipitation of heart block, Postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication.
CNS:	Hallucinations, psychoses, mood changes, confusion.
Skin:	Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.
Neurological:	Paraesthesia.
Eyes:	Dry eyes, visual disturbances.
Respiratory:	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome.

Very rare (<0.01%)

Endocrine system:	Hypoglycaemia in elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported.
Investigations:	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.
Nervous system:	Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.

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.

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 gastrointestinal tract, the use of plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1-2mg intravenously and/or a cardiac pacemaker. 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 or isoprenaline 10 to 25 micrograms given as an infusion at a rate not exceeding 5 micrograms/minute 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

Pharmacotherapeutic group: Betablocking 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, 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.

Propranolol is a racemic mixture and the active form is the S (-) isomer. With the exception of inhibition of the conversion of thyroxine to triodothyronine 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.

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

The sustained release preparation of propranolol maintains a higher degree of beta-blockade 24 hours after dosing compared with conventional propranolol.

5.2 Pharmacokinetic properties

Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1-2 hours after dosing in fasting patients. Following oral dosing with the sustained release preparation of propranolol the blood profile is flatter than after conventional Inderal but the half life is increased to between 10 and 20 hours.

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

Erythrosine (E127)
Ethyl cellulose (E462)
Gelatin (E441)
Iron oxide (E172)
Methylhydroxypropylcellulose (E464)
Microcrystalline cellulose (E460)
Titanium dioxide (E171)
Sodium laurylsulphate
Shellac (E904)
Glycerol (E422)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the blisters or outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Store below 25°C. Store in the original package. Keep the strip in the outer carton to protect from light and moisture.

6.5 Nature and contents of container

Calendar blister strips of 14 capsules, 28 capsules to a pack, in an over labelled carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

IPS Healthcare Limited
Sterling House
501 Middleton Road
Chadderton,
Oldham
Lancashire
OL9 9LY
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1659/053/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th September 2011

10 DATE OF REVISION OF THE TEXT