Presentation
‘Inderal’ LA and ‘Inderal’ LA 80 are presented as capsules containing 160 mg and 80 mg respectively of Propranolol Hydrochloride Ph.Eur. in a controlled release formulation.

Indications
I) Control of Hypertension
II) Management of Angina Pectoris
III) Prophylaxis of migraine
IV) Management of essential tremor
V) Control of anxiety
VI) Adjunctive management of thyrotoxicosis
VII) Long-term prophylaxis after recovery from acute myocardial infarction.

Dosage and Administration
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 160 mg ‘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 80 mg ‘Inderal’ LA 80 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 ‘Inderal’ LA 80.

One ‘Inderal’ LA 80 capsule 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 ‘Inderal’ LA 80 capsule 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 160 mg ‘Inderal’ LA capsule per day and an additional ‘Inderal’ LA 80 increment may be given.

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

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 ‘Inderal’ LA 80 are not recommended for use in children.

Contra-indications
‘Inderal’ LA and ‘Inderal’ LA 80 must not be used if there is a history of bronchial asthma or bronchospasm.

Bronchospasm can usually be reversed by beta2-agonist bronchodilators such as salbutamol. Large doses of the beta2-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 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.

‘Inderal’ LA and ‘Inderal’ LA 80 as with other beta-blockers must not be used in patients with any of the following: known hypersensitivity to propranolol 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; Prinzmetal's angina.

‘Inderal’ LA and ‘Inderal’ LA 80 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.

**Warnings and Precautions**

‘Inderal’ LA and ‘Inderal’ LA 80 as with other beta-blockers:

- although contraindicated in uncontrolled heart failure (see Contra-Indications), may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

- although contraindicated in severe peripheral arterial circulatory disturbances (see Contra-Indications), 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 the hypoglycaemia (especially tachycardia). Inderal LA and ‘Inderal’ LA 80 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’ LA and ‘Inderal’ LA 80 has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of ‘Inderal’ LA and ‘Inderal’ LA 80 and hypoglycaemic therapy in diabetic patients. ‘Inderal’ LA and ‘Inderal’ LA 80 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’ LA/‘Inderal’ LA 80 should be gradual. This can be achieved by first substituting the daily ‘Inderal’ LA dose by the equivalent in ‘Inderal’ LA 80 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 doses of adrenalin used to treat the allergic reactions.

‘Inderal’ LA and ‘Inderal’ LA 80 must be used with caution in patients with decompensated cirrhosis. 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.

**Interactions with other medicaments and other forms of interaction**

‘Inderal’ LA and ‘Inderal’ LA 80 modify the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of ‘Inderal’ LA/‘Inderal’ LA 80 and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin (see Contraindications, Warnings and Precautions).

Caution must be exercised in prescribing a beta-blocker with Class I antiarrhythmic agents such as disopyramide.

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 hypoten-
sion, 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 dihydropyridine 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.
adrenalin, may counteract the effects of beta-block-
ers. Caution must be exercised in the parenteral
administration of preparations containing adrenalin
to patients taking beta-blockers as, in rare cases,
vasoconstriction, hypertension and bradycardia may
result.
Administration of ‘Inderal’ LA/’Inderal’ LA 80 during
infusion of lignocaine may increase the plasma
concentration of lignocaine by approximately 30%.
Patients already receiving ‘Inderal’ LA and ‘Inderal’
LA 80 tend to have higher lignocaine levels than
controls. The combination should be avoided.
Concomitant use of cimetidine will increase, where-
as concomitant use of alcohol will decrease, the
plasma levels of propranolol.
Beta-blockers may exacerbate the rebound hyper-
tension, which can follow the withdrawal of cloni-
dine. 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-block-
ers should be delayed for several days after cloni-
dine administration has stopped.
Caution must be exercised if ergotamine, dihy-
droergotamine or related compounds are given in
combination with ‘Inderal’ LA/’Inderal’ LA 80 since
vasoconstrictive reactions have been reported in a few
patients.
Concomitant use of prostaglandin synthetase
inhibiting drugs, e.g. ibuprofen and indomethacin,
may decrease the hypotensive effects of ‘Inderal’
LA/’Inderal’ LA 80.
Concomitant administration of ‘Inderal’ LA/’Inderal’
LA 80 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 ‘Inderal’ LA
/’Inderal’ LA 80.
Caution must be exercised when using anaesthetic
agents with ‘Inderal’ LA/’Inderal’ LA 80. The anaes-
thesiologist should be informed and the choice of anaes-
thetic should be an agent with as little negative ino-
tropic activity as possible. Use of beta-blockers with
anaesthetic drugs may result in attenuation of the
reflex tachycardia and increase the risk of hypo-
tension. Anaesthetic agents causing myocardial
depression are best avoided.
Pharmacokinetic studies have shown that the fol-
lowing agents may interact with propranolol due
ton effects on enzyme systems in the liver which
metabolise propranolol and these agents: quini-
dine, propafenone, rifampicin, theophylline, warfa-
in, thioridazine and dihydropyridine calcium channel
blockers such as nifedipine, nisoldipine, nicardipine,
srdipine and lacidipine. Owing to the fact that
blood concentrations of either agent may be affect-
ed dosage adjustments may be needed according to
clinical judgement. (See also the Interaction above
concerning the concomitant therapy with dihydro-
pyridine calcium channel blockers).

Pregnancy and lactation

Pregnancy
As with all drugs ‘Inderal’ LA/’Inderal’ LA 80 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 addi-
tion, adverse effects (especially hypoglycaemia and
bradycardia in the neonate and bradycardia in the
foetus) may occur. There is an increased risk of car-
diac 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 is therefore not recommended follo-
ing administration of these compounds.
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.

Overdosage
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 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 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 these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Pharmacological properties
Pharmacodynamic properties
Propranolol is a competitive antagonist at both the beta1- and beta2- adrenoceptors. It has no agonist activity at the beta-adrenoceptor, but has membrane stabilising activity at concentrations exceeding 1-3 mg/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 contraindicated 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 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.

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.

**Pharmacokinetic Properties**

Propranolol is completely absorbed after oral administration. 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%).

**Pharmaceutical Particulars**

Storage: Do not store above 30°C. Protect from light and moisture.

Shelf Life: Please refer to the expiry date on the blister strip or outer carton.

Pack Size: Please refer to the outer carton for pack size.

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