PHYSICIANS' PRESCIBING INFORMATION

DERALIN® TABLETS

1. NAME OF THE MEDICINAL PRODUCT

`DERALIN'

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Propranolol Hydrochloride 10mg, or 40mg.

3. PHARMACEUTICAL FORM

Pink round flat tablet bisected on one side and plain on the other side.
Pink round flat tablet bisected on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Management of angina pectoris.
2. Control of essential and renal hypertension, essential tremor, most forms of cardiac dysrhythmias.
3. As an adjunct in the management of tachycardias and arrhythmias due to thyrotoxicosis and thyrotoxic crises, hypertrophic obstructive cardiomyopathy, pheochromocytoma (with an alpha--blocker).
4. Deralin Tablets are also indicated for long-term prophylaxis following recovery from acute myocardial infarction (treatment to be initiated by a hospital physician).
5. Migraine prophylaxis.

4.2 Dosage 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.

As with any other potent beta-blocking agent, the optimum dosage of Deralin has to be determined individually for each patient.
Food may slow the hepatic metabolism of propranolol therapy, enhancing its bioavailability. In order to standardize conditions, it is recommended that Deralin should be taken with meals.

As a guide for the correct dosage, bradycardia (usually less than 45 beats/minute) is indicative that dosage should not be further increased.
When discontinuation of chronic administration of Deralin is planned in patients with ischemic heart disease, the dosage should be reduced gradually and the patients carefully monitored.

Angina Pectoris, Essential Tremor, Migraine Prophylaxis
Adults
The recommended initial dosage is 40 mg, 2-3 times daily. This may be increased by the same amount, at weekly intervals, according to patients response. An adequate response in the management of migraine and essential tremor is usually seen in the range of 80-160 mg/day, and in the treatment of angina in the range of 120-240 mg/day.

Children
The dosage for migraine prophylaxis in children is as follows:
Under the age of 12 years: 20 mg 2 or 3 times daily.
Over the age of 12 years: The adult dosage.

Hypertension
The recommended initial dosage is 80 mg, twice a day. This may be increased at weekly intervals, according to patient response. The usual dosage range is 160-320 mg/day. With concurrent diuretic or other antihypertensive drugs, a further reduction of blood pressure is obtained.

Arrhythmias, Hypertrophic Obstructive Cardiomyopathy, Thyrotoxicosis, Thyrotoxic Crises:

Adults
A dosage range of 10-40 mg, 3-4 times daily, usually achieves the desired response.

Children
For these indications as well as for pheochromcytoma, dosage should be individually determined, and the following is only a guide: A dosage of 0.25-0.5 mg per kg body weight 3-4 times daily, as required.

Pheochromocytoma
Use only with an alpha-receptor blocking drug. Preoperatively, a dosage of 60 mg/day, for 3 days, is recommended. In non-operable malignant cases, administer 30 mg/day.

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

Use in the Elderly
Evidence concerning the relation between blood level and age is conflicting. Propanolol should be used to treat the elderly with caution. It is suggested that treatment should start with the lowest dose With regard to the elderly, the optimum dose should be individually determined according to clinical response.

4.3 Contraindications

`Deralin' 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 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.

`Deralin' 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 (with an alpha adrenoceptor antagonist) phaeochromocytoma; uncontrolled heart failure; Prinzmetal's angina.

‘Deralin’ 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 Warnings and Precautions for Use

`Deralin' as with other beta-blockers:

-although contraindicated in uncontrolled heart failure (see Section 4.3), 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 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. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

-should not be used in patients with Prinzmetal's angina and beta-1 selective agents should be used with care. (see section 4.3).

-although contraindicated 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 the hypoglycaemia (especially tachycardia). 'Deralin' 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 patient suffering from overdose. Severe hypoglycemia associated with 'Deralin' has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of 'Deralin' and hypoglycaemic therapy in diabetic patients. 'Deralin' may prolong the hypoglycaemic response to insulin.

-may mask the signs of thyrotoxicosis.

-should not be used in untreated phaeochromocytoma. However, in patients with phaeochromocytoma, an alpha-blocker may be given concomitantly.

-should be used to treat the elderly with caution starting with a lower dose. (see section 4.2).

-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.

-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.

Abrupt withdrawal of beta-blockers 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.

When a patient is scheduled for surgery and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk/benefit of stopping beta blockade should be made for each patient

`Deralin' 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.

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.

Interference with laboratory tests: ‘Deralin’ has been reported to interfere with the estimation of serum bilirubin by the diazo method and with the determination of catecholamines by methods using fluorescence.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

`Deralin' modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of `Deralin' and hypoglycaemic therapy in diabetic patients. `Deralin' 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 Cmax 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 (eg 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 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 eg 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.

Administration of `Deralin' during infusion of lignocaine may increase the plasma concentration of lignocaine by approximately 30%. Patients already receiving `Deralin' tend to have higher lignocaine levels than controls. The combination should be avoided.

Concomitant use of cimetidine or hydralazine increases, whereas concomitant use of alcohol decreases, 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 `Deralin' since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting drugs eg ibuprofen and indomethacin, may decrease the hypotensive effects of `Deralin'.

Concomitant administration of `Deralin' 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 `Deralin'.

Caution must be exercised when using anaesthetic agents with `Deralin'. 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 Pregnancy and Lactation

Pregnancy:

As with all drugs `Deralin' should not be given during pregnancy unless its use is essential. There is no evidence of teratogenicity with `Deralin'. 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 is therefore not recommended following administration of these compounds.

4.7 Effect on Ability to Drive and Use Machinery

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

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

The following possible adverse reactions, listed by 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: Thrombocytopaenia.
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, memory loss.
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%)
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.

Frequency not known
Endocrine system: 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, seizure linked to hypoglycaemia.

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 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 1-2mg 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 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 dobutamide 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

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 contraindicated in uncontrolled heart failure. (Section 4.4)

Propranolol 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.

`Deralin' 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 to 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 to 95%).

5.3 Pre-Clinical Safety Data Relevant to the Prescriber

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate, magnesium stearate, gelatin, carmine powder

Lactose content per tablet: Deralin 10 mg: 91.75 mg; Deralin 40 mg: 152 mg.

6.2 Incompatibilities

None known

6.3 Special Precautions for Storage

`Deralin' tablets should be stored in a dry and dark place, under 25°C.

6.4 Instructions for Use/Handling

Use as directed by the prescriber.

7. REGISTRATION NUMBERS:

Deralin 10 mg: 023.52.21382.00.
Deralin 40 mg : 105.37.21381.00.

8. MANUFACTURER

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