

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Propranolol 80mg Tablets

2. Qualitative and Quantitative Composition

Each tablet contains Propranolol Hydrochloride B.P. 80mg.

3. Pharmaceutical Form

Pink, film-coated tablets, face I embossed 'P/80', face II embossed 'a' intended for oral administration to human beings.

Clinical Particulars

4.1 Therapeutic indications

- 1.) The control of hypertension.
- 2.) The management of angina pectoris.
- 3.) The long term prophylaxis after recovery from acute myocardial infarction.
- 4.) The control of most forms of cardiac dysrhythmias.
- 5.) The prophylaxis of migraine.
- 6.) The management of essential tremor.
- 7.) Relief of situational anxiety and generalised anxiety symptoms, particularly those of somatic type.
- 8.) Prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices.
- 9.) The adjunctive management of thyrotoxicosis and thyrotoxic crisis.
- 10.) Management of hypertrophic obstructive cardiomyopathy.
- 11.) Management of phaeochromocytoma perioperatively (with an alpha blocker).

4.2 Posology and method of administration

Adults:

Hypertension: A starting dose of 80mg twice a day may be increased at weekly intervals according to response. The usual dose range is 160 - 320mg per day. Lower doses may be effective when a diuretic or other antihypertensive drugs are given concurrently.

Angina, migraine and essential tremor: Initially, 40mg two or three times daily, increased by the same amount at weekly intervals according to patient response. An adequate

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

Situational and generalised anxiety: In acute situational anxiety, a dose of 40mg daily may provide short term relief. In generalised anxiety requiring longer term therapy, an adequate response may be expected with 40mg twice daily which, in individual cases, may be increased to 40mg three times daily. Treatment should be continued according to response and patients should be reviewed after six to twelve months' treatment.

Dysrhythmias, anxiety tachycardia, hypertrophic obstructive cardiomyopathy and thyrotoxicosis: 10 - 40mg three or four times a day.

Post myocardial infarction: For long-term prevention of sudden cardiac death in patients who have survived the acute phase of a myocardial infarct, 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.

Portal hypertension: Dosage should be titrated to achieve approximately 25% reduction in resting heart rate. Initially, 40mg twice daily, increasing to 80mg twice daily depending on heart rate response. If necessary, the dosage may be increased incrementally to a maximum of 160mg twice daily.

Phaeochromocytoma: Propranolol should be used only with an alpha-receptor blocking drug). Pre-operative: 60mg daily for three days. Non-operable malignant cases: 30mg daily.

Children: Dysrhythmias, phaeochromocytoma, thyrotoxicosis. Dosage should be determined individually. The following dosages are intended only as a guide: 0.25 - 0.5mg/kg three or four times daily as required.

Migraine: Under the age of 12: 20mg two or three times daily.

Over the age of 12: the adult dose.

Fallot's Tetralogy: Propranolol is used mainly to relieve right-ventricular outflow tract shut-down. It is also useful for treatment of associated dysrhythmias and angina. Dosage

should be individually determined and the following is only a guide: Up to 1mg/kg repeated three or four times daily as required.

Elderly patients: The optimum dose should be individually determined according to clinical response.

4.3 Contraindications

Propranolol tablets must not be used if there is a history of bronchial asthma or bronchospasm. The product label states the following warning: “Do not take Propranolol tablets if you have a history of asthma or wheezing”. A similar warning appears in the Patient Information Leaflet.

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.

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

Propranolol tablets, as with other beta-blockers, must not be used in patients with any of the following conditions: Cardiogenic shock; uncontrolled heart failure; sick sinus syndrome; second and third degree heart block; Prinzmetal’s angina; untreated phaeochromocytoma; metabolic acidosis; after prolonged fasting; bradycardia (heart rate less than 50/min); hypotension; hypersensitivity to propranolol; severe peripheral arterial circulatory disturbances.

4.4 Special warnings and precautions for use

In patients with ischaemic heart disease, sudden withdrawal of a beta-blocker may result in anginal attacks of increased frequency or severity. Withdrawal of propranolol should be gradual, especially in patients with ischaemic heart disease. The dosage should be reduced gradually, i.e. over one to two weeks; if necessary, replacement therapy should be initiated at the same time to prevent exacerbation of angina pectoris.

Hypertension and cardiac arrhythmias may develop following sudden withdrawal of a beta-blocker. When withdrawing a beta-blocker in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, although there may be an increased risk of hypertension. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs and the chosen anaesthetic should have as little negative inotropic activity as possible. The anaesthetist should always be

informed about the use of a beta-blocking drug. The patient may be protected against vagal reactions by the intravenous administration of atropine.

Although contraindicated in severe peripheral circulatory disturbances, beta-blockers may also aggravate less severe forms. Therefore, propranolol should be used with great caution in conditions such as Raynaud's disease/syndrome or intermittent claudication.

Beta-blockers are contraindicated in uncontrolled heart failure. Particular care is required when using a beta-blocker in patients whose signs of heart failure have been controlled, or in patients whose cardiac reserve is poor.

A reduction in heart rate is a pharmacological effect of propranolol. In rare cases where symptoms may be attributable to a slow heart rate and where the resting pulse rate decreases to less than 50 – 55/minute, the dosage should be reduced.

Due to its negative effect on conduction time, a beta-blocker should only be used with caution in patients with first degree heart block.

Beta-blockers may increase the number and duration of anginal attacks in patients with Prinzmetal's angina due to unopposed α -receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers should not be used in these patients, and beta-1 selective blockers may be used only with the utmost care.

In patients with chronic obstructive pulmonary disorders, airway obstruction may be aggravated. Non-selective beta-blockers should not be used in these patients, and beta-1 selective blockers may be used only with the utmost care.

Since the half-life of propranolol may be increased in patients with significant hepatic or renal impairment, caution should be exercised when starting treatment and selecting the initial dose. Elderly patients should be treated with caution, starting with a lower dosage, although tolerance is usually good in the elderly. Propranolol must be used with caution in patients with decompensated cirrhosis.

In patients with portal hypertension, hepatic 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.

Cardiac failure due to thyrotoxicosis may respond to propranolol alone, but if other adverse factors are also present, it is important to control signs of failure with digitalis and diuretics. Propranolol as with other beta-blockers may mask the signs of Thyrotoxicosis.

Propranolol may modify the tachycardia of hypoglycaemia and it may prolong the hypoglycaemic response to insulin. Propranolol 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 Propranolol has rarely presented with seizures and/or coma in isolated patients. Care should be exercised during the concomitant use of propranolol and hypoglycaemic therapy in patients with diabetes mellitus.

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

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

Care is required when transferring patients from clonidine to a beta-blocking drug. If the two drugs are given concurrently, the clonidine should not be discontinued for some time after withdrawal of the beta-blocker (see Interactions).

Care is required when prescribing a beta-blocker with a Class I anti-arrhythmic agent such as disopyramide.

Beta-blocking drugs should be used with caution in combination with verapamil or diltiazem and the combination should not be given to 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.

Care is also required during parenteral administration of preparations containing adrenaline. (See Interactions).

Beta-blocking drugs should be used only after careful consideration in patients with psoriasis or with a history of psoriasis.

Beta-blockers 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.

Propranolol has been reported to interfere with some laboratory tests, viz. estimation of serum bilirubin by the diazo method and determination of catecholamines by fluorescence methods.

The label shall contain the following statement:

Do not use if you have a history of wheezing or asthma.

4.5 Interaction with other medicinal products and other forms of interaction

Particular caution is required when a beta-blocker is used concurrently with any of the following drugs:

Calcium antagonists: verapamil or diltiazem (beta-blockers may exaggerate the negative influence on contractility and atrio-ventricular conduction, particularly in patients with impaired ventricular function and/or S-A or A-V 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.

Digitalis glycosides (association with beta-blockers may increase atrio-ventricular conduction time).

Clonidine (beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine). When the two drugs are administered concomitantly, treatment with clonidine should be continued for several days after the beta-blocker has been discontinued. If replacing clonidine with a beta-blocker, treatment with the latter should be delayed for several days after the clonidine has been discontinued.

Caution should also be exercised when a beta-blocker is used concomitantly with any of the following drugs:

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

Insulin and oral antidiabetic drugs (may intensify the blood sugar lowering effect). Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia) and may prolong the hypoglycaemic response to insulin.

Anaesthetic drugs (attenuation of the reflex tachycardia and increased risk of hypotension). Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthetist should be informed when the patient is receiving a beta-blocking agent. Anaesthetic drugs causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided.

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

Cimetidine, hydralazine and alcohol may increase plasma levels of propranolol, although alcohol has also been reported to decrease plasma levels of propranolol.

The possibility of an interaction between beta-blockers and other drugs, including the following ones, should be taken into account:

Dihydropyridine derivatives such as nifedipine (increased risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency).

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.

Prostaglandin synthetase inhibitors e.g. ibuprofen or 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 antipsychotic effect for chlorpromazine and an increased antihypertensive effect for propranolol.

Sympathomimetic agents, such as adrenaline, may counteract the effect of beta-blocking drugs. Parenteral administration of preparations containing adrenaline to

patients taking beta-blocking drugs may, in rare cases, result in vasoconstriction, hypertension and bradycardia.

Tricyclic antidepressants/barbiturates/phenothiazines/other antihypertensive drugs may increase the blood pressure lowering effect when administered concomitantly with a beta-blocking agent, although barbiturates have also been reported to reduce serum levels of propranolol.

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 concomitant therapy with dihydropyridine calcium channel blockers).

4.6 Pregnancy and lactation

Pregnancy

As with all drugs, Propranolol should not be given during pregnancy unless their use is essential. There is no evidence of teratogenicity with Propranolol.

However, Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in foetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

Lactation

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

4.7 Effects on ability to drive and use machines

The use of Propranolol is unlikely to result in any impairment of the ability of patients to drive or operate machinery.

When performing these tasks, it should be taken into account that dizziness or fatigue may occasionally occur.

4.8 Undesirable effects

Propranolol tablets are usually well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of propranolol.

The following undesired events, listed by body system, have been reported.

Common (1-9.9%)

General: Fatigue and/or lassitude (often transient) ; headache

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, 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%)

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.

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

Clinical features of overdosage may include bradycardia, hypotension, bronchospasm, hypoglycaemia, delirium and unconsciousness.

Following ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive care ward. Gastric lavage and administration of activated charcoal and a laxative can prevent absorption of any drug still present in the gastrointestinal tract. Artificial respiration may be required. Atropine 1 to 2mg intravenously should be used to treat severe bradycardia or extensive vagal reactions. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline, starting with a dosage of approximately 5 micrograms/minute, or dobutamine, starting with a dose of 2.5 micrograms/minute until the required response has been achieved. In refractory cases, isoprenaline can be combined with dopamine. If the desired effect has still not been achieved, intravenous administration of 8 to 10mg of glucagon may be considered. The injection should be repeated, if required, within one hour and may be followed, if required, by an intravenous infusion of glucagon administered at a rate of 1 to 3mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker may be considered.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Propranolol is a beta-adrenergic receptor blocking agent and a member of Division I (non-cardioselective), Group II (possessing membrane-stabilising activity) class of beta-blocking agents. By blocking beta-receptor sites, propranolol decreases the inotropic, chronotropic, and vasodilator responses to beta-adrenergic stimulation. The mechanisms of propranolol's antimigraine and antihypertensive effects have not been established, although factors contributing to the latter effects may possibly include a decrease in cardiac output, inhibition of renin release and a decrease in sympathetic outflow from the vasomotor centres in the brain.

5.2 Pharmacokinetic Properties

Propranolol is almost completely absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism in the liver. Peak plasma concentrations occur about two hours after administration and the plasma half-life is about 3 to 6 hours. Propranolol is highly bound to plasma proteins. Before excretion in the urine, propranolol is virtually completely metabolised and one of the metabolites, 4-hydroxy-propranolol, appears to exhibit beta-

adrenergic blocking activity. Other urinary metabolites of propranolol include naphthoxylactic acid, isopropylamine and propranolol glycol.

5.3 Preclinical Safety Data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

Pharmaceutical Particulars

6.1 List of Excipients

Lactose B.P./Ph. Eur.
Maize Starch B.P./Ph. Eur.
Povidone B.P./Ph. Eur.
(Industrial Methylated Spirits)
Colloidal Silicon Dioxide (Aerosil 200) U.S.P.
Magnesium Stearate B.P./Ph. Eur.
Methylcellulose (Methocel E5) B.P./Ph. Eur.
Ethylcellulose (Ethocel 10 cps) B.P./Ph. Eur.
Diethyl Phthalate B.P./Ph. Eur.
(Methylene Chloride)
(Methanol)
Opaspray K-I-1340

6.2 Incompatibilities

There are no known major incompatibilities with propranolol tablets.

6.3 Shelf Life

5 years (60 months).

6.4 Special Precautions for Storage

Store in a cool dry place below 25°C.
Protect from light and heat.

6.5 Nature and Contents of Container

Polypropylene securitainers with polypropylene tamper evident caps.
Pack sizes : 28, 56, 100, 250, 500 and 1000 tablets.

6.6 Instruction for Use/Handling

Do not take this medicine if you have a history of wheezing or asthma.

Administrative Data

7. Marketing Authorisation Holder

Goldshield Pharmaceuticals Ltd
NLA Tower
12-16 Addiscombe Road
Croydon
CR0 0XT
United Kingdom

8. Marketing Authorisation Number

PL 12762/0128

9. Date of First Authorisation/Renewal of Authorisation

25 July 2001

10 DATE OF REVISION OF THE TEXT

01/09/2010