SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Propranolol 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains propranolol hydrochloride BP 10mg.

Excipient with known effect

Lactose monohydrate 50mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Pink, round, film-coated tablets with an approximate diameter of 6.0mm, marked with P and 1 on either side of a score line on one side and plain on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Propranolol is a competitive blocker of adrenergic β-receptor sites. It is indicated in:

a)	The control of hypertension.
b)	The management of angina pectoris.
c)	The prevention of re-infarction after recovery from acute myocardial infarction.

d)	The control of most forms of cardiac arrhythmias including sinus tachycardia due to thyrotoxicosis, paroxysmal supraventricular tachycardia, atrial fibrillation and atrial flutter, ventricular extrasystoles, ventricular tachycardia and ventricular fibrillation (prophylaxis only), arrhythmias due to digitalis intoxication (if phenytoin cannot be used and no AV-block II or III is present).
e)	The adjunctive therapy in thyrotoxicosis.
f)	The prophylaxis of migraine.
g)	The management of essential tremor.
h)	The management of phaeochromocytoma (with an alpha-blocker).

4.2 Posology and method of administration

Dosage requires individual adjustment. The lowest appropriate dose should be given initially to be able to identify cardiac decompensation or bronchial phenomena at an early stage. Subsequent increases in dose should take place slowly on the basis of clinical response. A heart rate of 55/minute or less is an indication that dosage should be increased no further.

Posology

Adults:

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

Angina, migraine and essential tremor: A starting dose of 40mg, 2 or 3 times daily may be 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 to 160mg/day and in angina in the range 120 to 240mg/day.

Post myocardial infarction: Treatment should start between day 5 and 21 after myocardial infarction, with an initial dose of 40mg, 4 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.

Dysrhythmias, thyrotoxicosis: 10mg to 40mg, 3 or 4 times daily.

Phaeochromocytoma:
(Used only with an alpha-receptor blocking drug).
Pre-operative: 60mg daily for 3 days is recommended.
Non-operable malignant cases: 30mg daily.

Elderly people:

Evidence concerning the relationship between blood level and age is conflicting. Propranolol should be used to treat the elderly with caution. It is suggested that treatment should start with the lowest dose. The optimum dose should be individually determined according to clinical response.

Patients with renal and hepatic dysfunction:

The half-life of propranolol may be increased in patients with severe renal or hepatic impairment. Due caution should therefore be exercised when initiating treatment and selecting the dose to be employed.

Paediatric population:

Dysrhythmias, phaeochromocytoma, thyrotoxicosis: Dosage should be individually determined and the following is only a guide: Oral: 0.25mg/kg to 0.5mg/kg, 3 or 4 times daily as required.

Migraine: Oral: Children under the age of 12: 20mg, 2 or 3 times daily. Over the age of 12: The adult dose.

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.

Propranolol must not be used if there is a history of bronchial asthma or bronchospasm. The product label states the following warning: “do not take this medicine if you have a history of wheezing or asthma”. A similar warning appears in the patient information leaflet.

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.

Propranolol as with other beta-blockers must not be used in patients with any of the following conditions:

- Bradycardia
- Cardiogenic shock
- Hypotension
- Metabolic acidosis

- After prolonged fasting
- Severe peripheral arterial circulatory disturbances
- Second- or third-degree heart block
- Sick sinus syndrome (including sino-atrial block)
- Untreated pheochromocytoma
- Uncontrolled heart failure
- Prinzmetal’s angina
- History of chronic obstructive pulmonary disease

Propranolol 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

Propranolol 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.

– Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), may also aggravate less severe peripheral arterial circulatory disturbances. Therefore, propranolol should be used with great caution in conditions such as Raynaud's disease/syndrome or intermittent claudication.

– 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). Propranolol occasionally causes hypoglycaemia 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 Propranolol has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of Propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin (see section 4.3).

- Heart failure due to thyrotoxicosis often responds to propranolol alone, but if other adverse factors co-exist myocardial contractility must be maintained and signs of failure controlled with digitalis and diuretics. Propranolol may mask the important signs of thyrotoxicosis and hyperthyroidism.

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

- 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. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. In the rare event of intolerance, manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment for overdosage instituted. The sudden withdrawal of beta-receptor antagonists may result in severe exacerbation of angina pectoris, acute myocardial infarction, sudden death, malignant tachycardia, sweating, palpitation and tremor. The dosage should be withdrawn gradually over a period of 7 to 14 days. Either the equivalent dose of another beta-blocker may be substituted, or the withdrawal of Propranolol should be gradual. This can be carried out by substituting the equivalent dose in propranolol tablets and then reducing the dose. 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.

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.

Propranolol must be used with caution in patients with decompensated cirrhosis (see section 4.2).

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 (see section 4.2).

Interference with laboratory tests: Propranolol 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.

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

This medicine contains less than 1mmol sodium (23mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Propranolol modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of Propranolol and hypoglycaemic therapy in diabetic patients. Propranolol 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.

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, eg, 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 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.

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 Propranolol since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting drugs eg, 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 antipsychotic effect for chlorpromazine and an increased antihypertensive effect for Propranolol.

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

Concomitant use of moxonidine and beta blockers may result in an enhanced hypotensive effect. The steps for moxonidine withdrawal/introduction should be the same as for clonidine.

Hypotensive effect may be enhanced when propranolol is taken with diuretics, methyldopa or levodopa.

Barbiturates: The metabolism of propranolol may be increased by potent liver enzyme inducer barbiturates.

Imipramine: Propranolol may cause plasma concentrations of imipramine to increase.

Monoamine-oxidase Inhibitors: The hypotensive effects of beta-blockers may be enhanced by MAOIs.

Selective Serotonin Re-uptake Inhibitors: Fluvoxamine inhibits oxidative metabolism and increases plasma concentrations of propranolol. This may result in severe bradycardia.

Theophylline: Propranolol reduces the clearance and consequentially increases the plasma concentration of theophylline.

Tobacco: Smoking tobacco may oppose the effects of beta blockers in the treatment of angina or hypotension. Patients should be encouraged to stop smoking, apart from its other toxic effects, it aggravates myocardial ischaemia, increases heart rate and can impair blood pressure control. If patient continues to smoke, dosage of the beta blocker may need to be increased or a cardio-selective beta blocker may be more appropriate.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Propranolol has no or negligible influence on the ability to drive and use machines. However, patients should be warned that visual disturbances, hallucinations, mental confusion, dizziness, drowsiness or fatigue may occur and they should not drive or operate machinery if they feel affected.

4.8 Undesirable effects

Propranolol is 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.
The following definitions of frequencies are used:
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); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: thrombocytopenia.
Frequency not known: agranulocytosis.

Endocrine disorders
Frequency not known: 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, changes in lipid metabolism (changes in blood concentrations of triglycerides and cholesterol).

Psychiatric disorders
Frequency not known: depression, confusion.

Nervous system disorders
Common: Sleep disturbances, nightmares.
Rare: Hallucinations, psychoses, mood changes, confusion, memory loss, paraesthesia.
Very rare: Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.
Frequency not known: headache, seizure linked to hypoglycaemia.

Eye disorders

Rare: Dry eyes, visual disturbances.
Frequency not known: conjunctivitis.

Cardiovascular 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.
Frequency not known: worsening of attacks of angina pectoris.

Respiratory, thoracic and mediastinal disorders
Rare: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome.
Frequency not known: dyspnoea.

Gastrointestinal disorders
Uncommon: Gastrointestinal disturbance such as diarrhoea, nausea, vomiting.
Frequency not known: constipation, dry mouth.

Skin and subcutaneous tissue disorders
Rare: alopecia, purpura, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.

Musculoskeletal system and connective tissue disorders
Frequency not known: arthralgia.

Renal and urinary disorders
Frequency not known: reduced renal blood flow and GFR.

Reproductive system and breast disorders
Frequency not known: sexual dysfunction.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Propranolol is known to cause severe toxicity when used in overdose. Patients should be informed of the signs of overdose and advised to seek urgent medical assistance if an overdose of propranolol has been taken.

Clinical features:

Cardiac

Bradycardia, hypotension, pulmonary oedema, syncope, cardiogenic shock may develop. QRS complex prolongation, ventricular tachycardia, first to third degree AV block, ventricular fibrillation or asystole may also occur. Development of cardiovascular complications is more likely if other cardioactive drugs, especially calcium channel blockers, digoxin, cyclic antidepressants or neuroleptics have also been ingested. Older patients and those with underlying ischaemic heart disease are at risk of developing severe cardiovascular compromise.

CNS

Drowsiness, confusion, seizures, hallucinations, dilated pupils and in severe cases coma may occur. Neurological signs such as coma or absence of pupil reactivity are unreliable prognostic indicators during resuscitation.

Other features

Bronchospasm, hyperkalaemia and occasionally CNS-mediated respiratory depression may occur.

Management

In cases of overdose or extreme falls in heart rate or blood pressure, treatment with propranolol must be stopped. Management should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. In symptomatic patients, or patients with an abnormal ECG, early discussion with critical care should be considered.

Consult national clinical guidance for further information on the management of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking 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 to 3 mg/litre, though such concentrations are rarely achieved during oral therapy.

Competitive beta-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 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.

Propranolol 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 Preclinical safety data

Propranolol is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Cores:

Lactose monohydrate

Maize Starch

Pregelatinised Starch

Sodium Starch Glycolate
Microcrystalline Cellulose
Magnesium Stearate
Tablet Coating:
Hypromellose
Titanium dioxide (E171)
Ethylcellulose
Triacetin (E1518)
Erythrosine aluminium lake (E127)

6.2 Incompatibilities
Not known.

6.3 Shelf life
36 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Securitainers with polyethylene closures.

PVC/PVDC Blisters with 20µm Aluminium Foil

Pack size: 28 Tablets.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 40147/0064

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10 DATE OF REVISION OF THE TEXT

11/01/2024