

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Beta-Prograne 160mg Prolonged-Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Propranolol Hydrochloride 160 mg

Excipients - Contains Sucrose 6mg and Sulphur Dioxide (E220)

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

White size 2 hard gelatin capsules containing white uniform spherical microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Control of hypertension
- Long-term prophylaxis against re-infarction after recovery from acute myocardial infarction
- Management of angina pectoris
- Prophylaxis of migraine
- Management of essential tremor
- Management of anxiety
- Adjunctive management of thyrotoxicosis
- Prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices

4.2 Posology and method of administration

Posology

Adults

Hypertension:

The initial dose is usually 160mg daily, taken orally in the morning or evening. An adequate response is seen by most patients at this dosage. If necessary, it can be increased in 80mg increments until the desired response is achieved (up to a maximum of 320mg daily). A further reduction in blood pressure may be achieved by combining propranolol with other antihypertensive agent or a diuretic.

Angina, essential tremor, thyrotoxicosis, prophylaxis of migraine:

The usual dose is 80mg daily, taken orally in the morning or evening. The dose may be increased to 160mg.

Situational and generalised anxiety:

A daily dose of 80mg propranolol should be sufficient to provide short-term relief of acute situational anxiety. Generalised anxiety, requiring longer term therapy, usually responds adequately at the same dosage. In some cases, the dosage may be increased to 160mg. Patients should be reviewed after 6 – 12 months of treatment. Treatment should be continued in accordance with the patient's response.

Portal Hypertension:

Dosage should be titrated to achieve approximately 25% reduction in resting heart rate. Dosing should begin with one Half Beta-Prograne 80mg Capsule increasing to one Beta-Prograne 160mg Capsule depending on heart rate response. Further 80mg increments may be added up to a maximum dose of 320mg once daily.

For patients who are already established on 160mg propranolol daily, one Beta-Prograne 160mg Capsule may be given.

Post Myocardial Infarction:

Treatment should be started between days 5 and 21 after myocardial infarction, with an initial dose of propranolol 40mg four times a day for 2 or 3 days. In order to achieve maximum compliance, the total daily dosage may be given thereafter as a single 160mg Beta-Prograne or two 80mg Half- Beta-Prograne.

Renal or hepatic impairment:

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

Elderly

Evidence concerning the relationship between blood level and age is conflicting. Propranolol tablets 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.

Children

Beta-Prograne 160mg and Half Beta-Prograne 80mg Capsules are not suitable for use in children.

Method of administration

For oral use.

The capsule should be swallowed whole to ensure a prolonged release action.

4.3 Contraindications

Beta-Prograne 160mg Capsules and Half Beta-Prograne 80mg Capsules must not be used if any of the following conditions are present:

- hypersensitivity to propranolol (the active substance) or any of the other ingredients (listed in section 6.1)
- a history of bronchospasm, asthma or chronic obstructive airways disease
- bradycardia
- second or third degree heart block
- sick sinus syndrome
- cardiogenic shock
- uncontrolled heart failure
- hypotension
- severe peripheral arterial circulatory disturbances
- Prinzmetal's angina
- untreated phaeochromocytoma
- patients where the risk of hypoglycaemia is significantly increased, e.g. after prolonged fasting or in diabetics with hypoglycaemic episodes
- metabolic acidosis

4.4 Special warnings and precautions for use

In patients with ischaemic heart disease treatment must not be discontinued abruptly. Either the equivalent dosage of another beta-blocker may be substituted or the withdrawal of Beta-Prograne/Half- Beta-Prograne should be gradual.

Propranolol may aggravate peripheral arterial circulatory disturbances. Therefore, propranolol should be used with great caution in conditions such as Raynaud's disease/syndrome or intermittent claudication.

Although contraindicated in patients with uncontrolled heart failure (see section 4.3), propranolol can be given to patients whose signs of heart failure have been controlled. Caution should be taken in patients with a poor cardiac reserve.

As propranolol has a negative effect on conduction time, care must be taken when giving it to patients with first degree heart block.

Propranolol will reduce the heart rate due to its pharmacological action. Rarely a patient taking this medicine may develop a slower heart rate, in this instance the dose may be reduced.

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

Propranolol should not be used concomitantly 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 could result in severe hypotension, bradycardia and cardiac failure. Neither the beta blocker nor the calcium channel blocker should be given intravenously within 48 hours of discontinuing the other (see section 4.5).

Intolerance to propranolol, shown as bradycardia and hypotension may occur, in which case propranolol should be withdrawn. If necessary, treatment for overdose should be started.

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions, they also may make patients less responsive to doses of adrenaline used to treat the allergic reactions.

Propranolol may mask the signs of thyrotoxicosis and hyperthyroidism.

Propranolol should not be used in untreated phaeochromocytoma (see section 4.3), but in patients with phaeochromocytoma, an alpha-blocker may be administered concomitantly.

Propranolol should not be used to treat the elderly with cautions and start on the lowest possible dose (see section 4.2).

Care must be taken in patients with renal or hepatic dysfunction when beginning treatment and choosing the initial dose.

Propranolol should be used with care in patients with decompensated cirrhosis.

In patients with portal hypertension, liver function may deteriorate. There have been reports that treatment with propranolol may increase the risk of developing hepatic encephalopathy.

Since the half-life may be increased in patients with a significant hepatic or renal impairment, cautions should be taken especially at the start of treatment and the initial dosage.

Propranolol, as with other beta-blocking drugs, may block the symptoms of hypoglycaemia (especially tachycardia). It may even cause 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. It has rarely caused seizures and/or coma in isolated patients. Caution should be exercised in the concurrent use of propranolol therapy in diabetic patients as it may prolong the hypoglycaemic response to insulin (see section 4.3).

Bronchospasm can usually be reversed by beta₂ agonist bronchodilators such as salbutamol. Large doses of the beta₂ agonist bronchodilators may be needed 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 ipratropium (given via a nebuliser) should 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 necessary in severe cases.

When a patient is going to have 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.

Withdrawal of the drug for any reason should be gradual over a period of 7 to 14 days.

Interference with laboratory tests:

Propranolol has been reported to interfere with the estimation of serum bilirubin using the diazo method and with the determination of catecholamines by methods when using fluorescence.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Patients with rare hypersensitivity for sulfur dioxide should not take this medicine as it may cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Caution must be exercised when co-prescribing a beta-adrenoceptor blocking drug with Class 1 anti-arrhythmic agents such as disopyramide, flecainide and amiodarone, as they may have potentiating effects on atrial-conduction time and induce negative inotropic effect.

Digitalis glycosides, in association with beta-blockers could increase the atrio-ventricular conduction time.

There is an increased risk of myocardial depression and bradycardia, there is also an increased risk of, lidocaine toxicity. The antiarrhythmic propafenone increases plasma concentration of propranolol.

Beta-adrenoceptor blocking drugs should be used with caution in combination with calcium channel blockers such as verapamil or diltiazem in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This could result in severe hypotension, bradycardia and cardiac failure. These should not be given intravenously within 48 hours of discontinuing either one or the other.

Use with nifedipine or other dihydropyridines may cause an increased risk of hypotension, and heart failure may occur in patients with undiscovered cardiac insufficiency.

Propranolol modifies the tachycardia of hypoglycaemia and care should be taken when treating diabetic patients with propranolol whether or not they are also taking hypoglycaemic agents. Propranolol may prolong the hypoglycaemic response to insulin.

Use of adrenaline (epinephrine) or other sympathomimetics with propranolol may counteract the effect of propranolol. Care should be taken in giving parenteral administration of adrenaline to (epinephrine) patients taking beta-blocking drugs as, rarely, vasoconstriction, hypertension and bradycardia may result.

Rebound hypertension which can follow after withdrawal of clonidine may be exacerbated by beta-blockers. Therefore, if the patient is transferring from clonidine to propranolol, the latter treatment should be started several days after clonidine has been stopped. If propranolol and clonidine are given together, clonidine should be discontinued several days after stopping treatment with propranolol.

Digitoxin or digoxin taken at the same time as beta-blockers can increase atrioventricular conduction time.

Ergotamine, dihydroergotamine or related compounds given with propranolol have resulted in reports of vasospastic reactions in some patients.

The hypotensive effects of propranolol may be decreased if the patient also takes prostaglandin synthetase inhibitors, e.g. ibuprofen or indomethacin.

If propranolol is taken with chlorpromazine, plasma levels of both agents may be increased, leading to enhanced antipsychotic and elevated antihypertensive effects.

Concomitant administration of rifampicin with propranolol may result in reduced plasma concentrations of propranolol. Thyroxine taken at the same time as propranolol also has this effect.

Cimetidine taken at the same time as propranolol will increase propranolol plasma levels. Fluvoxamine taken with propranolol also has this effect.

Alcohol enhances hypotensive effect, and may increase the plasma levels of propranolol.

Propranolol may affect lidocaine by increasing the plasma concentration of lidocaine by approximately a third and therefore this should be avoided.

Propranolol may increase plasma concentration of rizatriptan, hydralazine and imipramine when taken concomitantly.

Prazosin or other alpha-adrenoreceptor blockers may potentiate postural hypotension, tachycardia and palpitations.

Concomitant administration of moxonidine, diuretics, methyldopa, levodopa, Monoamine oxidase inhibitors (MAOIs) may result in enhanced hypotensive effect.

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

Caution must be exercised when using anaesthetic agents with propranolol. The anaesthetist should be informed and the choice of anaesthetic should be the 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.

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.

Pharmacokinetic studies have shown the following agents may interact with propranolol due to the effects on enzyme systems in the liver, which metabolise propranolol and the following agents: quinidine, propafenone, rifampicin, theophylline, warfarin, thioridazine, dihydropyridine, calcium channel blockers (e.g. nifedipine, nisoldipine, nicardipine, isradipine and lacidipine). Due 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 therapy with dihydropyridine calcium channel blockers).

4.6 Fertility, pregnancy and lactation

Pregnancy

Although there is no evidence that propranolol is teratogenic, propranolol should not be used in pregnancy unless absolutely necessary. Beta- blockers reduce placental perfusion which may result in intra-uterine foetal death, immature and premature deliveries. Bradycardia may occur in the foetus and there may be an increased risk of cardiac and pulmonary problems in the post-natal period. Hypoglycaemia or bradycardia may occur in the neonate.

Breast-feeding

Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast feeding is not recommended as beta-blockers taken by the mother will pass into the breast-milk.

4.7 Effects on ability to drive and use machines

Propranolol should not impair the ability to drive and use machines. However, sometimes dizziness or tiredness may occur. If so, the patient should not drive or operate machines.

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.

Very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ to $<1/1,000$); very rare ($<1/10,000$); Frequency not known (cannot be estimated from the available data).

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

Common (may affect up to 1 in 10 people)

General: Fatigue and/or lassitude (often transient).

Cardiovascular: Bradycardia, cold extremities, Raynaud's Phenomenon.

Psychiatric: Sleep disturbances, nightmares.

Uncommon (may affect up to 1 in 100 people)

Gastrointestinal: Nausea, vomiting, diarrhoea.

Rare (may affect up to 1 in 1,000 people)

General: Dizziness.

Blood: Thrombocytopenia.

Cardiovascular: Heart failure deterioration, precipitation of heart block, Postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication.

Psychiatric: Hallucinations, psychoses, mood changes,

Confusion, memory loss.

Skin: Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, rash.

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 (may affect up to 1 in 10,000 people)

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.

Not known (frequency cannot be estimated from the available data)

Blood: Agranulocytosis.

Metabolic: Changes in lipid metabolism (changes in blood concentrations of triglycerides and cholesterol)

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.

Psychiatric: Depression, confusion.

Nervous system: Headache, seizure linked to hypoglycaemia.

Eyes: Conjunctivitis.

Cardiovascular: Worsening of angina pectoris.

Respiratory: Dyspnoea.

Gastrointestinal: Constipation.

General: Dry mouth.

Musculoskeletal: Arthralgia.

Renal: Reduced renal blood flow and GFR.

Reproductive: Sexual dysfunction.

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 overdose 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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Propranolol is known to cause severe life-threatening 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 and 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 β_1 and β_2 -adrenoceptors, but has membrane stabilising activity at concentrations exceeding 1 to 3mg/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 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 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 β_1 -blockade 24 hours after dosing compared with conventional propranolol.

5.2 Pharmacokinetic properties

Absorption

Propranolol is almost completely absorbed from the gastrointestinal tract, but it is subject to considerable first-pass metabolism.

Distribution

Peak plasma concentrations occur 1-2 hours after dosing in fasting patients.

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%).

Biotransformation and Elimination

It is metabolised in the liver, the metabolites being excreted in the urine together with only small amounts of unchanged propranolol; at least one of its metabolites is considered to be biologically active.

The biological half-life of propranolol is longer than would be anticipated from its plasma half-life of about 3-6 hours.

5.3 Preclinical safety data

Propranolol is a drug where an extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in this SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Neutral microgranules (sucrose and maize starch)

Povidone

Ethylcellulose

Talc

Capsule Components:

Gelatin

Titanium Dioxide (E171)

Sulphur Dioxide (E220)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister packs:

PVC: Colourless 250 micron thickness.

Aluminium: 25 microns thickness.

28 capsules per pack, 14 capsules per blister strip.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Pharma GmbH
Manhagener Allee 36
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8 MARKETING AUTHORISATION NUMBER

PA22720/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 09th September 2009

10 DATE OF REVISION OF THE TEXT

June 2024