Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Half Beta-Prograne 80 mg Prolonged-Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Propranolol Hydrochloride 80 mg
Excipients - Contains Sucrose 3mg and Sulphur Dioxide (E220)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsules, hard.

Capsules with opaque white cap and colourless, transparent body containing white microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

For oral use. The capsule must not be chewed, but swallowed whole to ensure a prolonged release action.
Since the half-life may be increased in patients with significant hepatic or renal impairment, care should be taken when starting treatment and selecting the initial dose.

Adults
Hypertension:
The usual starting dose is one 160mg Beta-Prograne capsule daily, taken either morning or evening. An adequate response is seen in most patients at this dosage. If necessary, it can be increased in 80mg Half Beta-Prograne increments until adequate response is achieved.
A further reduction in blood pressure can be attained if a diuretic or other antihypertensive agent is given in addition to Half Beta-Prograne.

One Half-Beta-Prograne capsule 80mg daily is unlikely on its own to be sufficient to treat hypertension but it may be used as a starting dose in appropriate patients (e.g. the elderly) or to provide a convenient method of gradual dose alteration.

Angina, anxiety, essential tremor, thyrotoxicosis, propylaxis of migraine:
Adequate control is gained in most patients on one half Beta-Prograne 80mg capsule per day (either morning or evening). If necessary,the dose may be increased to one 160mg Beta-Prograne capsule per day and an additional Half Beta-Prograne increment may be given.

Patients who are already established on equivalent daily doses of Beta-Prograne capsules should be transferred to the equivalent doses of 80mg Half Beta-Prograne capsule or 160mg Beta-Prograne capsule taken either morning or evening.

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

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

Renal or hepatic impairment
Since the half-life may be increased in patients with significant hepatic or renal impairment, care should be taken when starting and selecting the initial dose.

Elderly Patients
Evidence concerning the relation between blood level and age is conflicting. With regard to the elderly, the optimum dose should be individually determined according to clinical response.

Children
Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules are not intended for use in children.

4.3 Contraindications

Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules must not be taken 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 inhalation 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 2mg given intravenously) has also been reported to produce a bronchodilator effect in asthmatic patients. Oxygen or artificial ventilation may be required in severe cases.

Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules, as with other beta-adrenoceptor blocking drugs, must not be used in patients with any of the following conditions:
- known hypersensitivity to the active substance or any of the excipients listed in section 6.1
- bradycardia
- cardiogenic shock
- hypotension
- metabolic acidosis
- after prolonged fasting
- severe peripheral arterial circulatory disturbances
- second or third degree heart block
- sick sinus syndrome
- untreated phaeochromocytoma
- uncontrolled heart failure or digitalis/diuretic refractory
- Prinzmetal's angina

Beta-prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules 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

Beta-Prograne 160mg Prolonged-Release Capsules or Half Beta-Prograne 80mg Prolonged-release Capsules as with other beta-adrenoceptor blocking drugs:

- Although contra-indicated 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 be used with caution in patients with controlled congestive cardiac failure. Evidence of development of the condition should be regarded as a signal to discontinue therapy.
- Patients with a family or personal history of asthma are at risk of suffering attacks of refractory asthma.
- The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic pressure with impairment of autoregulatory mechanisms.
- Although contra-indicated 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). Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules occasionally causes hypoglycaemia, even in non-diabetic patients, e.g., neonates, infants, children, elderly patients, patients on haemodialysis or patients suffering from chronic liver disease and patients suffering from overdose. Severe hypoglycaemia associated with Beta-Prograne 160mg Prolonged-release Capsules and Half-Beta-Prograne 80mg Prolonged-Release Capsules has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of Beta-Progane 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules and hypoglycaemic therapy in diabetic patients. Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules may prolong the hypoglycaemic response to insulin (see Section 4.3).
- 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 that may be attributable to a slow heart rate, the dose may be reduced.
- Should not be given to patients with uncontrolled or incipient cardiac decompensation.
- Should not be discontinued abruptly in patients suffering from ischaemic heart disease. Either the equivalent dosage of another beta-blocker may be substituted or the withdrawal of Beta-Prograne /Half- Beta-Prograne should be gradual. This can be achieved by first substituting the daily Beta-Prograne dose by the equivalent in Half- Beta-Prograne capsule and then gradually reducing the number of capsules.
- May cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

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.

Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules must be used with caution in patients with decompensated cirrhosis (see Section 4.2).
When this agent is administered to patients in renal failure, the interval between doses may need to be increased or the dosage reduced to avoid accumulation of drug.

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).

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 sulphur dioxide should not take this medicine; which may cause hypersensitivity reactions and bronchospasm.

Interference with laboratory tests:
Beta-Prograne 160mg Prolonged-release Capsules or Half Beta-Prograne 80mg Prolonged-Release Capsules have 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 Interaction with other medicinal products and other forms of interactions

If Beta-Prograne 160mg Prolonged-Release Capsule and Half Beta-Prograne 80mg Prolonged-Release Capsule is administered in conjunction with other antihypertensives an adjustment of dosage may be required.

Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules modify the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin (see Section 4.3 and 4.4).

Adjustment of dosage of hypoglycaemic agents may be necessary if Beta-Prograne 160mg Prolonged-Release Capsule is given to patients with uncontrolled or 'brittle' diabetes mellitus.

Beta-Prograne 160mg Prolonged-Release Capsules or Half Beta-Prograne 80mg Prolonged-Release Capsules should be used with great caution in patients who are receiving concomitant myocardial depressants such as chloroform, ether or related anaesthetics, antiarrhythmic agents such as quinidine, lidocaine, procainamide (which accentuate depressant effects).

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.

Caution must be exercised when prescribing a beta-adrenoceptor blocking drug with Class 1 antiarrhythmic agents such as disopyramide. 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-adrenoceptor blocking drugs, may increase atrio-ventricular conduction time.

Combined use of beta-adrenoceptor blocking drugs and calcium channel blockers with negative inotropic effects e.g. verapamil, diltiazem, can lead to an exaggeration of these effects, particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities.

This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-adrenoceptor blocking drug nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridine calcium channel blockers e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant use of sympathomimetic agents, e.g. adrenaline, may counteract the effect of beta-adrenoceptor blocking drugs. Caution must be exercised in the parenteral administration of preparations containing adrenaline to patients taking beta-

adrenoceptor blocking drugs as, in rare cases, vasoconstriction, hypertension and bradycardia may result. Care should also be taken with preparations such as isoprenaline and noradrenaline.

Adrenergic neurone blocking agents (such as guanethidine and reserpine), diuretics and other antihypertensive agents, including the vasodilator group will have an additive effect on the antihypertensive action of the drug.

Administration of Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules during infusion of lignocaine may increase the plasma concentration of lignocaine by approximately 30%. Patients already receiving propranolol tend to have higher lignocaine levels than controls. The combination should be avoided.

Concomitant use of cimetidine will increase plasma levels of propranolol, and concomitant use of alcohol may increase , the plasma levels of propranolol.

Beta-adrenoceptor blocking drugs may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-adrenoceptor blocking drug should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-adrenceptor blocking drug therapy, the introduction of beta-adrenoceptor blocking drugs 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, e.g. ibuprofen or indomethacin, 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 Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules. 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-adrenoceptor blocking drugs 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 therapy with dihydropyridine calcium channel blockers).

4.6 Fertility, pregnancy and lactation

Pregnancy:
As with all drugs, Beta- Prograne 160mg Prolonged- Release Capsules and Half Beta- Prograne 80mg Prolonged- Release Capsules should not be given during pregnancy unless their use is essential. There is no evidence of teratogenicity.

However beta-adrenoceptor blocking drugs 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-adrenoceptor blocking drugs 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

There are no studies on the effect of propranolol on the ability to drive. Use is unlikely to result in any impairment of the ability of patients to drive or operate machinery. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Beta-Prograne 160mg Prolonged-Release Capsules and Half Beta-Prograne 80mg Prolonged-Release Capsules are usually well tolerated. In clinical studiesthe adverse reactions reported are usually attributable to the pharmacological actions of propranolol.

The following possible undesired events, listed by frequency and 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: 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.

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 elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported (see Section 4.3, 4.4 and 4.5).

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-adrenoceptor blocking drug 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

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 to 2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1 to 10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 microgram/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect, could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Betablocking agents, non-selective
ATC Code: C07AA05
Propranolol is a competitive antagonist at both $beta_1$ 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-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-adrenoceptor blocking drugs, 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 $beta_1$-blockade 24 hours after dosing compared with conventional propranolol.

5.2 Pharmacokinetic properties

Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1-2 hours after dosing in fasting patients. Following oral dosing with the sustained release preparation of propranolol, the blood profile is flatter than after conventional Propranolol tablets but the half-life is increased to between 10 and 20 hours. The liver removes up to 90% of an oral dose with an elimination half-life of 3 to 6 hours. Propranolol is widely and rapidly distributed throughout the body with highest levels occurring in the lungs, liver, kidney, brain and heart. Propranolol is highly protein bound (80 to 95%).

5.3 Preclinical safety data

There is no evidence of teratogenicity with propranolol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Neutral microgranules (corn starch, sucrose).

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^{o}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
Mittelstrasse 5/5A
12529 Schonefeld
Germany

8 MARKETING AUTHORISATION NUMBER

PA22720/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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