SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Propranolol 160 mg Sustained Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 160 mg of propranolol hydrochloride .

Excipients with known effect: The capsule contains Neutral micograngnules (sugar-starch) and Sulfur Dioxide (E220)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sustained Release Capsule

White body/ white caps hard gelatine capsule, size 2 filled with white microgranules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Control of hypertension
- Management of angina
- Management of essential tremor
- Management of situational anxiety and generalised anxiety symptoms
- Adjunctive management of thyrotoxicosis
- Prophylaxis of migraine
- 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 usual starting dose is one Propranolol 160 mg Sustained-Release 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 80 mg increments until an adequate response is achieved (up to a maximum of 320 mg daily).

A further reduction in blood pressure can be attained if a diuretic or other antihypertensive agent is given in addition.

Angina, essential tremor, thyrotoxicosis, prophylaxis of migraine:
Adequate control is gained in most patients on one Propranolol 80 mg Capsule per day (either morning or evening). If necessary, further control may be gained by increasing the dose in 80 mg increments (one 80 mg Capsule) to a maximum of 240 mg per day, taken either morning or evening, which may be administered in the most convenient form using either Propranolol 160 mg or 80 mg Capsules.

Situational and generalised anxiety:
An 80 mg Capsule taken daily 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 individual cases, the dosage may be increased to one Propranolol 160 mg Capsule per day. Treatment should be continued according to patient's response. Patients should be reviewed after 6 to 12 months' treatment.

Portal Hypertension:
Since portal blood pressure cannot normally be monitored directly, dosage should be titrated to achieve approximately 25% reduction in resting heart rate. Dosing should begin with one Propranolol 80 mg Capsule daily, increasing to one 160 mg Capsule daily depending on heart rate response. Further 80 mg Capsule increments may be added up to a maximum dose of 320 mg once daily.

Patients who are already established on equivalent daily doses of Propranolol should be transferred to the equivalent doses of 80 mg or 160 mg Sustained-Release Capsules daily, taken either morning or evening.

Older People
Evidence concerning the relation between blood level and age is conflicting. Treatment should start with one Propranolol 80 mg Capsule once daily. The dose may be increased to one 160 mg Capsule daily or higher as appropriate.

Paediatric population
Propranolol 160 mg Sustained-Release Capsules and 80 mg Sustained-Release Capsules are not intended for use in children.

Method of administration
For oral administration.

4.3 Contraindications

Propranolol 160 mg and 80 mg Sustained-Release Capsules, as with other beta-adrenoceptor blocking drugs, must not be used in patients with any of the following conditions:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- history of bronchial asthma or bronchospasm
- bradycardia
- cardiogenic shock
- hypotension
- metabolic acidosis
- severe peripheral arterial circulatory disturbances
- second or third degree heart block
- sick sinus syndrome
- untreated phaechromocytoma
- uncontrolled heart failure
- Prinzmetal's angina
- Patients prone to hypoglycaemia i.e. patients after sustained fasting or patients with restricted counter-regulatory reserves.

4.4 Special warnings and precautions for use

Propranolol 160 mg or 80 mg Sustained-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.
- 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.
- 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 not the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.
- beta-blockers may increase the number and duration of anginal attacks in patients with Prinzmetal's angina, due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers, such as propranolol, should not be used in patients with Prinzmetal's angina and beta-1 selective agents should be used with care (see section 4.3).
- in patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta-blockers should be used with great caution as aggravation of these disorders may occur. 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). Propranolol 160 mg and 80 mg Sustained-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 Propranolol 160 mg and 80 mg Sustained-Release Capsules has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of Propranolol 160 mg and 80 mg

Sustained-Release Capsules and hypoglycaemic therapy in diabetic patients. Propranolol 160 mg and 80 mg Sustained-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 lowest possible dose (see section 4.2).
- will reduce heart rate as a result of its pharmacological action. In the rare instances, if the pulse rate decreases to below 50-55 beats per minute at rest, when a treated patient develops symptoms that may be attributable to a slow heart rate, the dose may be reduced.
- may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

Abrupt withdrawal of beta-blockers is to be avoided. The dosage should be withdrawn gradually over a period of 7 to 14 days. An equivalent dosage of another beta-blocker may be substituted during the withdrawal period to facilitate a reduction in dosage below Propranolol 80 mg Sustained-Release Capsules. Patients should be followed during withdrawal especially those with ischaemic heart disease.

Anaesthesia: As with all beta-adrenoceptor blocking drugs it may be decided to withdraw Propranolol before surgery. In this case 24-48 hours should be allowed to elapse between the last dose and anaesthesia. If treatment is continued care should be taken when using anaesthetic agents which cause myocardial depression such as cyclopropane and trichloroethylene, which are best avoided. Anaesthetics may cause attenuation of the reflex tachycardia and increase the risk of hypotension. Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking agent. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg I.V.).

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 160 mg and 80 mg Sustained-Release Capsules 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).

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.

Patients with a history of wheezing or asthma should not take propranolol unless it is considered essential. The product label states the following warning: “Do not take Propranolol 160 mg Sustained-Release Capsules if you have a history of asthma or wheezing”. 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.

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.

Interference with laboratory tests:
Propranolol 160 mg or 80 mg Sustained-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 interaction

Propranolol 160 mg and 80 mg Sustained-Release Capsules modify the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of Propranolol 160 mg and 80 mg Sustained-Release Capsules 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.

Caution must be exercised when prescribing a beta-adrenoceptor blocking drug with Class 1 antiarrhythmic agents such as disopyramide and amiodarone (may have potentiating effect on atrial-conduction time and induce negative inotropic effect).

Digitalis glycosides, e.g. digitoxin or digoxin taken at the same time as beta-blockers can increase atrioventricular conduction time.

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

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.

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 lignocaine levels than controls. The combination should be avoided.

Monoamine oxidase inhibitors, excepting MAO-B inhibitors.

Concomitant use of cimetidine and hydralazine will increase the plasma levels of propranolol. Fluvoxamine taken with propanol also has this effect. Concomitant use of alcohol may increase the plasma levels of propranolol and enhances hypotensive effect.

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 indometacin, may decrease the hypotensive effects of propranolol.

Tricyclic antidepressants, barbiturates, phenothiazines and other medicines used to reduce blood pressure - may increase the blood pressure-lowering effect 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.

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.

ACE inhibitors and Angiotensin-II Antagonists taken at the same time as propranolol may result in enhanced hypotensive effects. Aldesleukin and Alprostadil also has this effect.

Concomitant administration of corticosteroid may result in antagonism of hypotensive effect.

Beta blockers including propranolol when taken with moxisylyte may result in severe postural hypotension

Concomitant administration of muscle relaxants may result in enhanced hypotensive effect.
Oestrogen and progestrogens, as used in the contraceptive pill, when taken with propranolol may antagonise the hypotensive effect.

The manufacturer of tropisetron advises caution for the co-administration with propranolol.
The concomitant administration of xamoterol with propranolol may result in a reduction in the beta-blockade.

Parasympathomimetics when used with propranolol increase the possibility of arrhythmias.

Caution must be exercised when using anaesthetic agents with Propranolol 160 mg and 80 mg Sustained-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.

Interference with laboratory test:
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.

Pharmacodynamic 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 (increased risk of myocardial depression and bradycardia), 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 Pregnancy and lactation

Pregnancy
As with all drugs, Propranolol 160 mg and 80 mg Sustained-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.

Breastfeeding
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

The use of Propranolol 160 mg or 80 mg Sustained-Release Capsules is unlikely to result in any impairment of the ability of patients to drive or operate machinery.

However, when driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur. If so, the patient should not drive or operate machines.

4.8 Undesirable effects

Propranolol 160 mg and 80 mg Sustained-Release Capsules are usually well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of propranolol.

Adverse reactions frequency is defined using the following convention:
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).

Frequency / **Organ System**	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
General	Fatigue and/or lassitude (often transient)		Dizziness		
Cardiovascular	Bradycardia, cold extremities, Raynaud's phenomenon		Heart failure deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication		

CNS	Sleep disturbance, nightmares.		Hallucinations, psychoses, mood changes, confusion, memory loss		
GI		Gastrointestinal disturbance, such as nausea, vomiting, diarrhoea			
Blood			Thrombocytopaenia		
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		
Endocrine system					Hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported.

					Seizure linked to hypoglycaemia.
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	Headaches
Reproductive System & Breast Disorders					Impotence

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 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 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 and other Hypertensives

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 3mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta-adrenoceptor blockade has been demonstrated in man by a parallel shift to the right in the dose-heart rate response curve to beta-agonists such as isoprenaline.

Propranolol, as with other beta-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.

Propranolol reduces the myocardial oxygen requirement and protects the heart against ischaemia. It also helps to divert blood from the sub-epicardiac zones to the less well irrigated sub-endocardiac zones.

5.2 Pharmacokinetic properties

Sustained release form. The coating of the multiple microgranules provides a sustained release of the active principle, propranolol, and allows a 24 hours sustained action.

Propranolol is completely absorbed after oral administration. Following oral dosing with the sustained release preparation of propranolol, the blood profile is flatter than after conventional Propranolol. Peak blood level is reached after 5 hours for the controlled-release form. The apparent half-life of elimination is 3-6 hours. The liver removes up to 90% of an oral dose. 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%).

Propranolol crosses the placental barrier and is found in the blood of the umbilical cord (concentration: about 1.5 times that of the concentration in the maternal blood). The concentration in the mother’s milk is about half the concentration in the blood.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Neutral microgranules
Povidone
Ethylcellulose
Talc

Capsule Components
Gelatine
Titanium Dioxide
Sulfur Dioxide (E220)

6.2. Incompatibilities

None known.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25º C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

- Blister packs:

PVC: Colourless 250 micron thickness.

Aluminium: 32 microns thickness.

28 capsules per pack, 14 capsules per blister strip.

- Securitainer:

Polypropylene body, polyethylene cap with a tear strip closure.

100 capsules per pack.

Not all packs sizes and pack types may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
220 Butterfield
Great Marlings
Luton
LU2 8DL

8. MARKETING AUTHORISATION NUMBER

PL 11311/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 July 1991

10 DATE OF REVISION OF THE TEXT

02/10/2023