SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Propranolol Thame 5mg/5ml Oral Solution
Propranolol Thame 10mg/5ml Oral Solution
Propranolol Thame 40mg/5ml Oral Solution
Propranolol Thame 50mg/5ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral solution contains 5mg Propranolol hydrochloride.
Each 5ml of oral solution contains 10mg Propranolol hydrochloride.
Each 5ml of oral solution contains 40mg Propranolol hydrochloride.
Each 5ml of oral solution contains 50mg Propranolol hydrochloride.

Excipients with known effect:
Each 5ml of oral solution contains 0.002g methyl parahydroxybenzoate (E218), 6.3mg propylene glycol (E1520) and 2.25g liquid maltitol (E965).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution
Clear, colourless solution with orange flavour

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) the control of hypertension
b) the management of angina pectoris
c) long term management against re-infarction after recovery from acute myocardial infarction
d) the control of most forms of cardiac dysrhythmias
e) the prophylaxis of migraine
f) the management of essential tremor
g) relief of situational anxiety and generalised anxiety symptoms, particularly those of somatic type
h) prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices;
i) the adjunctive management of thyrotoxicosis and thyrotoxic crisis
j) management of hypertrophic obstructive cardiomyopathy
k) management of phaeochromocytoma peri-operatively (with an alphablocker).

4.2 Posology and method of administration

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 160 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 two or three 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.

Situational and generalised anxiety
A dose of 40mg daily may provide short term relief of acute situational anxiety. Generalised anxiety, requiring longer term therapy, usually responds adequately to 40mg twice daily which, in individual cases, may be increased to 40mg three times daily. Treatment should be continued according to response. Patients should be reviewed after 6 to 12 months treatment.

Arrhythmias, anxiety tachycardia, hypertrophic obstructive cardiomyopathy and thyrotoxicosis
A dosage range of 10 to 40mg three or four times a day usually achieves the required response.

Post myocardial infarction
Treatment should start between days 5 and 21 after myocardial infarction, with an initial dose of 40mg four times a day for 2 or 3 days. In order to improve compliance the total daily dosage may thereafter be given as 80mg twice a day.

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

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

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

Paediatric population

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

Migraine
Oral: Under the age of 12: 20 mg two or three times daily.
Over the age of 12: The adult dose.

Fallot's tetralogy
The value of Propranolol hydrochloride in this condition is confined mainly to the relief of right-ventricular outflow tract shut-down. It is also useful for treatment of associated dysrhythmias and angina. Dosage should be individually determined and the following is only a guide:
Oral: Up to 1 mg/kg repeated three or four times daily as required.

It is recommended to use the lower strength (5mg/5ml) of Propranolol Oral Solution when a lower dose (<5mg) is required.

Method of administration
For oral administration.

4.3 Contraindications

Hypersensitivity to the Propranolol hydrochloride or to any of the excipients listed in section 6.1.

Propranolol hydrochloride must not be used if there is a history of bronchial asthma or bronchospasm. The product label states the following warning: "Do not take Propranolol hydrochloride 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.

Propranolol hydrochloride as with other beta-blockers must not be used in patients with any of the following conditions: known hypersensitivity to the substance; 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 Prinzmetal's angina.

Propranolol hydrochloride 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 hydrochloride 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.
- 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 hydrochloride 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 hydrochloride has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of Propranolol hydrochloride and hypoglycaemic therapy in diabetic patients. Propranolol hydrochloride 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.
- 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. The dosage should be withdrawn gradually over a period of 7 to 14 days. 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 hydrochloride 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 hydrochloride 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.

Excipients Warning
This product contains:
Methyl parahydroxybenzoate (E218): May cause allergic reactions (possibly delayed)
Liquid Maltitol (E965): Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This product contains 6.3mg/5ml propylene glycol (E1520) as an ingredient necessary for the medicine to work properly. Co-administration with any substrate of alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

4.5 Interaction with other medicinal products and other forms of interaction

Propranolol hydrochloride modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of Propranolol hydrochloride and hypoglycaemic therapy in diabetic patients. Propranolol hydrochloride 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 Cmax 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 (e.g., 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, 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-blockers. Caution must be exercised in the parenteral administration of preparations containing adrenaline to patients taking betablockers as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

Administration of Propranolol hydrochloride during infusion of lidocaine may increase the plasma concentration of lidocaine by approximately 30%. Patients already receiving Propranolol hydrochloride 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 betablocker 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 hydrochloride 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 hydrochloride.

Concomitant administration of Propranolol hydrochloride 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 hydrochloride.

Caution must be exercised when using anaesthetic agents with Propranolol hydrochloride. 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Fertility
No relevant data on effect of fertility in humans is available.

4.7 Effects on ability to drive and use machines

Propranolol hydrochloride has no or negligible influence on the ability to drive and use machines. However it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Propranolol hydrochloride 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 (≥/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).

System Organ class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Rare	Thrombocytopaenia
Endocrine disorders	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, seizure linked to hypoglycaemia
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
Eye disorders	Rare	Dry eyes, visual disturbances
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
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome
Gastrointestinal disorders	Uncommon	Gastrointestinal disturbance, such as nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Rare	Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes
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 ADR Reporting at www.medicinesauthority.gov.mt/adrportal.

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.

ATC code: C07AA05

Propranolol hydrochloride 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 hydrochloride 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 hydrochloride 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 this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Citric acid monohydrate (E330)
Liquid maltitol (E965)
Orange flavour (containing propylene glycol (E1520))
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months
Discard 90 days after first opening

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bottle: Ph. Eur Type III Amber glass

Closure: Tamper evident, child resistant, plastic (Polypropylene/ Polyethylene) cap with EPE liner

Dosing device: 5ml oral syringe with 0.1ml graduation and 30ml cup with 5ml graduation with intermediate graduation at 2.5ml and 7.5ml for measuring and administering the dose and a bottle adaptor.

Pack size: 150ml

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Syri Pharma Limited t/a Thame Laboratories
Floor 0, 1 WML,
1 Windmill Lane,
Dublin 2, D02 F206, Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

MA1296/01901
MA1296/01902
MA1296/01903
MA1296/01904

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12th April 2019
Renewal 21st August 2022

10. DATE OF REVISION OF THE TEXT

April 2020