# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Propranolol Azure 40 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of propranolol hydrochloride.
Excipient(s) with known effect: Each tablet contains 140.03 mg of lactose, around 0.07 mg of sunset yellow FCF (E-110) and 0.02 mg of allura red AC (E-129).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink, round film-coated tablets scored on one side.
The tablet can be divided into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Treatment of renal and essential arterial hypertension.
- Treatment of angina pectoris.
- Long-term prophylaxis after recovery from acute myocardial infarction.
- Treatment of tachyarrhythmias.
- Migraine prophylaxis.
- Treatment of essential tremor.
- Treatment of peripheral symptoms of anxiety (tachycardia, tremor).
- Prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices.
- Coadjuvant treatment of thyrotoxicosis.
- Treatment of hypertrophic obstructive cardiomyopathy.
- Treatment of pheochromocytoma (in conjunction with an alpha-adrenergic blocker).

### 4.2 Posology and method of administration

As the half-life may be increased in patients with significant hepatic or renal insufficiency, caution should be exercised when starting treatment and the starting dose should be selected by adjusting the dosage to the degree of insufficiency.

Posology

***Adults***

*Hypertension:*

The initial dose is 80 mg of propranolol twice a day, which may be increased in weekly intervals according to the response. The usual dose range is 160-320 mg per day and the maximum daily dose should not exceed 640 mg per day (see Table 1). With the concomitant administration of a diuretic or other antihypertensive treatment, a greater reduction in blood pressure is obtained.

It is unlikely that a dose of 80 mg (one propranolol tablet 40 mg twice a day) is in itself sufficient to treat hypertension, but it can be used as an initial dose in certain patients (e.g., elderly patients) or to provide a suitable gradual dose modification method.

*Angina pectoris, peripheral symptoms of anxiety, migraine prophylaxis and essential tremor:*

The initial dose of 40 mg twice or three times a day may be increased in the same amount at weekly intervals, according to the patient's response. A suitable response is usually obtained to the peripheral symptoms of anxiety, migraine and essential tremor with a dose interval of 80-160 mg/day. The maximum daily dose of 240 mg for migraine prophylaxis and 480 mg for angina should not be exceeded (see Table 1).

*Treatment of tachyarrhythmia, tachycardia due to anxiety, obstructive hypertrophic cardiomyopathy and thyrotoxicosis:*

The required response is normally obtained with a dose interval of 10-40 mg three or four times a day. The maximum daily dose of 240 mg should not be exceeded for tachyarrhythmias, or 160 mg for the treatment of tachycardia due to anxiety, obstructive hypertrophic cardiomyopathy and thyrotoxicosis (see Table 1).

*Long-term prophylaxis after recovery of acute myocardial infarction:*

Treatment should be started between days 5 and 21 after the myocardial infarction, with a starting dose of 40 mg four times a day for 2 or 3 days. In order to increase treatment compliance by the patient, the total daily dose can then be administered as 80 mg twice a day (see Table 1).

*Prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and esophageal varices:*

The dose should be adjusted to approximately 25% reduction in heart rate at rest. The dose should be started with 40 mg twice daily, increasing the dose up to 80 mg twice daily depending on heart rate response. If necessary, the dose may be increased incrementally to a maximum of 160 mg twice a day (see Table 1).

*Pheochromocytoma:*

(Propranolol must only be used together with an effective alpha-adrenergic block)
Pre-operative: 60 mg per day for three days. Malignant cases that cannot be operated on: 30 mg daily (see Table 1).

**Table 1. Summary of doses of propranolol - Adults** (divided into daily doses)

| | **Min/day** | **Max/day** |
|---|---|---|
| Hypertension | 160 mg | 640 mg |
| Angina pectoris | 80 mg | 480 mg |
| Treatment of tachyarrhythmia | 30 mg | 240 mg |
| Migraine prophylaxis | 80 mg | 240 mg |
| Essential tremor | 40 mg | 160 mg |
| Peripheral anxiety symptoms | 80 mg | 160 mg |
| Tachycardia due to anxiety | 30 mg | 160 mg |
| Portal hypertension / esophageal varices | 80 mg | 320 mg |
| Thyrotoxicosis | 30 mg | 160 mg |
| Hypertrophic cardiomyopathy | 30 mg | 160 mg |
| Pheochromocytoma | 60 mg (pre-op)<br>30 mg (maintenance) | 60 mg<br>30 mg |
| Prophylaxis after acute myocardial infarction | 160 mg | 160 mg |

***Elderly patients***

The evidence relating to the relationship between plasma levels and age is unclear. Regarding elderly patients, optimal dose should be determined individually according to clinical response.

***Paediatric population***

*Arrhythmias*

The dose should be determined individually, with the information indicated below being merely for the purpose of guidance.
Children and adolescents: 0.25-0.5 mg/kg three or four times a day, adjusted according to response.
Up to 1 mg/kg four times a day, not exceeding a maximum total dose of 160 mg per day.

Method of administration

Propranolol tablets should be swallowed whole with liquid and should not be chewed.

**4.3 Contraindications**

- Hypersensitivity to propranolol, to other beta-blockers or to any of the excipients listed in section 6.1.
- Asthma or history of bronchospasm.
- Severe bradycardia.
- Cardiogenic shock.
- Hypotension.
- Metabolic acidosis.
- Severe peripheral arterial circulation disturbances (Raynaud's phenomenon).
- Second or third degree atrioventricular block.
- Disease of the sinus node (including sinoatrial block)
- Untreated pheochromocytoma.
- Heart failure not controlled by treatment
- Prinzmetal's angina.
- Patients proned to hypoglycemia, i.e., patients after prolonged fasting or patients with limited counter-regulatory reserves.

**4.4 Special warnings and precautions for use**

Like other beta-blockers, propranolol:

- 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, care should be taken if administered to patients with first-degree heart block.
- may block/modify the signs and symptoms of hypoglycemia (especially tachycardia). Occasionally propranolol causes hypoglycemia, even in non-diabetic patients (e.g., newborns, infants, children, elderly patients, patients undergoing hemodialysis or patients with chronic liver disease, as it affects catecholamine-induced glycogenolysis, and patients with overdose). Severe hypoglycaemia associated with Propranolol has rarely presented with seizures and/or coma in isolated patients. Caution should be exercised with the concomitant use of propranolol and hypoglycemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin (see section 4.3).
- may mask signs of thyrotoxicosis.
- should not be used in untreated phaeochromocytoma. However, in patients with phaeochromocytoma, an alpha-blocker may be given concomitantly.
- 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.
- will reduce heart rate due to its pharmacological action. In rare cases where a treated patient develops symptoms that may be attributable to low heart rate, the dose may be reduced.
- may cause a more serious reaction to a variety of allergens when administered patients with a history of anaphylactic reaction to such allergens. These patients may not respond to the usual doses of adrenaline used in the treatment of allergic reactions.
- may block/modify the signs and symptoms of the hypoglycaemia (especially tachycardia). Propranolol 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 has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of Propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin (see section 4.3).
- 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 48 hours prior to the procedure. The risk/benefit of stopping beta blockade should be made for each patient.

Since the half-life may be increased in patients with significant hepatic or renal impairment, caution must be exercised when starting treatment and selecting the initial dose.

Propranolol must be used with caution in patients with decompensated cirrhosis (see section 4.2). In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop. There have been reports suggesting that treatment with propranolol may increase the risk of developing hepatic encephalopathy (see section 4.2).

In patients with chronic obstructive pulmonary disease, non-selective beta blockers such as propranolol may aggravate the obstructive condition. Therefore propranolol should not be used in this condition (see section 4.3).

Bronchospasm can usually be reversed by beta2 agonist bronchodilators such as salbutamol. Large doses of the beta 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.

Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported in patients administered propranolol.

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.

Athletes should be informed that this medicine contains a component that can establish a positive result in doping controls.

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

This medicine may cause allergic reactions because it contains sunset yellow FCF (E-110) and allura red AC (E-129).

**4.5 Interaction with other medicinal products and other forms of interaction**

*Combination not recommended:*

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects (e.g., verapamil, diltiazem) can lead to an exaggeration of the negative AV conduction and sinus node function particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. This may result in severe hypotension and bradycardia. The combination with proproanolol should be avoided, especially in patients with cardiac decompensation.

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 beta-blockers as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

Administration of propranolol during infusion of lidocaine may increase the plasma concentration of lidocaine by approximately 30%. Patients already receiving Propranolol tend to have higher lidocaine levels than controls. The combination should be avoided.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta- blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta- blockers should be delayed for several days after clonidine administration has stopped.

In a study on diclofenac no such interaction could be detected. Data for COX-2 inhibitors are missing.

Beta-agonist bronchodilators:
Non-cardioselective beta-blockers oppose the bronchodilator effects of beta-agonist bronchodilators, propranolol is contraindicated in patients with asthma (see section 4.3).

Fingolimod:
Potentiation of bradycardia effects with possible fatal outcomes. Treatment with Fingolimod should not be initiated in patients receiving beta blockers. In case of combination, appropriate monitoring for treatment initiation, at least overnight monitoring is recommended.

Barbiturates:
The plasma levels and the effects of beta-blockers are reduced by the barbiturates. Barbiturates are potent liver enzyme inducers which may increase the metabolism of propranolol.

Propafenone:
Plasma propranolol levels can be raised up to 100% by propafenone. This probably was because propranolol is partially metabolized by the same enzyme like propafenone (CYP2D6). This combination is also not advisable because propafenone has negative inotropic effects.

Warfarin:
Propranolol may cause a reduction in clearance and an increase in plasma concentrations of warfarin.

MAO inhibitors:
Concomitant use of MAO inhibitors (except MAO-B inhibitors) with antihypertensive agents may diminish the antihypertensive effect and lead to hypertensive reactions.

Glycosides:
Digitalis glycosides, in association with beta-blockers, may increase atrio-ventricular conduction time.

*Combination to be used with caution, dose adjustment may be required*

Amiodarone:
A few case reports suggest that patients treated with amiodarone can have severe sinus bradycardia when treated concomitantly with propranolol. Amiodarone has an extremely long half-life (about 50 days), which means that interactions may occur long after discontinuation of therapy.

Class I antiarrhythmic drugs (disopyramide, quinidine):
Class I antiarrhythmic drugs and beta-blockers have additive negative inotropic effects which may result in hypotension and severe hemodynamic side effects in patients with impaired left ventricular function. This may result in hypotension and severe hemodynamic side effects in patients with impaired left ventricular function.

Non-steroidal anti-inflammatory / anti-rheumatic drugs (NSAIDs):
Anti-inflammatory drugs of NSAID-type counter the antihypertensive effect of beta-blockers. It has been studied mainly in indomethacin. In a study on diclofenac no such interaction could be detected. Data for COX-2 inhibitors are missing.

Anaesthetics:
Concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension (see section 4.4). As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anaesthesiologist should be informed when the patient is receiving beta-adrenergic antagonists. Anaesthetic agents causing myocardial depression are best avoided.

Epinephrine (adrenaline):
A number of reports are available for severe hypertension and bradycardia in patients treated with propranolol and epinephrine. These clinical observations have been confirmed by studies in healthy volunteers. It has also been suggested that the intravascular administration of epinephrine may trigger these reactions.

Fluvoxamine:
Fluvoxamine inhibits oxidative metabolism and increases plasma concentrations of propranolol. This may result in severe bradycardia.

Centrally-acting antihypertensives (clonidine, moxonidine, methyldopa):
Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".
If the two drugs are co administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Rifampicin:
The metabolism of propranolol may be increased by potent liver enzyme inducer rifampicin.

Alpha blockers:
Concomittant use with alpha blockers increases the risk of hypotension, especially orthostatic hypotension, and tachycardia and palpitations

Theophylline:
Propranolol reduces the metabolic clearance of theophylline by about 30% at a dosage of 120 mg / day and 50% at doses of 720 mg / day.

Insulin and oral antidiabetic drugs:
Concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia). Propranolol may prolong the hypoglycaemic response to insulin.

Tobacco:
Tobacco smoking can reduce the beneficial effects of the beta-blockers on heart rate and blood pressure.

Laboratory tests:
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.

**4.6 Fertility, pregnancy and lactation**

*Pregnancy*

Propranolol should not be administered during pregnancy unless its use is patently essential. There is no evidence of teratogenicity with this medicinal product. Preclinical teratogenic results have reported embryotoxic effects in animals. However, beta-blockers reduce placental perfusion, which can cause fetal intrauterine death, immaturity and premature births. In addition, certain adverse reactions may occur (especially hypoglycemia and bradycardia in the neonate and bradycardia in the fetus). There is a greater risk of cardiac and pulmonary complications in newborns during the post-natal period. Beta-blockers have been used in various indications (hyperthyroidism, pheochromocytoma, heart disease, hypertension), and it has been shown that they pass through the placenta. It is advisable not to use in the first trimester of pregnancy; use the lowest doses and preferably use beta-blockers with cardioselectivity, intrinsic sympathomimetic activity or alpha-blocker activity.

*Breast-feeding*

Most beta-blockers, particularly lipophilic, pass into breast milk, although at varying concentrations. Breast-feeding is therefore not recommended after the administration of these medicinal products.
Fertility: Although some reversible effects on male and female fertilities were rep orted in adult rats receiving high doses of propranolol in the literature, the study performed in juvenile animals did not show any effect on fertility (see section 5.3).

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

In clinical studies, the possible undesirable effects reported are generally attributed to pharmacological actions of propranolol. Adverse reactions related to propranolol are listed below by system organ class and frequency. Frequencies are defined as: 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); frequency not known (cannot be estimated from the available data).

The following possible undesirable effects, classified by frequency, have been reported:

| System Organ Class | Common | Uncommon | Rare | Very Rare | Not known |
|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | Thrombocytopaenia | | Agranulocytosis |
| **Immune system disorders** | | | Angioedema | | |
| **Metabolism and nutrition disorders** | | | | Hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported. Changes in lipid metabolism (changes in blood concentrations of triglycerides and cholesterol). Severe hypoglycemia may rarely lead to seizures or coma. | |
| **Psychiatric disorders** | Sleep disturbances, | | Hallucinations, psychoses, mood | | Depression |

| | | | | | |
|---|---|---|---|---|---|
| | nightmares | | changes | | |
| **Nervous system disorders** | | | Confusion, memory loss, paraesthesia, dizziness | Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported | Headache, seizure linked to hypoglycaemia |
| **Eye disorders** | | | Dry eyes, visual disturbances | | Conjunctivitis |
| **Ear and labyrinth disorders** | | | | | |
| **Cardiac disorders** | Bradycardia, cold extremities | | Heart failure deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope | | Worsening of attacks of angina pectoris |
| **Vascular disorders** | Raynaud's phenomenon | | Exacerbation of intermittent claudication | | |
| **Respiratory, thoracic and mediastinal disorders** | Breathlessness | | Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome | | Dyspnoea |
| **Gastrointestinal disorders** | | Gastrointestinal disturbance, such as nausea, vomiting, diarrhoea | | | Constipation, dry mouth |
| **Skin and subcutaneous tissue disorders** | | | Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes | Isolated cases of hyperhidrosis has been reported | |
| **Musculoskeletal and connective tissue disorders** | | | | | Arthralgia |
| **Renal and urinary disorders** | | | | | Reduced renal blood flow and GFR |
| **Reproductive system and breast disorders** | | | | | Impotence |
| **General disorders and administration site conditions** | Fatigue and/or lassitude (often transient) | | Dizziness | | |
| **Investigations** | | | An increase in ANA (Antinuclear Antibodies) has | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | been observed, however the clinical relevance of this is not clear | | |

Discontinuation of treatment should be considered if, in clinical judgment, the well-being of the patient is adversely affected by any of the aforementioned reactions. Discontinuation of beta-blocker therapy should be gradual. In the rare case of intolerance, manifested by bradycardia and hypotension, administration of the medicinal product should be discontinued and, if necessary, the treatment indicated in case of overdose will be established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows for continued monitoring of the benefit/risk balance of the medicinal product. Health professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

**4.9 Overdose**

**Toxicity:**
Individual response varies greatly, death in adults has followed ingestion of about 2 g, and ingestion of more than 40 mg may cause serious problems in children.
**Symptoms:**
**Cardiac** - Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. Conduction abnormalities such as first or second degree AV block may occur. Rarely arrhythmias may 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. The elderly 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, vomiting and occasionally CNS-mediated respiratory depression may occur. The concept of cardioselectivity is much less applicable in the overdose situation and systemic effects of beta-blockade include bronchospasm and cyanosis. Particularly in those with pre-existing airways disease. Hypoglycaemia and hypocalcaemia are rare and occasionally generalised spasm may also be present.

**Treatment:**
In cases of overdose or extreme falls in the heart rate or blood pressure, treatment with propranolol must be stopped. In addition to primary poison elimination measures, vital parameters must be monitored and corrected accordingly in intensive care. In case of cardiac arrest, the resuscitation of several hours may be indicated.
This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal (50 g for adults, 1 g/kg for children) if an adult presents within 1 hour of ingestion of more than a therapeutic dose or a child for any amount. Atropin should be administrated before gastric lavage, when required as there is a risk of vagal stimulation. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.
Excessive bradycardia may respond to large doses of atropine (3 mg intravenously for an adult and 0.04 mg/kg for a child) and/or a cardiac pacemaker.

For severe hypotension, heart failure or cardiogenic shock in adults a 5-10mg IV bolus of glucagon (50-150 micrograms/kg in a child) should be administered over 10 minutes to reduce the likelihood of vomiting, followed by an infusion of 1-5 mg/hour (50 micrograms/kg/hour), titrated to clinical response. If glucagon is not available or if there is severe bradycardia and hypotension, which is not improved by glucagon, the beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, dopamine or noradrenalin. In severe hypotension additional inotropic support may be necessary with a beta agonist such as dobutamine 2.5-40 micrograms/kg/min (adults and children). 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.

Nebulised salbutamol 2.5-5 mg should be given for bronchospasm. Intravenous aminophylline may be of benefit in severe cases (5 mg/kg over 30 mins followed by an infusion of 0.5-1 mg/kg/hour). Do not give the initial loading dose of 5 mg/kg if the patient is taking oral theophylline or aminophylline.

Cardiac pacing may also be effective at increasing heart rate but does not always correct hypotension secondary to myocardial depression.
In cases of generalised spasm, a slow intravenous dose of diazepam may be used (0.1-0.3 mg/kg body weight).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: beta blocking agents, non-selective
ATC code: C07AA05

Mechanism of action and pharmacodynamic effects
Propranolol is a competitive beta1- and beta2-adrenergic receptor antagonist (non-cardioselective beta-adrenergic block, with no intrinsic sympathomimetic activity and marked membrane stabilizing activity). Beta blockade confers negative chronotropic and inotropic activity, a fundamental basis for its principal pharmacological effects. It lacks beta-adrenergic receptor agonist activity, but has membrane stabilizing activity in concentrations that exceed 1-3 mg/liter, although such concentrations are rarely reached during oral therapy. Parallel displacement to the right has been observed on the dose-response curve of heart rate obtained with beta-agonists such as isoprenaline, showing competitive beta-adrenergic block in humans.

Like other beta-blockers, propranolol has negative inotropic effects and is therefore contraindicated in uncontrolled heart failure (see sections 4.3 and 4.4).
This medicinal product is a racemic mixture and the active form is the S(-) isomer of propranolol. With the exception of the inhibition of the conversion of thyrotoxin to triiodothyronine, it is unlikely to increase the different therapeutic effects due to an additional secondary property of R(+) propranolol, in comparison with the racemic mixture.

Propranolol is effective and well tolerated by most ethnic populations, although the response may be lower in black patients.

### 5.2 Pharmacokinetic properties

After intravenous administration, the plasma half-life of propranolol is approximately 2 hours and the ratio of metabolites with respect to the original blood medicinal product is lower than after oral administration. In particular, 4-hydroxypropranolol is not present after intravenous administration. Oral administration: Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1-2 hours after administration to patients on an empty stomach. Propranolol is widely distributed and rapidly distributed through the body, with the highest levels presenting in the lungs, liver, kidneys, brain and heart. Propranolol is highly bound to proteins (80-95%). Its bioavailability is low (around 36%) due to significant first-pass metabolism. It is metabolized in the liver, with the formation of active metabolites, and is then eliminated in urine. The liver eliminates up to 90% of an oral dose, with an elimination half-life of 3 to 6 hours.

Propranolol should be used with caution in patients with impaired hepatic or renal function. In general, the dose should be chosen with caution, usually starting with the lowest dose of the dosage interval. In patients with portal hypertension, liver function may be impaired and hepatic encephalopathy may develop. Some reports suggest that treatment with propranolol may increase the risk of developing hepatic encephalopathy.

### 5.3 Preclinical safety data

In animals, after an acute dosing, propranolol is considered as a moderately toxic drug with an oral LD50 of about 600 mg/kg. The main effects reported after repeated administration of propranolol in adult and juvenile rats were a transient decrease in body weight and body weight gain associated with a transient decrease in organ weight. These effects were completely reversible when treatment was discontinued.
In dietary administration studies in which mice and rats were treated with propranolol hydrochloride for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis.
Although some data were equivocal, based on the overall available *in vitro* and *in vivo* data, it can be concluded that propranolol is devoid of genotoxic potential.
In adult female rats, propranolol given into the uterus or by intravaginal administration is a powerful anti-implantation agent at dose ≥4 mg per animal, the effects being reversible. In adult male rats, repeated administration of propranolol at high dose levels (≥7.5 mg/kg) induced histopathological lesions of the testes, epididymis, and seminal vesicles, decrease in sperm motility, sperm cell concentration, plasma testosterone levels and significant increase in sperm head and tail abnormalities. The effects generally totally reversed after treatment cessation. Similar results were obtained following intra-testicular administration of propranolol and using in vitro models. However, in the study conducted in juvenile animals treated all over the development

period corresponding to infancy, childhood and adolescence, no effect on male and female fertilities was observed (See section 4.6).

The potential effects of propranolol on the development of juvenile rats were evaluated following daily oral administration from post-natal Day 4 (PND 4) to PND 21 at dose-levels of 0, 10, 20 or 40 mg/kg/day.

Mortality with unknown although unlikely relationship to treatment was observed at 40 mg/kg/day, leading to a NOAEL of 20 mg/kg/day for juvenile toxicity.

In terms of reproductive development, growth and neurological development there were no propranolol-related effects or toxicologically significant findings at 40 mg/kg/day, correlating to safety margins of 1.2 in females and 2.9 in males, based on mean propranolol exposures on PND 21.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Carmellose calcium
Gelatin
Lactose monohydrate
Magnesium stearate

Coating:
Opadry II pink 85F240137 (containing partially hydrolysed polyvinyl alcohol (E-1203), macrogol (E-1521), titanium dioxide (E-171), talc (E-553b), carmine (E-120), sunset yellow FCF (E-110) and allura red AC (E-129)).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

48 months.

### 6.4 Special precautions for storage

Do not store above 30ºC.

### 6.5 Nature and contents of container

Each pack contains 50 film-coated tablets, packed in PVC/PVDC/Aluminum blister packs.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Azure Pharmaceuticals Ltd
12 Hamilton Drive
The Rock Road
Blackrock
Co. Louth
A91 T997
Ireland

## 8 MARKETING AUTHORISATION NUMBER

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