SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Propranolol 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg Propranolol Hydrochloride
Also contains 78.97 mg lactose, for a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet
Pink, round, film-coated tablets with MP64 engraved on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Management of angina pectoris
Control of hypertension
Long-term prophylaxis against re-infarction after recovery from acute myocardial infarction
Management of essential tremor
Relief of situational anxiety and generalised anxiety symptoms, particularly those of somatic type
Control of most forms of cardiac dysrhythmias
Management of hypertrophic obstructive cardiomyopathy
Management of phaeochromocytoma peri-operatively (with an alpha-blocker)
Adjunctive management of thyrotoxicosis and thyrotoxic crises
Prophylaxis of migraine
Prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices

4.2 Posology and method of administration
The tablets should preferably be administered before meals.
Adults and children over 12 years:
Angina, migraine and essential tremor:
Initially 40mg two or three times daily, increasing by the same amount at weekly intervals according to response. An adequate response in migraine and essential tremor is usually seen in the range 80-160mg daily, and in angina 120-240mg daily.

Hypertension:
Initially 80mg twice daily, which may be increased at weekly intervals according to response. The usual dose range is 160-320mg/daily. With concurrent diuretic or other antihypertensive drugs a further reduction of blood pressure is obtained.

Arrhythmias, anxiety tachycardia, hypertrophic obstructive cardiomyopathy and thyrotoxicosis:
Most patients respond within the dosage range of 10-40mg three or four times daily.

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 six to twelve months' treatment.

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

Phaeochromocytoma (used only in conjunction with an alpha-receptor blocking drug):
Preoperatively; 60mg daily for three days is recommended.
Non-operable malignant cases, 30mg daily.

Portal Hypertension:
Dosage should be titrated to achieve approximately 25% reduction in resting heart rate. Dosing 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.

Children under 12 years:
Arrhythmias, phaeochromocytoma, thyrotoxicosis:
Dosage should be determined according to the cardiac status of the patient and the circumstances necessitating treatment. The doses given are intended only as a guide: 0.25-0.5mg/kg bodyweight three or four times daily as required.

Migraine:
20mg two or three times daily.

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

Elderly:
Evidence concerning the relationship between blood level and age is conflicting. The optimum dose should be individually determined according to clinical response.

Hepatic impairment
The bioavailability of propranolol may be increased in patients with hepatic impairment and dose adjustments may be required. In patients with severe liver disease (e.g. cirrhosis) a low initial dose is recommended (not exceeding 20mg three times a day) with close monitoring of the response to treatment (such as the effect on heart rate).

Renal impairment
Concentrations of propranolol may increase in patients with significant renal impairment and haemodialysis. Caution should be exercised when starting treatment and selecting the initial dose.

Route of administration: Oral

4.3 Contraindications

- Hypersensitivity to propranolol or to any of the excipients
- In the presence of 2nd and 3rd degree heart block
- Sick sinus syndrome
- Bradycardia (heart rate <45-50 beats/min)
- Cardiogenic shock
- Hypotension
- Untreated phaeochromocytoma
- Uncontrolled heart failure
- Severe peripheral circulatory disturbances
- Prinzmetal’s angina
- If there is a history of bronchospasm or bronchial asthma
- Chronic obstructive airways disease
- After prolonged fasting (i.e. hypoglycaemia)
- In metabolic acidosis (e.g. in diabetes)

Its use may lead to hypertensive crisis.
The text on the label for this product will carry this following warning: ‘Do not use if you have a history of wheezing or asthma.’

4.4 Special warnings and precautions for use
One of the pharmacological actions of propranolol is to reduce the heart rate; in the instance when symptoms may be attributable to slow heart rate, the dose may be reduced.
Special care should be taken with patients whose cardiac reserve is poor. Beta-adrenoceptor blocking drugs should be avoided in overt heart failure; however, they may be used in patients whose signs of failure have been controlled. Beta-blockers should only be given with caution to patients with first degree heart block.

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. Propranolol may mask the important signs of thyrotoxicosis and hyperthyroidism.

It is important that in patients with ischaemic heart disease treatment with a beta-blocking agent is not discontinued abruptly. Either the equivalent dosage of another beta-blocker may be substituted or the withdrawal of propranolol should be gradual.

Beta-blockers may induce bradycardia - reduction in dose may be necessary. Since the half-life may be increased in patients with liver and renal impairment, care should be taken when starting treatment and selecting the initial dose.

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

Liver function will deteriorate in patients with portal hypertension and hepatic encephalopathy may develop. There have been some reports suggesting that treatment with propranolol may increase the risk of developing hepatic encephalopathy.

Psoriasis may be aggravated by the use of beta adrenoreceptor blocking drugs. Patients with psoriasis should take beta-blockers only after careful consideration.

Beta-blockers may cause a more severe reaction to a variety of allergens when given to patients with a history of anaphylactic reactions to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions. Particular caution is necessarily, when beta adrenoceptor blocking drugs are used in patients with a history of anaphylaxis. Although contraindicated in patients with severe peripheral circulatory disturbances beta adrenoceptor blocking drugs may also aggravate less severe forms. Therefore, propranolol should be used with great caution in conditions such as Raynaud's disease/syndrome or intermittent claudication. Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported in patients administered propranolol. Beta adrenoreceptor blocking drugs should not be used in untreated phaeochromocytoma (see section 4.3); however, in patients with phaeochromocytoma an alpha-blocker may be given concomitantly.

Withdrawal

Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. In the rare event of intolerance, manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment for overdosage instituted. The sudden withdrawal of beta-receptor antagonists may result in severe exacerbation of angina pectoris, acute myocardial infarction, sudden death, malignant tachycardia, sweating, palpitation and tremor. Withdrawal should be accomplished over 10 to 14 days however caution must be exercised as this does not always prevent rebound effects.
Propranolol can cause an altered response to stress and therefore it may be necessary to withdraw the drug before surgery. When withdrawing a beta-blocker in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, although there may be an increased risk of hypertension. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs and the chosen anaesthetic should have as little negative inotropic activity as possible. The anaesthetist should always be informed about the use of a beta-blocking drug. The patient may be protected against vagal reactions by the intravenous administration of atropine. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction of beta-blocker therapy with the following drugs should be considered with the following risks:

- Anaesthetics: enhanced hypotensive effect; increased risk of bupivacaine toxicity. Care should be taken when using anaesthetic agents with propranolol. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible.

- Anti-arrhythmics: Caution must be exercised in co-prescribing beta-adrenoceptor blockers with Class I anti-arrhythmic agents such as disopyramide, quinidine, flecaainide and amiodarone may have potentiating effects on arterial conduction time and induce negative inotropic effect. 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.

- Combined use of beta-adrenoceptor blocking drugs and calcium channel blockers with negative inotropic effects e.g. verapamil, diltiazem can lead to prolongation of SA and AV conduction particularly in patients with impaired ventricular function or 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. Digitalis glycosides used in association with beta-adrenoceptor blockers may increase AV conduction time.

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

- Antidepressants; Fluvoxamine inhibits oxidative metabolism and increases plasma concentration of propranolol. This may result in severe bradycardia.

Propranolol may cause plasma concentrations of imipramine to increase. The hypotensive effect of beta-blockers may be enhanced by monamine-oxidase inhibitors.
• **Antihypertensives:** Beta-adrenoceptor blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the drugs are co-administered, the beta-adrenoceptor blocking drug should be withdrawn several days before discontinuing clonidine. If replacing clonidine with beta-adrenoceptor therapy the introduction of the beta-adrenoceptor blocking drug should be delayed for several days after clonidine administration has stopped. Concomitant use of moxonidine and beta blockers may result in an enhanced hypotensive effect. The steps for moxonidine withdrawal/introduction should be the same as for clonidine. Hypotensive effect may be enhanced when propranolol is taken with diuretics, methyldopa or levodopa.

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

• **Insulin and oral antidiabetic drugs:** Enhanced hypoglycaemic effect and masking of warning signs such as tremor. Propranolol modifies the tachycardia of hypoglycaemia; caution should therefore be exercised in the concomitant use of propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin.

• **Antimigraine drugs:** Caution is necessary if ergotamine, dihydroergotamine or related compounds are given in combination with propranolol since vasopastic reactions have been reported in a few patients. Propranolol inhibits the metabolism of rizatriptan which can significantly increases plasma concentration levels. A dose reduction to 5mg is recommended. Administration should be separated by 2 hours.

• **Chlorpromazine:** 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.

• **Cimetidine:** Concomitant use of cimetidine will increase plasma levels of propranolol

• **Hydralazine:** Concomitant use of hydralazine will increase plasma levels of propranolol.

• **Alcohol:** Concomitant use of alcohol will decrease plasma levels of propranolol

• **Adrenaline (epinephrine):** Care should be taken in the parenteral administration of preparations containing adrenaline (epinephrine) to patients taking beta-adrenoceptor blocking drugs as, in rare cases, vasoconstriction, severe hypertension and bradycardia may result

• **Dihydropyridine derivatives:** Increased risk of bradycardia and AV block.

• **Prostaglandin synthetase inhibiting drugs:** Hypotensive effect may be decreased.

• **Phenothiazines:** Enhanced hypotensive effect.

• **Barbiturates:** The metabolism of propranolol may be increased by potent liver enzyme inducer barbiturates.
- Sympathomimetic agents: Severe hypertension
- Non-steroidal anti-inflammatory drugs: NSAIDs notably indometacin, may cause an increase in blood pressure. This may be particularly significant in patients with poorly controlled hypertension.
- Rifampicin: The metabolism of propranolol may be increased by potent liver enzyme inducer rifampicin.
- Theophylline: Propranolol reduces the clearance and consequentially increases the plasma concentration of theophylline.
- Tobacco: Smoking tobacco may oppose the effects of beta blockers in the treatment of angina or hypotension. Patients should be encouraged to stop smoking, apart from its other toxic effects; it aggravates ocordial ischaemia, increases heart rate and can impair blood pressure control. If patient continues to smoke, dosage of the beta blocker may need to be increased or a cardio-selective beta blocker may be more appropriate.

*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:**
As with all other drugs, Propranolol should not be given in pregnancy unless its use is essential. There is no evidence of teratogenicity with propranolol. However, beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, 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 postnatal 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**
The use of propranolol is unlikely to result in any significant impairment of the ability of patients to drive or operate machinery. However, patients should be warned that the side effects of visual disturbances, hallucinations, mental confusion, dizziness, drowsiness, fatigue, bradycardia and hypotension may occur and they should not drive or operate machinery if they feel affected.

4.8 **Undesirable effects**
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 undesired events, listed by body system, have been reported:
Blood and lymphatic system disorders
Rare: Thrombocytopenia
Frequency not known: Agranulocytosis

Endocrine disorders
Frequency not known: Masking signs of thyrotoxicosis

Metabolic and nutritional disorders
Frequency not known: Changes in lipid metabolism (changes in blood concentrations of triglycerides and cholesterol)
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

Psychiatric disorders
Common: Sleep disturbances, nightmares.
Frequency not known: Depression, confusion

Nervous system disorders
Rare: Hallucinations, psychoses, mood changes, confusion, memory loss, dizziness, paraesthesia
Very rare: Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported
Frequency not known: Headache

Eye disorders
Rare: Visual disturbances, dry eyes
Frequency not known: Conjunctivitis

Cardiac disorders
Common: Bradycardia
Rare: Heart failure deterioration, precipitation of heart block, postural hypotension which may be associated with syncope
Frequency not known: Worsening of attacks of angina pectoris

Vascular disorders
Common: Cold extremities, Raynaud's syndrome
Rare: 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.
Frequency not known: Dyspnoea.

Gastrointestinal disorders
Uncommon: Diarrhoea, nausea, vomiting
Frequency not known: Constipation, dry mouth

**Skin and subcutaneous tissue disorders**

Rare: Alopecia, purpura, psoriasiform skin reactions, exacerbation of psoriasis, rash

**Musculoskeletal system and connective tissue disorders**

Frequency not known: Arthralgia

**Renal and urinary disorders**

Frequency not known: Reduced renal blood flow and GFR

**Reproductive system and breast disorders**

Frequency not known: Sexual dysfunction

**General disorders and administration site conditions**

Common: Fatigue and/or lassitude (often transient)

**Investigations:**

Very rare: An increase in ANA (antinuclear antibodies) has been observed with many beta blockers; 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 (see section 4.4). In the rare event of intolerance manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment for overdosage instituted (see section 4.9).

**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.

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**4.9 Overdose**

**Clinical features:**

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.

Management
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.
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. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.
Bradyarrhythmia may respond to large doses of atropine (3 mg intravenously for an adult and 0.04 mg/kg for a child).
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, isoprenaline at an infusion rate of 5-10 micrograms/minute (0.02 micrograms/kg/min in children increasing to a maximum of 0.5 micrograms/kg/min) and increased as necessary depending on clinical response.
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).
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
ATC Code: C07A A05
Propranolol hydrochloride is a beta-adrenoceptor blocking agent.
Mode of Action
Propranolol is a competitive antagonist at both beta-1, and beta2- adrenoceptor, but has membrane stabilising activity at concentrations exceeding 1-3mg/litre, though such concentrations are rarely achieved during oral therapy.

Competitive beta-blockade has been demonstrated in man by a parallel shift to the right in the dose-heart rate response curve to beta-agonists such as isoprenaline.

5.2 Pharmacokinetic properties
Propranolol is almost completely absorbed from the gastro-intestinal tract, but is subject to considerable first-pass metabolism. Peak plasma concentrations occur about 2 hours after a dose. It is metabolised in the liver, the metabolites being excreted in the urine together with only small amounts of unchanged propranolol; at least one of its metabolites is considered to be biologically active. The biological half-life of propranolol is longer than would be anticipated from its plasma half-life of about 3 to 6 hours. Propranolol crosses the placenta and traces are found in milk. It also crosses the blood-brain barrier. It is highly protein bound and not reported to be significantly dialysable.

5.3 Preclinical safety data
No relevant information additional to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Gelatin
Stearic acid
Magnesium stearate

Coating:
Ethylcellulose
Hypermellose
Diethyl phthalate
Opaspray K-1-5506 (titanium dioxide, hypermellose and carmine E120)
Beeswax yellow

6.2 Incompatibilities
Not applicable
6.3 Shelf life
36 months

6.4 Special precautions for storage
Containers: Do not store above 25°C. Keep the container tightly closed.
Strips: Do not store above 25°C. Store in the original package

6.5 Nature and contents of container
High density polystyrene containers with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane or polythene inserts.

Pack sizes: 50, 100, 250, 500 and 1000 tablets

250 micron PVC glass-clear/bluish rigid PVC (pharmaceutical grade). 25 micron hard-tempered aluminium foil strips coated on the dull side with 6-7 gsm heat seal lacquer and printed on the bright side.

Pack size: 28 tablets

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
Genethics Europe Limited
41 - 43 Klimentos
Klimentos Tower
Nicosia 1061
Cyprus

8 MARKETING AUTHORISATION NUMBER(S)
PL 42976/0058
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY:
13/03/2009

10 DATE OF REVISION OF THE TEXT:
30/08/2016