**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Propranolol 40 mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of propranolol hydrochloride. For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet
Dark pink, biconvex, film-coated tablets engraved Berk 2Z1 or 2Z1 on one side with a breakline on the reverse.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Propranolol is a competitive blocker of adrenergic β-receptor sites. It is used in the treatment of hypertension, angina pectoris, cardiac dysrhythmias, tachycardia, anxiety, essential tremor and for the long term prevention of sudden cardiac death in patients who have shown evidence of dysrhythmias during the acute phase of myocardial infarction. It may also be used as a prophylactic in migraine, and as adjunctive therapy in thyrotoxicosis.

### 4.2 Posology and method of administration

Posology
For oral administration.

Dosage requires individual adjustment. A heart rate of 55/minute or less is an indication that dosage should be increased no further.
Paediatric population

Dysrhythmias, thyrotoxicosis: the minimum effective dosage based on 0.25 - 0.5 mg/kg body weight three or four times daily.

Migraine: children under the age of 12 may be given 20 mg two or three times daily. Older children may be given adult dosage.

*Adults*

*Hypertension:* initially 80 mg twice daily, increased where necessary at weekly intervals. The usual maintenance dosage is 160 - 320 mg daily. Lower doses may be effective when a diuretic or other antihypertensive drug is given concurrently.

*Angina pectoris:* initially 40 mg twice or three times daily, increased by the same amount at weekly intervals. Control is usually achieved at a dose in the range 120 - 240 mg per day.

*Prophylaxis against recurrence of myocardial infarction:* for long term prevention of sudden cardiac death in patients who have survived the acute phase of myocardial infarction. Treatment should be commenced five to twenty one days after the infarction at a dose of 40 mg four times daily which should then be maintained for two or three days. Subsequently this dose may then be given as 80 mg twice per day to simplify compliance. As the over-riding principle is to maintain adequate beta-blockade the dose may need to be varied for some patients.

*Anxiety:* 40 mg daily may be used for immediate relief of acute situational anxiety. Longer term treatment for generalised anxiety should begin with 40 mg twice daily, which may be increased on an individual basis to 40 mg three times per day. Continued treatment should be determined by response. After six months to one year the patient should be reviewed.

*Migraine, essential tremor:* 40 mg twice or three times daily; increments at weekly intervals if needed to a daily total of 80 - 160 mg.

*Dysrhythmias, anxiety tachycardia, hypertrophic obstructive cardiomyopathy, thyrotoxicosis:*
10 - 40 mg three or four times daily.

*Elderly*

No specific dosage recommendations. However the optimum dose should be determined individually according to clinical response. In patients with impaired renal function a reduced dosage should be considered initially.

**4.3 Contra-indications**

History of bronchospasm or asthma. The label will state - Do not take this medicine if you have a history of wheezing or asthma.

Propranolol, in common with other beta-adrenoceptor blockers, is contraindicated in the following circumstances: prolonged fasting; metabolic acidosis; hypersensitivity; hypotension; severe peripheral arterial circulatory disturbance; cardiogenic shock; bradycardia; Prinzmetal's angina; uncontrolled heart failure; second or third degree heart block; untreated phaeochromocytoma; sick sinus syndrome.

**4.4 Special Warnings and special precautions for use**

Although propranolol is contra-indicated in uncontrolled heart failure, it may be used in patients whose signs of heart failure have been controlled. In patients whose cardiac reserve is poor, caution must be advised.

Particular care should be taken in the elderly and in other patients where renal or hepatic clearance may be reduced thus requiring an appropriate reduction in dosage. In cases of decompensated cirrhosis propranolol should be used with caution.

Propranolol should be withdrawn 24 hours before elective surgery, as it may interfere with response to stress. If this cannot be done, 1-2 mg atropine should be given intravenously before anaesthesia commences and anaesthetics such as ether, chloroform, cyclopropane and trichloroethylene, which may cause myocardial depression, should not be used.

Treatment with beta-blocking agents must not be stopped suddenly. If it is necessary to withdraw propranolol, this should be done gradually, or another beta-blocker should be substituted.

Bradycardia and hypotension are usually a sign of overdosage, but may rarely be due to intolerance of the drug. In the latter case propranolol should be withdrawn and, if necessary, the patient should be treated as for overdosage. Heart block and congestive heart failure have been reported due to propranolol.

There have been reports suggesting that treatment with propranolol may increase the risk of developing hepatic encephalopathy. In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop.

Propranolol, in common with other beta-adrenoceptor blocking drugs:-

- may exacerbate less severe peripheral arterial circulatory disturbances;
- if given to patients with first degree heart block, should be administered with caution (because of the negative effect on conduction time);
- may modify the tachycardia of hypoglycaemia;
- may conceal signs of thyrotoxicosis;
- reduces heart rate - where, rarely, symptoms attributable to this develop, dosage should be reduced.
- May potentiate reactions to a number of allergens. Where this occurs, and adrenaline is used as treatment, the patient may prove unresponsive to the normal dosage.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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

Treatment with propranolol modifies the tachycardia of hypoglycaemia. In diabetic patients the concurrent use of propranolol with hypoglycaemic therapy requires caution. The hypoglycaemic response to insulin may be prolonged by the use of propranolol.

Care is required when a beta-adrenoceptor blocker is used with a class 1 antiarrhythmic agent.

When a beta-adrenoceptor blocker is used in combination with a calcium channel blocker with negative inotropic effects, this can produce an enhancement of the effects, especially in patients with sino-atrial or atrio-ventricular conduction abnormalities, and/or impaired ventricular function. Severe hypotension, bradycardia and cardiac failure may result. Neither drug class should be administered i.v. within 48 hours of the other.

Simultaneous use with dihydropyridines increases the risk of hypotension in some patients. Where there is latent cardiac insufficiency, cardiac failure may occur.

Beta-adrenoceptor blockers may aggravate rebound hypertension resulting from withdrawal of clonidine. If the two are administered concomitantly, treatment with the beta-adrenoceptor blocker should cease several days before clonidine is withdrawn. If a beta-adrenoceptor blocker is replacing clonidine, a period of several days should be allowed to elapse between the two treatments.
Digitalis glycosides, when used in combination with beta-adrenoceptor blockers, may increase atrio-ventricular conduction time.

The effect of beta-adrenoceptor blockers may be counteracted by simultaneous use of sympathomimetics such as adrenaline. Caution is required when adrenaline containing preparations are parenterally administered to patients taking a beta-adrenoceptor blocker, as on rare occasions this may result in vasoconstriction, hypertension and bradycardia.

Where propranolol is administered during lidocaine infusion, the plasma concentration of lidocaine may be increased by up to 30%. Where a patient is already receiving propranolol prior to administration of lidocaine, serum lidocaine levels have tended to be higher than those found in controls. Combined use of the two drugs should be avoided.

If one of the ergotamine family of drugs is used in combination with a beta-adrenoceptor blocker caution is required, as vasospastic reactions have occasionally been reported.

Where prostaglandin synthetase inhibitors are used concomitantly, there may be a decrease in the hypotensive action of propranolol.

Where propranolol and chlorpromazine are used simultaneously there may be a resultant increase in plasma levels of both. An increase in the antipsychotic effect of the chlorpromazine and the antihypertensive effect of the propranolol may be observed.

Plasma levels of propranolol are increased by cimetidine or hydralazine, and reduced by alcohol.

It has been reported that propranolol interferes with laboratory tests for the estimation of serum bilirubin (diazo method) and determination of catecholamines (fluorescence methods).

Caution is advised when using anaesthetic agents with propranolol. The use of beta-adrenoceptor blocking drugs with anaesthetic drugs may result in reduction of reflex tachycardia and increase the risk of hypotension. The anaesthetist should be aware that the patient is taking propranolol and the anaesthetic should be one with as little negative inotropic activity as possible. Anaesthetic agents causing myocardial depression should be 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. Blood concentrations of either agent may be affected and dosage adjustments may be needed according to clinical judgement.

### 4.6 Fertility, Pregnancy and lactation

Although there is no evidence that propranolol is teratogenic, propranolol should not be used in pregnancy unless it is considered essential.

As a class beta-adrenoceptor blockers diminish placental perfusion, which may lead to foetal death, or immature or premature delivery. Other adverse effects may occur, especially bradycardia in the foetus, and bradycardia and hypoglycaemia in the neonate. In the neonate, the risk of cardiac and pulmonary complications in the post-natal period is increased.

Most beta-adrenoceptor blockers will, to some degree, pass into breast milk. Breast feeding is not recommended.

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

None likely. Fatigue or dizziness are possible effects of propranolol use.

### 4.8 Undesirable effects

Dry eyes and skin rash have been reported during treatment with β-adrenergic blocking agents. If these symptoms are not attributable to some other cause, propranolol should be withdrawn. Rarely hypotension and bradycardia are the result of intolerance, in which case propranolol should be discontinued, with treatment for overdose if required.

Propranolol may cause or precipitate Raynaud's phenomenon, intermittent claudication or peripheral arterial insufficiency. Bronchospasm may occur, particularly in patients with a history of asthma (sometimes with a fatal outcome) or hay fever.

There have been rare reports of blood dyscrasias during treatment propranolol.

Other effects that have been reported include: heart failure deterioration; heart block; postural hypotension, associated syncope; psychoses and hallucinations; nightmares; confusion; visual disturbances; mood changes; dizziness; thrombocytopenia, purpura; alopecia; aggravation of psoriasis or the production of psoriasiform skin reactions; paraesthesia. In addition to the above propranolol may produce an increase in antinuclear antibody (ANA) levels.

Hypoglycaemia in children may occur (frequency is not known), seizure linked to hypoglycaemia (frequency is not known).

Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.

Minor side effects include cold extremities, nausea, vomiting, diarrhoea, fatigue or insomnia. These are usually transient and are less common if the drug is introduced gradually.

Where it is considered necessary to cease treatment, propranolol should be withdrawn gradually.

<u>Reporting of suspected adverse reactions</u>

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.

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### 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

ATC Code: C07A A05 (beta blocking agents, non-selective).

Propranolol is a non-selective β-adrenergic blocking agent, blocking both β-1 and β-2 receptors competitively and not exhibiting any intrinsic agonistic properties. Propranolol decreases heart rate and cardiac output, prolongs mechanical systole and slightly decreases blood pressure in resting subjects. Its principal effect is to reduce the response of the heart to stress and exercise and to reduce blood pressure in patients with hypertension. In the treatment of hypertension, propranolol is often combined with a thiazide diuretic; propranolol does not produce postural hypotension and the full benefit of treatment may not be evident for 6 to 8 weeks.

### 5.2 Pharmacokinetic properties

Propranolol is almost completely absorbed from the gastrointestinal tract, but is subject to considerable hepatic tissue binding and first pass metabolism. Only about one third reaches the systemic circulation. Peak plasma concentrations occur 1 to 2 hours after a dose but levels vary greatly between individuals (up to 20 fold). The plasma half life is about 3 to 6 hours but the biological half life is longer. Chronic dosing causes a gradual increase in the half life as less drug is lost during the first circulation through the liver, due to the hepatic binding. Propranolol is 90 to 95% bound to plasma proteins and is excreted in the urine virtually completely metabolised.

### 5.3 Preclinical safety data

Preclinical information has not been included because the safety profile of propranolol has been established after many years of clinical use. Please refer to section 4.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

The tablets contain:
Maize starch
Lactose monohydrate
Starch pregelatinised
Sodium starch glycolate
Magnesium stearate (E572)
Silica Colloidal Anhydrous

The coating contains
Hypromellose (E464)
Macrogol
Erythrosine (E127)
Brilliant blue (E133)
Titanium dioxide (E171)
Iron oxide (E172)

The tablets are polished with carnauba wax.

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store in a dry place, at or below 25°C. Protect from light.

### 6.5 Nature and contents of container

Polypropylene containers or snap-secure containers with polyethylene lids or HDPE containers with LDPE lids or child resistant caps in pack sizes of 100, 500 and 1000 (shelf life 36 months).

Polythene buckets with polythene lid and polythene bag liner in pack sizes of 20000 (shelf life 36 months).

Amber glass bottles with plastic screw caps (shelf life 24 months) or HDPE containers with LDPE lids or child resistant caps (shelf life 36 months) in pack sizes of 10 x 50.

Blister strips in packs of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not applicable.

## 7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

## 8. MARKETING AUTHORISATION NUMBER

PL 00289/0169

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

14/05/02

## 10. DATE OF (PARTIAL) REVISION OF THE TEXT

21/12//2020

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