SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Propranolol 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg Propranolol Hydrochloride.
Excipients with known effect: Also contains Lactose 101.00 mg
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
Pink biconvex film coated tablets embossed with ‘2’ on one side and break line on the other side.
The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Angina pectoris.
- Hypertension.
- Long-term prophylaxis against myocardial reinfarction after recovery from acute myocardial infarction Hypertrophic obstructive cardiomyopathy.
- Essential tremor.
- Supraventricular cardiac arrhythmia.
- Ventricular cardiac arrythmias.
- Hyperthyroidism and thyrotoxicosis Phaeochromocytoma (with an alpha-blocker).
- Migraine.

- Prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices.

4.2 Posology and method of administration

Posology

Adults:

Angina pectoris:

The starting dose is 40 mg two to three times daily, increasing by the same amount at weekly intervals according to the response. The dose may be increased to120 - 240 mg daily.

Migraine:
The starting dose is 40 mg two to three times daily. The dose may be increased to 80mg -160 mg daily.

Essential tremor:

The starting dose is 40 mg two to three times daily. For these indications the dosage and the dose intervals should be adapted to individual patient needs.

Hypertension: Initially 40 mg two or three times daily, which may be increased by 80 mg per day at weekly intervals according to response. The usual dose range is 160-320 mg daily. With concurrent diuretic and/or peripheral vasodilators a further reduction of blood pressure is obtained.

Arrhythmias The starting dose is 10 mg to -40 mg two or three times a day.

Hypertrophic obstructive cardiomyopathy:

Most patients respond within the dosage range of 10-40mg three or four times daily.

Post myocardial infarction: Treatment should be initiated when myocardial infarction has been stabilized with an initial dose of 40 mg 2-3 times daily for two or three days. In order to improve compliance, the total daily dosage may thereafter be given as 80 mg twice a day.

Thyrotoxicosis:
Most patients respond within the dosage range of 10-40 mg three or four times daily.

Hyperthyroidism: The dose is adjusted according to clinical response.

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

Portal Hypertension: Dosage should be titrated to achieve approximately 25% reduction in heart rate at rest. Dosing should begin with 40 mg twice daily, increasing 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 daily.

Pediatric population:

Arrhythmias: Dosage should be determined according to the cardiac status of the patient and the circumstances necessitating treatment. The dose should be adjusted individually and the following is a guide: Children and adolescents: 0.25-0.5 mg/kg 3-4 times daily, adjusted according to clinical response.

Elderly:

Evidence concerning the relationship between blood level and age is conflicting. Propranolol 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.

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 20 mg 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.

As with other beta-adrenoceptor blocking agents, treatment should not be discontinued abruptly. The dosage should be withdrawn gradually over a period of 7 to 14 days. Either the equivalent dosage of another beta-adrenoceptor blocker may be substituted or the withdrawal of propranolol should be gradual. Patients should be followed during withdrawal especially those with ischaemic heart disease. The risk/benefit of stopping beta blockade should be made for each patient.

Method of administration:

The tablets should preferably be administered before meals.
For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Cardiac decompensation which is not adequately treated.
- Sick sinus syndrome/SA-block.
- History of bronchospasm or bronchial asthma, chronic obstructive pulmonary disease.
- Metabolic acidosis.
- Second and third-degree heart block.
- Patients prone to hypoglycaemia, e.g. due to prolonged fasting or restricted counter regulatory reserve.
- Cardiogenic shock.
- Untreated phaeochromocytoma.
- Severe bradycardia
- Severe hypotension
- Severe peripheral arterial disturbances
- Prinzmetal's angina

This warning will appear on the label: **DO NOT TAKE THIS MEDICINE IF YOU HAVE A HISTORY OF WHEEZING OR ASTHMA**.

4.4 Special warnings and precautions for use

Propranolol as with other beta-blockers:

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. Special care should be taken with patients whose cardiac reserve is poor.

Propranolol 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 circulatory disturbances, beta adrenoreceptor blocking drugs may also aggravate less severe forms.

AV block grade I: due to its negative effect on conduction time, caution must be exercised if propranolol is given to patients with first degree heart block. May block/modify the signs and symptoms of the hypoglycaemia (especially tachycardia). Propranolol may occasionally cause hypoglycemia even in non-diabetics, such as neonates, infants, children, elderly, patients on hemodialysis, patients with chronic liver disease, patients taking an overdose and prolonged fasting. Severe hypoglycaemia associated with propranolol has rarely presented with seizures and/or coma in isolated patients. Care must be taken in diabetic patients with concomitant hypoglycemic therapy. Propranolol may prolong the hypoglycaemic response to insulin Propranolol can cause prolonged hypoglycemic episodes in these patients (see section 4.3).

Propranolol may mask signs of thyrotoxicosis.

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.

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.

Propranolol may enhance an anaphylactic reaction. Beta adrenoceptor blocking drugs 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. Particular caution is necessarily, when beta adrenoceptor blocking drugs are used in patients with a history of anaphylaxis.

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. Therefore, propranolol should be used with great caution in conditions such as Raynaud's disease/syndrome or intermittent claudication.

Surgery: When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 48 hours. Patients should be followed during withdrawal especially those with ischaemic heart disease. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypotension may be increased as well. If treatment is continued, caution should be observed with the use of

certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine.

Severe hepatic or renal impairment: Since the half-life may be increased in patients with significant hepatic or renal impairment, care should be taken when starting treatment and selecting the initial dose.

Propranolol must be used with caution in patients with decompensated cirrhosis (see section 4.2). 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.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Combination not recommended

Calcium channel blockers (Verapamil, diltiazem or bepridil):
Calcium channel blockers and beta-blockers have additive effects on AV conduction and sinus node function and can cause bradycardia and hypotension. The combination with propranolol should be avoided, especially in patients with cardiac decompensation (see section 4.4).

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.

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.

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

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. Quinidine appears to increase propranolol plasma levels by inhibiting the CYP2D6, thereby reducing its clearance. Therefore dose of propranolol should be reduced at the initiation of treatment with quinidine.

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.

Cimetidine:
Cimetidine increases levels of propranolol in plasma, probably by inhibiting its first pass metabolism. There may be a risk of e.g. bradycardia with oral dosing.

Alcohol:
Concomitant use of alcohol may increase the plasma levels of propranolol

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

Dihydropyridine calcium channel blockers: e.g nifedipine
Concomitant use may increase the risk of hypotension, and cardiac failure may occur with latent cardiac insufficiency.

Chlorpromazine:
The concurrent use of chlorpromazine with propranolol can result in a marked rise in plasma levels of both drugs, and thereby enhance its effects on heart

rate and blood pressure as well as an enhanced antipsychotic effect for chlorpramazine and an increased antihypertensive effect for propranolol.

Lidocaine:

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.

Antimigraine drugs:
During concomitant treatment with propranolol it inhibited the first-pass metabolism of rizatriptan whose AUC increases by 70-80%. A dose of 5 mg of rizatriptan is recommended for combination therapy. Ergotamine with propranolol has resulted in reports of vasospastic reactions in some patients.

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

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

4.7 Effects on ability to drive and use machines

Regular medical follow up is required during treatment with this medicinal product. Because reactions differ between individuals the ability to react can be affected to such an extent that the ability to drive, operate machines or work without a secure footing is impaired. This effect is greater at the start of treatment, when the dose is increased, following a treatment switch and in conjunction with alcohol. It should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Summary of the safety profile
Side effects are mostly related to the pharmacological effect. Most common are fatigue, including muscle weakness reported in between 3-5%.
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 undesired events, listed by body system, have been reported:

Blood and lymphatic system disorders
Rare: thrombocytopenia,
Frequency not known: agranulocytosis

Immune system disorders
Rare: angioedema.

Endocrine disorders

Frequency not known: masking signs of thyrotoxicosis.

Metabolic and nutritional disorders
Very rare : 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
Common: Sleep disturbances, nightmares.
Rare: Hallucinations, psychoses, mood changes
Frequency not known: depression

Nervous system disorders
Rare: 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, seizure linked to hypoglycaemia

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
Common: breathlessness
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
Very rare: isolated cases of hyperhidrosis has been reported.

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: impotence

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 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 wellbeing 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 side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Toxicity:

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 the 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 (beta blocker)
ATC code: C07AA05
Propranolol is a competitive antagonist at both the beta1- and beta2 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 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 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, local tolerance, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Maize starch

Povidone

Sodium starch glycolate

Magnesium stearate

Hydroxypropylmethyl cellulose

Polyethylene glycol 400

Titanium dioxide (E171)

Opaspray M-1-1300B Pink

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack comprising of PVC/PVDC white opaque 250/40 gsm; Aluminium Foil 20 microns.

Blister pack comprising of PVC/PVDC white opaque 250/90 gsm; Aluminium Foil 20 microns.

Pack size of 28, 56 Tablets.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories
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8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0327

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation 3rd April 2002

Date of Renewal of Authorisation: 22 May 2008

10 DATE OF REVISION OF THE TEXT

09/04/2021