1. NAME OF THE MEDICINAL PRODUCT
Propranolol Rosemont 5mg/5ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Propranolol Hydrochloride 5mg/5ml.
For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Oral Solution
Clear colourless liquid with odour of orange/tangerine.

Clinical Particulars

4.1. Therapeutic Indications
Propranolol is indicated in:
- the control of hypertension
- the management of angina pectoris
- the long term prophylaxis against reinfarction after recovery from acute myocardial infarction
- the control of most forms of cardiac arrhythmia
- the prophylaxis of migraine
- the management of essential tremor
- relief of situational anxiety and generalised anxiety symptoms, particularly those of the somatic type.
- prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices.
- the adjunctive management of thyrotoxicosis and thyrotoxic crisis
- management of hypertrophic obstructive cardiomyopathy
- management of phaeochromocytoma perioperatively (with an alpha-adrenoceptor blocking drug).

4.2. Posology and method of administration

Posology

For oral administration only.

Adults:
Hypertension – A starting dose of 80mg twice a day may be increased at weekly intervals according to response. The usual dose range is 160–320mg per day. With concurrent diuretic or other antihypertensive drugs a further reduction of blood pressure is obtained.
Angina, migraine and essential tremor – A starting dose of 40mg two or three times daily may be increased by the same amount at weekly intervals according to patient response. An adequate response in migraine and essential tremor is usually seen in the range 80–160mg/day and in angina in the range 120–240mg/day.

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

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

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

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

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

Children
Arrhythmias, phaeochromocytoma, thyrotoxicosis – Dosage should be individually determined and the following is only a guide: 250 – 500 micrograms per kilogram three or four times daily as required.

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

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 and the following is only a guide: Up to 1mg/Kg repeated three or four times a day as required.

Elderly
With regard to the elderly the optimum dose should be individually determined according to the clinical response.

4.3 Contraindications

Propranolol must not be used if there is a history of bronchial asthma or bronchospasm. The product label states the following warning: “Do not take propranolol if you have a history of asthma or wheezing”. A similar warning appears in the patient information leaflet.

Bronchospasm can usually be reversed by beta2-agonist bronchodilators such as salbutamol. Large doses of the beta2-agonist bronchodilator may be required to overcome the beta-
blockade produced by propranolol and the dose should be titrated according to the clinical
response; both intravenous and inhalational administration should be considered. The use of
intravenous aminophylline and/or the use of ipratropium (given by nebuliser) may also be
considered. Glucagon (1 to 2mg given intravenously) has also been reported to produce a
bronchodilator effect in asthmatic patients. Oxygen or artificial ventilation may be required in
severe cases.

Propranolol as with other beta-adrenoceptor blocking drugs must not be used in patients with
any of the following:
hypersensitivity to propranolol hydrochloride or any of the ingredients; the presence of
second or third degree heart block; in cardiogenic shock; metabolic acidosis; after prolonged
fasting; bradycardia; hypotension; severe peripheral arterial circulatory disturbances; sick
sinus syndrome; untreated phaeochromocytoma; uncontrolled heart failure or Prinzmetal’s
angina.

Propranolol must not be used in patients prone to hypoglycaemia, i.e., patients after prolonged
fasting or patients with restricted counter-regulatory reserves. Patients with restricted counter-
regulatory reserves may have reduced autonomic and hormonal responses to hypoglycaemia
which includes glycogenolysis, gluconeogenesis and/or impaired modulation of insulin
secretion. Patients at risk for an inadequate response to hypoglycaemia includes individuals
with malnutrition, prolonged fasting, starvation, chronic liver disease, diabetes and
concomitant use of drugs which block the full response to catecholamines.

4.4 Special warnings and precautions for use

Although contra-indicated in uncontrolled heart failure, propranolol may be used where the
signs of heart failure have been controlled by the use of appropriate concomitant medication.
Propranolol should be used with caution in patients whose cardiac reserve is poor.

Treatment should not be discontinued abruptly in patients with ischaemic heart disease. Either
the equivalent dose of another beta-adrenoceptor blocking drug may be substituted or the
withdrawal of propranolol should be gradual.

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.

Propranolol may block/modify the signs and symptoms of 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).

When a patient is scheduled for surgery and a decision is made to discontinue betablocker
therapy, this should be done at least 24 hours prior to the procedure. The risk/benefit of
stopping beta blockade should be made for each patient.
Propranolol should not be used in untreated phaeochromocytoma. However, in patients with phaeochromocytoma, an alpha-blocker may be given concomitantly.

Although contra-indicated in severe peripheral arterial circulatory disturbances, propranolol may also aggravate less severe peripheral arterial circulatory disturbances.

One of the pharmacological actions of propranolol is to reduce the heart rate. Therefore the dosage should be reduced in those rare cases where symptoms are attributable to a slow heart rate.

Due to propranolol having a negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.

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.

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.

Propranolol 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.

Propranolol may mask the signs of thyrotoxicosis.

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

Propranolol should be used to treat the elderly with caution starting with a lower dose (see section 4.2)

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.

Excipient Warnings
This product contains para-hydroxybenzoates which may cause allergic reactions (possibly delayed).

This product also contains liquid maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

In addition, this product contains Sunset Yellow (E110) which may cause allergic reactions.

4.5. Interactions with other medicinal products and other forms of interaction

Hypoglycaemic agents: Tachycardia associated with hypoglycaemia may be modified by propranolol. Use of propranolol alongside hypoglycaemic therapy in diabetic patients should be with caution since it may prolong the hypoglycaemic response to insulin.

Clonidine: Caution should be exercised when transferring patients from clonidine to beta-adrenoceptor blocking drugs. If propranolol and clonidine are given concurrently, clonidine should not be discontinued until several days after the withdrawal of the beta blocker. If
replacing clonidine by beta-adrenoceptor blocking drug therapy, the introduction of the beta-
adrenoceptor blocking drugs should be delayed for several days after clonidine administration
has stopped.

*Anti-arrhythmics:* Class I anti-arrhythmic drugs (e.g. disopyramide and flecainide) may have
a potentiating effect on atrial-conduction time and induce negative inotropic effect.
Concomitant use with class III anti-arrhythmic drugs (e.g. amiodarone) increases the risk of
bradycardia, AV block and myocardial depression.

*Calcium Channel Blockers:* Combined use of beta-adrenoceptor blocking drugs and calcium
channel blockers with negative inotropic effects (e.g. verapamil, diltiazem) can lead to an
exaggeration of these effects particularly in patients with impaired ventricular function and/or
SA or AV conduction abnormalities. This may result in severe hypotension, bradycardia and
cardiac failure. Neither drug should be administered intravenously within 48 hours of
discontinuing the other.

*Dihydropyridines:* Concomitant therapy with dihydropyridines e.g. nifedipine, may increase
the risk of hypotension, and cardiac failure may occur in patients with latent cardiac
insufficiency.

*Digitalis Glycosides:* These preparations in association with beta-adrenoceptor blocking drugs
may increase atrio-ventricular conduction time.

*Drugs with hypotensive effects:* Dynamic interactions between propranolol and other drugs
with hypotensive effects are to be expected. Reactions are sometimes severe and careful
monitoring is advised in co-administration of propranolol with other drugs including ACE
inhibitors, diuretics, angiotensin II receptor antagonists, vasodilator antihypertensives,
diazoxide, adrenergic neurone blockers, alpha blockers, moxisylyte, moxonidine, nitrates and
methyldopa.

*Anaesthesia:* Caution must be exercised 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. Use of beta-adrenoceptor blocking drugs with
anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of
hypotension. Anaesthetic agents causing myocardial depression are best avoided.

*Lidocaine / Bupivacaine:* 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. There is an increased risk of bupivacaine toxicity when used with
propranolol.

*Neostigmine and other anticholinesterases:* Propranolol reduces the efficacy of these
compounds in treatment of myasthenia gravis.

*Sympathomimetic Agents and Parenteral Adrenaline:* Concomitant use of sympathomimetic
agents e.g. adrenaline and dobutamine, may counteract the effect of beta-adrenoceptor
blocking drugs. Caution should be taken in the parenteral administration of preparations
containing adrenaline to people taking beta-adrenoceptor blocking drugs as, in rare cases,
vasoconstriction, hypertension and bradycardia may result.

*Muscle relaxants (e.g. baclofen):* Concomitant use may result in a fall in blood pressure.
Tizanidine may also result in bradycardia.
**Antidepressants, anxiolytics and hypnotics:** Plasma levels of propranolol can be increased by fluvoxamine. Anxiolytics, hypnotics and MAOIs when given with propranolol may have an enhanced hypotensive effect. Propranolol may increase plasma concentration of imipramine. Barbiturates may reduce the plasma concentration of propranolol.

**Chlorpromazine:** Concomitant administration with propranolol 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.

**Corticosteroids:** Can antagonise the effects of beta-blockers.

**Ergotamine:** Caution should be exercised if ergotamine, dihydroergotamine or related compounds are given in combination with propranolol since vasospastic reactions have been reported in a few patients.

**Prostaglandin Synthetase Inhibiting Drugs:** Concomitant use of these e.g. ibuprofen or indomethacin, may decrease the hypotensive effects of propranolol.

**Mefloquine:** May lead to an increased risk of bradycardia.

**Cimetidine, hydralazine:** Concomitant use of cimetidine and hydralazine will increase the plasma level of propranolol.

**Alcohol (ethanol):** Concomitantly administered with alcohol may increase plasma propranolol levels (by enzyme inhibition), whereas chronic use of alcohol may lower propranolol levels (by enzyme induction). Alcohol can have variable effects on the hypotensive action of propranolol.

**Dopaminergics (e.g. Levodopa), Aldesleukin, Prostaglandins (alprostadil):** May have an enhanced hypotensive effect when used concomitantly with propranolol.

**Oestrogens:** May antagonise the hypotensive effect of propranolol.

**5HT1 agonists:** Propranolol may increase plasma concentrations of rizatriptan.

Pharmacokinetic studies have shown that the following agents may interact with propranolol due to effects on enzyme systems in the liver which metabolise propranolol and these agents: quinidine, propafenone, rifampicin, theophylline, warfarin, thioridazine and dihydropyridine calcium channel blockers such as nifedipine, nisoldipine, nicardipine, isradipine and lacidipine. Owing to the fact that blood concentrations of either agent may be affected, dosage adjustments may be needed according to clinical judgement. (See also the interaction above concerning the concomitant therapy with dihydropyridine calcium channel blockers).

### 4.6 Pregnancy and Lactation

As with all drugs, propranolol should not be given in pregnancy unless absolutely essential. There is no evidence of teratogenicity with propranolol. However, beta adrenoceptor blocking agents reduce placenta perfusion, which may result in intrauterine 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.
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

Use is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

### 4.8. Undesirable Effects

Propranolol is usually well tolerated, however, listed below are the side effects that may occur:

<table>
<thead>
<tr>
<th>System</th>
<th>Common ≥1/100 to &lt;1/10</th>
<th>Uncommon ≥1/1,000 to &lt;1/100</th>
<th>Rare ≥1/10,000 to &lt;1/1,000</th>
<th>Very Rare &lt;1/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders:</td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td></td>
<td></td>
<td>Hypoglycaemia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders:</td>
<td>Sleep disturbances,</td>
<td>Confusion,</td>
<td>Seizures have been linked to</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nightmares,</td>
<td>Mood changes,</td>
<td>hypoglycaemia [Hypoglycaemic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>Psychoses,</td>
<td>seizure], Isolated reports</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hallucinations</td>
<td>of myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders:</td>
<td></td>
<td>Dizziness,</td>
<td>have been reported in</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Memory loss,</td>
<td>patients administered</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paraesthesia especially of</td>
<td>propranolol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>the hands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders:</td>
<td></td>
<td>Dry eyes,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual disturbances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders:</td>
<td>Bradycardia</td>
<td>Heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>deterioration,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart block,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congestive cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders:</td>
<td>Cold extremities,</td>
<td>Exacerbation of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raynaud's phenomenon</td>
<td>claudication, Postural</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypotension which</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
may be associated with syncope

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders:</th>
<th>Bronchospasm (especially in patients with a history of asthma) sometimes with a fatal outcome (see Section 4.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders:</td>
<td>Gastrointestinal disturbance, Nausea, Vomiting, Diarrhoea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders:</td>
<td>Purpura, Alopecia, Psoriasiform skin reactions, Exacerbation of psoriasis, Skin rashes</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders:</td>
<td>Muscle fatigue</td>
</tr>
<tr>
<td>General disorders and administration site conditions:</td>
<td>Lassitude</td>
</tr>
<tr>
<td>Investigations:</td>
<td>An increase in ANA (antinuclear antibodies) although the clinical relevance of this has not been established.</td>
</tr>
</tbody>
</table>

If these effects occur, thought should be given to withdrawing the drug. However, it should be withdrawn gradually.

Bradycardia and hypotension are usually a sign of overdosage but may be rarely linked to intolerance. If this occurs the drug should be withdrawn and overdosage treatment initiated.

4.9. Overdose

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1-2mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon.
10mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/Kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Propranolol is a competitive antagonist at both beta1 and beta2-adrenoceptors.

It has no agonist activity at the beta-adrenoceptor, but has membrane stabilising activity at concentrations exceeding 1-3mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta-adrenoceptor 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-adrenoceptor blocking drugs, has negative inotropic effects, and is therefore contra-indicated in uncontrolled heart failure.

Propranolol is a racemic mixture and the active form is the S(-) isomer. 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 1-2 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 (80-95%).

5.3. Preclinical Safety Data

Propranolol is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (E330), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), propylene glycol (E1520), liquid maltitol (E965), orange/tangerine flavour (including ethanol (0.12%v/v) and butylhydroxyanisol (E320)) and purified water.

6.2 Incompatibilities

None known.

6.3 Shelf Life

24 months unopened
3 months opened.

6.4 Special Precautions for Storage

Do not store above 25°C. Do not refrigerate or freeze.

6.5 Nature and Contents of Container

Bottle: Amber (Type III) glass bottles
Closure: HDPE, EPE wadded, tamper evident, child resistant closure.
Pack Size: 150ml

6.6. Instruction for Use/Handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Rosemont Pharmaceuticals Ltd.
Rosemont House,
Yorkdale Industrial Park,
Braithwaite Street,
Leeds,
LS11 9XE,
United Kingdom.

8. Marketing Authorisation Number

PL 00427/0122

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th December 2000,
Date of renewal 30th August 2006

10 DATE OF REVISION OF THE TEXT

26/02/2016