AUSTRALIAN PRODUCT INFORMATION – APO- PROPRANOLOL (PROPRANOLOL HYDROCHLORIDE)

1 NAME OF THE MEDICINE

Propranolol hydrochloride.

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Each tablet contains propranolol hydrochloride as the active ingredient. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, maize starch, sunset yellow FCF aluminium lake, quinoline yellow, povidone, sodium starch glycollate, magnesium stearate and brilliant blue FCF aluminium lake (40 mg only).

Excipients with known effect

Lactose monohydrate

10 mg tablets

Each tablet contains 10 mg of propranolol hydrochloride.

Orange coloured, round, biconvex tablets, embossed with "P" and "10" on either side of the breakline on one side and plain on the other side.

40 mg tablets

Each tablet contains 40 mg of propranolol hydrochloride.

Green coloured, round, biconvex tablets, embossed with "P" and "40" on either side of the breakline on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Angina pectoris
- Hypertension
- Prevention of migraine
- Cardiac dysrhythmias: certain intrinsic cardiac dysrhythmias; dysrhythmias associated with thyrotoxicosis; anxiety tachycardia; certain drug-induced dysrhythmias (e.g. tachycardia due to digitalis or adrenaline overdosage)
- Essential tremor, including familial and senile tremor
- Phaeochromocytoma (only with concurrent α-receptor blockade)
- Hypertrophic subaortic stenosis
- Suspected or definite myocardial infarction
- Fallot’s tetralogy

4.2 DOSE AND METHOD OF ADMINISTRATION

NOTE: Tablets may be taken before or after food.

Adult

Hypertension

The standard starting dose is 40 mg twice daily, increasing by the same amount at weekly intervals according to patient response. An adequate response is usually seen in the range 120–320 mg/day. Although higher doses may be required, and have been used, the value and safety of doses exceeding 320 mg/day have not been established.

Angina pectoris and essential tremor

40 mg two or three times daily, increasing by the same amount at weekly intervals according to patient response. An adequate response in essential tremor is usually seen in the range 80–160 mg/day and in angina 120–320 mg/day.

Migraine

The standard starting dose is 40 mg twice daily. If a response occurs, this is usually in the range 80–160 mg/day and should be evident within three months.

Cardiac dysrhythmias, anxiety tachycardia, dysrhythmias associated with thyrotoxicosis and hypertrophic subaortic stenosis

Most patients respond within the dosage range of 10–40 mg three or four times a day.

Phaeochromocytoma

The patient must always receive concurrent alpha-receptor blockade.

Preoperative: 60 mg/day propranolol in divided doses for three days.

Maintenance: 30 mg/day propranolol in divided doses.

Myocardial infarction

Treatment should start with 40 mg four times a day for 2 or 3 days. In order to improve compliance, the total daily dosage may then be given as 80 mg twice a day.

Paediatric

The dose of propranolol should always be determined according to the cardiac status of the patient and the circumstances necessitating treatment. The doses given below are intended only as a guide:

Cardiac dysrhythmias, phaeochromocytoma, thyrotoxicosis

0.25–0.5 mg/kg three or four times daily as required.

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 dysrhythmias and

angina. Dosage should be individually determined according to circumstances and the following is only a guide:

Up to 1 mg/kg repeated 3 or 4 times daily as required.

Migraine

Commence with 10 mg once or twice daily and increase as required up to 2 mg/kg bodyweight/day in divided doses. If a response is to occur it should be evident in three months. There is no experience in children under the age of seven years.

NOTE: With both children and adults in the treatment of migraine, if the attack frequency is reduced significantly, consideration may be given to gradually ceasing therapy as remission may be sustained in a proportion of patients.

Elderly

Evidence concerning the relation between blood levels and age is conflicting. With regard to the elderly, the optimum dose should be individually determined according to clinical response.

4.3 CONTRAINDICATIONS

Cardiovascular:

- Congestive heart failure
- Right ventricular failure secondary to pulmonary hypertension
- Significant right ventricular hypertrophy
- Sick sinus syndrome
- Sinus bradycardia (less than 45 to 50 beats/minute)
- Second and third degree A-V block
- Hypotension
- Severe peripheral arterial circulatory disturbances
- Prinzmetal's angina

Hypoglycaemia, prolonged fasting and metabolic acidosis

Propranolol must not be used in patients prone to hypoglycaemia, i.e. patients after prolonged fasting or patients with restricted counter regulatory reserves (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.8 Adverse Effects (Undesirable Effects)**).

In metabolic acidosis (e.g. in diabetes), the premonitory signs of hypoglycaemia may be masked in patients receiving hypoglycaemic agents.

Asthma/bronchospasm

β-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airways resistance. These drugs also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients.

Therefore β-blockers are contraindicated in any patient with a history of bronchial asthma, airways obstruction or a tendency to bronchospasm. Use of cardioselective β-blockers can also result in severe bronchospasm. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.

Other

- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to asthma or bronchospasm
- Shock (including cardiogenic and hypovolaemic shock)
- Hypersensitivity to the drug
- Anaesthesia with agents that produce myocardial depression (e.g. ether, chloroform)
- Untreated phaeochromocytoma

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Asthma/bronchospasm

β-adrenergic blockade of the smooth muscle of bronchi and bronchioles results in an increased airways resistance. This may be dangerous in susceptible patients and associated sometimes with a fatal outcome (see **Section 4.3 Contraindications**).

Cardiac failure

β-blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency or unsuspected cardiomyopathy as may occur in chronic alcoholism. In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If signs of cardiac failure present, the patients should be fully digitalised and/or given an ACE inhibitor or vasodilators with or without a diuretic and carefully monitored. If cardiac failure persists, the β-blocker should be withdrawn (see **Section 4.4 Special Warnings and Precautions for Use - Abrupt withdrawal of therapy**).

NOTE: Although congestive heart failure has been considered to be a contraindication to the use of β-blockers, there is a growing literature on the experimental use of β-adrenergic blocking drugs in heart failure. As further trials are needed to identify which patients are most likely to respond to which drugs β-blockers should not normally be prescribed for heart failure outside of specialist centres.

Abrupt withdrawal of therapy

Care should be taken if β-blockers have to be discontinued abruptly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of β-blockade in patients with ischaemic heart disease. Therefore, it is recommended that the dosage be reduced gradually over a period of about 8–14 days during which time the patient's progress should be assessed. The drug may be reinstituted temporarily if the angina worsens. If the drug must be withdrawn abruptly, close observation is required. In the peri-operative period, β-blockers should not be withdrawn, unless indicated.

Patients with angina should be warned against abrupt withdrawal of the drug and the need to ensure that supplies do not run out.

Concomitant therapy with calcium antagonists

The concomitant use of β-blockers and calcium antagonists with myocardial depressant and sinus node activity (e.g. verapamil, and to a lesser extent, diltiazem) may cause hypotension, bradycardia and asystole, particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. Extreme caution is required if these drugs have to be used together.

The dihydropyridine calcium antagonists (e.g. nifedipine) have a weaker myocardial depressant effect and can be administered cautiously with β-blockers. If excessive hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

First degree heart block

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

Peripheral circulation

β-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease.

Antiarrhythmic drugs

Care should be taken when prescribing β-blockers with antiarrhythmic drugs. Interactions have been reported during concomitant β-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; Class IB agents, mexiletine and lignocaine; Class IC agent flecainide, the Class III agent, amiodarone; and the Class IV antiarrhythmic agents.

Prinzmetal angina

There is a risk of exacerbating coronary artery spasm if patients with Prinzmetal or variant angina are treated with a β-blocker. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

Euthyroid hyperthyroxinaemia

The effects of β-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T4) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

History of anaphylactic reaction

While taking β-blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reaction.

Lignocaine

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

Heart rate

One of the pharmacological actions of β-adrenoreceptor blocking medicines is to reduce heart rate. In the rare instance when symptoms may be attributable to the slow heart rate, the dose may be reduced.

Hypoglycaemia

Propranolol may block/modify the signs and symptoms of hypoglycaemia (especially tachycardia). Propranolol occasional 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 (see **Section 4.4 Special Warnings and Precautions for Use - Diabetes, Section 4.6 Fertility, Pregnancy and Lactation - Use in Pregnancy** and **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**). Propranolol may prolong the hypoglycaemic response to insulin.

Anaesthesia and the peri-operative period

β-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the post-operative period. It is currently recommended that maintenance β-blockade be continued perioperatively. The anaesthetist must be made aware of β-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal-induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported. Modern inhalational anaesthetic agents are well tolerated, although older agents (ether, methoxyflurane) were sometimes associated with severe circulatory depression in the presence of β-blockade.

Diabetes

β-blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia.

In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, β-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia (see **Section 4.4 Special Warnings and Precautions for Use - Hypoglycaemia** and **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**). The dose of insulin or oral hypoglycaemic agent may need adjustment.

Other metabolic effects

β-adrenoreceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some drugs affect the lipid profile adversely although the long-term clinical significance of this change is unknown and the effect appears to be less for drugs with intrinsic sympathomimetic activity.

Decompensated cirrhosis

Propranolol hydrochloride should be used with caution in decompensated cirrhosis.

Portal hypertension

In patients with portal hypertension, liver function will deteriorate and hepatic encephalopathy may develop. Propranolol may increase the risk of hepatic encephalopathy.

Use of catecholamine-depleting agents

Concomitant use of drugs such as guanethidine requires careful monitoring since the added effect of β-blockade may produce an excessive reduction of the resting sympathetic nervous tone.

Clonidine

Concurrent use of β-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the β-blocker. If replacing clonidine by β-blocker therapy, the introduction of β-blockers should be delayed for several days after clonidine administration has stopped.

Phaeochromocytoma

In patients with this condition, an alpha-blocking drug (e.g. hentolamine/phenoxybenzamine) should be administered before the β-blocker to avoid exacerbation of hypertension.

Eye and skin reactions

Various skin rashes and conjunctival xerosis have been reported with β-blockers. Cross-reactions may occur between β-blockers, therefore, substitutions within the group may not necessarily preclude occurrence of symptoms.

During the long-term treatment with the β-blocking drug, practolol, a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of patients affected, this rash was accompanied by adverse effects on the eye (xerophthalmia and/or keratoconjunctivitis) of varying severity. This condition is called the oculo-mucocutaneous syndrome, or practolol syndrome. In a few patients, these eye changes occurred independently of a skin rash. On rare occasions, serous otitis media, sclerosing peritonitis, pericarditis and pleurisy have been reported. Although the practolol syndrome has not been observed in patients taking other β-blockers the possibility of such side effects occurring should be borne in mind.

More recently, an association between Peyronie's disease (a fibrosing induration of the penis) and various β-blockers has been suggested but is not proven.

Allergic conditions

These may be exaggerated by β-blockade (e.g. allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings). β-blockers should be avoided if there is a risk of bronchospasm.

Hyperthyroidism

Because β-blockers may mask the clinical signs of developing or continuing hyperthyroidism, resulting in symptomatic improvement without any change in thyroid hormone status, special care should be exercised in those patients who are hyperthyroid and are also receiving β-blockers.

Use in hepatic impairment

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

Use in renal impairment

Since the half-life may be increased in patients with significant renal impairment, caution must be exercised when starting treatment and selecting the initial dose. In patients with severe renal disease, haemodynamic changes following β-blockade may impair renal function further. β-blockers which are excreted mainly by the kidney may require dose adjustment in patients with renal failure.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Digitalis glycosides, in association with β-blockers, may increase atrioventricular conduction time.

Concomitant use of sympathomimetic agents (e.g. adrenaline), may counteract the effects of β-blockers. Caution must be exercised in the parenteral administration of preparations containing adrenaline to patients taking β-adrenoreceptor blocking drugs as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

Propranolol modifies the tachycardia of hypoglycaemia. Caution should be exercised in the concurrent use of propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin (see **Section 4.4 Special Warnings and Precautions for Use - Hypoglycaemia**).

Simultaneous administration of rizatriptan and propranolol can cause an increase in rizatriptan plasma concentrations. The increased rizatriptan exposure is presumed to be caused by inhibition of first-passage metabolism of rizatriptan through inhibition of monoamine oxidase-A. If both drugs are to be used, a rizatriptan dose of 5 mg has been recommended.

Concomitant use of cimetidine or hydralazine will increase plasma levels of propranolol and concomitant use of alcohol may also increase the plasma levels of propranolol.

Care should be taken when using propranolol with ergotamine, dihydroergotamine or related compounds, since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting drugs, e.g. ibuprofen and indomethacin, may decrease the hypotensive effects of β-blockers.

The 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.

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, rifampicin, theophylline, warfarin, thioridazine and dihydropyridine calcium channel blockers such as nifedipine, nisoldipine, and isradipine. Owing to the fact that blood concentrations of either agent may be affected dosage adjustments may be needed according to clinical judgement. See also **Section 4.4 Special Warnings and Precautions for Use - Concomitant therapy with calcium antagonists** concerning the concomitant therapy with dihydropyridine calcium antagonists.

See also entries in **Section 4.4 Special Warnings and Precautions for Use -** for calcium antagonists, antiarrhythmic drugs, lignocaine, anaesthesia and peri-operative period, catecholamine-depleting agents and clonidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy (Category C)

Propranolol should not be given during pregnancy unless its use is essential. β-blockers reduce placental perfusion, which may result in intra-uterine foetal death, immature and premature deliveries.

Perinatal complications, such as a small placenta and intra-uterine growth retardation, have been reported in a few cases where the mother took propranolol hydrochloride during pregnancy. Some infants born to mothers treated with propranolol hydrochloride were reported to have hypoglycaemia and/or bradycardia. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period.

β-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the foetus and newborn infant. During the final part of pregnancy and parturition these drugs should therefore only be given after weighing the needs of the mother against the risk to the foetus.

Use in lactation

Most β-blockers, 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 adversely affect the ability of patients to drive or operate machinery. When driving vehicles or operating machinery, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Propranolol hydrochloride is usually well tolerated and side effects are transient in nature, rarely necessitating withdrawal of treatment. The most serious adverse reactions encountered are congestive heart failure and bronchospasm in susceptible patients (see

Section 4.3 Contraindications and **Section 4.4 Special Warnings and Precautions for Use**).

Common adverse reactions include fatigue and/or lassitude (often transient), bradycardia, cold extremities and exacerbation of Raynaud's phenomenon, sleep disturbances including vivid dreams/nightmares. Other less frequently reported adverse reactions include: gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea, abdominal pain), congestive heart failure, dizziness, bronchospasm. Rare cases of thrombocytopenia and purpura have been reported. CNS symptoms including mood changes and hallucinations have been reported rarely.

Reported adverse reactions according to organ systems are recorded below:

Cardiovascular

Occasionally a patient may react to small doses and bradycardia and hypotension may develop with subjective dizziness or weakness. In such patients treatment should be discontinued. If this occurs it is advisable to regard such hypersensitivity as idiosyncratic and to try some other form of treatment. Alternatively, the drug may be reintroduced at a lower dosage level and the dose increased more slowly. Propranolol hydrochloride may exacerbate intermittent claudication in patients with peripheral vascular disease. There have also been some reports of paraesthesia of the hands or of coldness of the extremities in patients showing no signs of vascular disease.

Other cardiovascular adverse reactions reported include congestive heart failure, deterioration of previously controlled heart failure and intensification of A-V block. Propranolol hydrochloride may rarely cause heart block in susceptible patients. Rare cases of postural hypotension which may be associated with syncope have been recorded.

Gastrointestinal

Gastrointestinal disturbances, including nausea, vomiting, flatulence and diarrhoea have been observed in some patients.

Endocrine

Hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant anti-diabetic therapy, patients with prolonged fasting and patients with chronic liver have been reported (see **Section 4.3 Contraindications**, **Section 4.6 Fertility, Pregnancy and Lactation - Use in Pregnancy** and **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Isolated reports of impotence have been recorded.

Central Nervous System

Lassitude, "muzziness", insomnia and visual disturbances have been reported in about 2% of patients but these complaints have been mild and are generally avoided by the gradual introduction of the drug. More serious side effects include severe nightmares and hallucinations. Psychiatric complications (depression, psychoses, psychotic reactions and acute confusional states) may occasionally occur but are unlikely to be severe. It would, however, be wise to restrict treatment in patients who have suffered previous depressive illness.

Respiratory

Asthma/bronchospasm, laryngospasm and respiratory distress (see **Section 4.3 Contraindications** and **Section 4.4 Special Warnings and Precautions for Use**).

Skin and Eyes

Isolated reports of purpura or erythematous rash have been received. Psoriasiform skin reactions and exacerbation of psoriasis have also been reported. Various other skin rashes and conjunctival xerosis have been reported with β-blocking agents, including propranolol hydrochloride. Such reactions may occur between β-blockers and substitution within the group may not necessarily preclude recurrence of symptoms.

Haemopoietic

Reduction of platelet adhesiveness; thrombocytopenic purpura; nonthrombocytopenic purpura; agranulocytosis; eosinophilia. An increase in ANA (Antinuclear Antibodies) has been observed, however, the clinical relevance of this is not clear.

Miscellaneous

Reduction or loss of libido; alopecia and rarely diminution and loss of hearing; tinnitus; visual disturbances; diminished vision; conjunctivitis; dry eyes; pharyngitis; fever combined with aching and sore throat; urinary retention associated with repeated bouts of paroxysmal tachycardia; flushing of the face. Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.

Discontinuance of propranolol hydrochloride 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 β-blocker should be gradual. In the rare event of intolerance, manifested as bradycardia and hypotension, the β-blocker should be withdrawn and, if necessary, treatment for overdosage instituted.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems or contact Apotex Medical Information enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

The common signs to be expected in overdosage are bradycardia, hypotension, bronchospasm or acute cardiac failure. If overdosage occurs, in all cases therapy with propranolol hydrochloride should be discontinued and the patient observed closely. In addition the following therapeutic measures are suggested:

General treatment should include: close supervision in a monitored environment (which may include 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 intravenous fluids to treat hypotension and shock.

Bradycardia

Excessive bradycardia can be countered with atropine 1–2 mg intravenously (incrementally in 0.6 mg doses) and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required this may be repeated or followed by an intravenous infusion of glucagon (1–10 mg/hour) depending on response. If no response to glucagon occurs or if glucagon is unavailable, a β-adrenoreceptor stimulant such as isoprenaline (25 µg initially) or orciprenaline (0.5 mg) may be given by slow intravenous injection.

Cardiac Failure

Digitalisation and diuretics.

Hypotension

Vasopressors e.g. noradrenaline or adrenaline. There is evidence that adrenaline is the drug of choice.

Bronchospasm

Administer isoprenaline and aminophylline.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Propranolol hydrochloride is a β-adrenoreceptor blocking agent which acts non-selectively on β-receptors (β_1 and β_2). It has little intrinsic sympathomimetic activity. It has some membrane stabilising effect. Propranolol is a racemic mixture and the active form is the *S*(-) isomer of propranolol. The most important effect of propranolol hydrochloride is to reduce the influence of excessive sympathetic nervous stimulation on the heart. Pulse rate, force of cardiac contraction and cardiac output are all reduced resulting in a significant reduction in myocardial oxygen demand, greater than the reduction in work. These effects, singly or in combination, are of therapeutic value in several cardiovascular diseases.

Propranolol hydrochloride reduces elevated blood pressure by an unknown mechanism. The drug also inhibits exercise-induced tachycardia and this effect is related to plasma concentration. No correlation has been found between the plasma concentration of propranolol and its antihypertensive effect.

The possible mechanism of the anti-anginal activity of propranolol hydrochloride appears to be due to a reduction in left ventricular work and oxygen utilisation resulting from inhibition of cardiac sympathetic nerve stimulation. Serotonin antagonism has been demonstrated with propranolol hydrochloride. The therapeutic benefit of this property in centrally mediated disorders is uncertain.

Propranolol hydrochloride, as with other β-adrenoreceptor blocking agents, has negative inotropic effects and is therefore contraindicated in congestive heart failure.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Studies with propranolol hydrochloride in humans indicate that it is almost completely absorbed from the intestine. A large part of the absorbed drug is lost to the systemic circulation due to the first pass metabolism in the liver. After repeated administration, the first pass removal process becomes saturated and, at steady state, the plasma concentration is proportional to the dose, although there is some variation between patients as to the blood levels achieved at a given dose. In addition, correlation of plasma level to therapeutic effect varies considerably with propranolol as with some other β-blockers. Blood level measurements show that after intravenous administration, the concentration in the circulation decreases rapidly due mainly to uptake by tissues generally.

Distribution

Propranolol is absorbed from the circulation and is widely distributed throughout the body tissues.

Metabolism

Propranolol is completely metabolised, primarily by the liver. Hydroxylation of the aromatic nucleus occurs with degradation of the isoprenaline side chain. Over 20 metabolites have been identified. One of these, the 4-hydroxy metabolite, found only after oral administration has β-adrenergic blocking properties.

Excretion

Some 95–100% of a dose of propranolol hydrochloride is excreted as metabolites and their conjugates in the urine.

Bioavailability

In general, the peak blood level occurs between 1–3 hours after oral administration, and will have an average value of 0.1 µg/mL per 80 mg single dose. The peak blood level is proportional to the dose. With chronic administration the mean plasma half-life is from 3–6 hours, determined by clearance and plasma binding.

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.

Protein binding

Approximately 93% is plasma bound in humans.

Half-life

The plasma half-life of oral propranolol is of the order of 3–6 hours. The pharmacological effect lasts much longer.

Clinical implications of pharmacokinetic data

Propranolol hydrochloride has a variable bioavailability due to an avid hepatic binding mechanism. This first pass effect varies from individual to individual and will determine the drug plasma concentration. A good estimation of β-blockade and bioavailability can be clinically gauged by checking for reduction in standing or exercise heart rate. This also gives a simple guide to compliance.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

Teratogenicity

There is no evidence of teratogenicity with propranolol hydrochloride.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.

6.2 INCOMPATIBILITIES

See **Section 4.5-Interactions with other medicines and other forms of interactions**.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mg tablets:

Bottle pack (HDPE) of 100 tablets (AUST R 222958).

40 mg tablets:

Bottle pack (HDPE) of 100 tablets (AUST R 222969).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

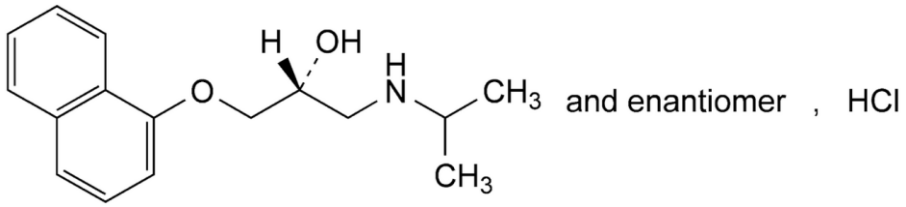
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Propranolol hydrochloride is an off-white to white crystalline solid with little or no odour. Propranolol hydrochloride dissolves in water to the extent of one part in twenty at 20°C and has a similar solubility in 95% ethanol, but is only slightly soluble in chloroform.

Propranolol is a β-adrenoreceptor blocking agent which is structurally related to other β-blocking agents such as atenolol, pindolol and oxprenolol, differing from these compounds by substitution on the aromatic ring.

Chemical structure



Chemical Name : (2*RS*)-1-[(1-Methylethyl)amino]-3-(naphthalen-1-yloxy)propan-2-ol hydrochloride

Molecular Formula : $C_{16}H_{21}NO_2$•HCl

Molecular Weight : 295.8

CAS number

318-98-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine.

8 SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia

APO and APOTEX are registered trade marks of Apotex Inc.

Tel: +61 2 8877 8333
Web: www1.apotex.com/au

9 DATE OF FIRST APPROVAL

13 February 2015.

10 DATE OF REVISION

15 August 2018

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information
2, 3	Minor Editorial Changes Update of ingredient names to comply with the new Australian Approved Name (AAN) as per current TGA approved terminology for medicines in the TGA eBusiness Services code tables