Propranolol Hydrochloride

Stabeta-40

40 mg Tablet
Non-selective Beta-adrenoceptor Blocker

℞

FORMULATION:
Each tablet contains:
Propranolol Hydrochloride BP .....40 mg

PRODUCT DESCRIPTION:
A white to off-white coloured, round, biconvex both sides plain uncoated tablet.

PHARMACOLOGICAL PROPERTIES:
Pharmacotherapeutic group: Beta blocking agents, non-selective, ATC Code: C07AA05
Pharmacodynamic Properties
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.

PHARMACOKINETICS:
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%).

INDICATIONS:
-Control of hypertension
-Management of angina pectoris
- Long term prophylaxis after recovery from acute myocardial infarction
- Control of cardiac arrhythmias
-Prophylaxis of migraine
-Management of essential tremor
-Control of anxiety and anxiety tachycardia
-Adjunctive management of thyrotoxicosis and thyrotoxic crisis
-Management of hypertrophic obstructive cardiomyopathy
-Management of phaeochromocytoma (Propranolol) should only be started in the presence of effective alpha blockade

DOSAGE AND ADMINISTRATION:
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.

Oral Dosage:
Adults:
Hypertension:
A starting dose of 80 mg twice a day may be increased at weekly intervals according to response. The usual dose range is 160-320 mg per day and the maximum daily dose must not exceed 640 mg per day (see summary table as follows). With concurrent diuretic or other antihypertensive drugs a further reduction of blood pressure is obtained.

Angina, anxiety, migraine and essential tremor:
A starting dose of 40 mg two or three times daily may be increased by the same amount at weekly intervals according to patient response. An adequate response in anxiety, migraine and essential tremor is usually seen in the range 80-160 mg/day, and in angina in the range 120-240 mg/day. A maximum daily dose of 240 mg for migraine and 480 mg for angina must not be exceeded (see summary table).

Arrhythmias, anxiety tachycardia, hypertrophic obstructive cardiomyopathy and thyrotoxicosis:
A dosage range of 10-40 mg three or four times a day usually achieves the required response. A maximum daily dose of 240 mg for arrhythmias must not be exceeded (see summary table).

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

Phaeochromocytoma:
Propranolol is to be used only in the presence of effective alpha-blockade Preoperative: 60 mg daily for three days is recommended. Non-operable malignant cases: 30 mg daily (see summary table).

Summary Table of Propranolol Oral Dosage -Adults (in divided daily doses)

	Min/day	Max/day
Hypertension	160 mg	640 mg
Angina pectoris	80 mg	480 mg
Arrhythmias	30 mg	240 mg
Migraine	80 mg	240 mg
Tremor	40 mg	160 mg
Anxiety	80 mg	160 mg
Anxiety Tachycardia	30 mg	160 mg
Thyrotoxicosis	30 mg	160 mg
Cardiomyopathy	30 mg	160 mg
Phaeochromocytoma	60 mg (pre op) 30 mg (maintenance)	60 mg 30 mg
Post-infarction	160 mg	160 mg

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

Children
Dosage should be individually determined and the following is only a guide: *Arrhythmias, phaeochromocytoma, thyrotoxicosis:*
Oral: 0.25 - 0.5 mg/kg three or four times daily as required.
Migraine: Oral: Under the age of 12: 20 mg two or three times daily.
Over the age of 12: the adult dose.
Or as prescribed by the physician.

CONTRAINDICATIONS:
Propranolol must not be used if there is a history of bronchial asthma or bronchospasm.

Bronchospasm can usually be reversed by beta-2 agonist bronchodilators such as salbutamol. Large doses of the beta-2 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 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.

Propranolol as with other beta-blockers must not be used in patients with any of the following conditions: known hypersensitivity to the substance; bradycardia; cardiogenic shock; hypotension; metabolic acidosis; after prolonged fasting; severe peripheral arterial circulatory disturbances; second or third degree heart block; 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.

WARNINGS AND PRECAUTIONS:
Propranolol as with other beta-blockers:
- Although contraindicated in uncontrolled heart failure (see Contraindications), may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- Although contraindicated in severe peripheral arterial circulatory disturbances (see Contraindications), may also aggravate less severe peripheral arterial circulatory disturbances.
- Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.
- May block/modify the signs and symptoms of the 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 Contraindications).
- May mask the signs of thyrotoxicosis.
- Will reduce heart rate as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate, the dose may be reduced.
- Should not be discontinued abruptly in patients suffering from ischaemic heart disease. Either the equivalent dosage of another beta-blocker may be substituted or the withdrawal of Propranolol should be gradual.
- 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 must be used with caution in patients with decompensated cirrhosis.
In patients with significant hepatic or renal impairment care should be taken 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:
Propranolol modifies the tachycardia of hypoglycaemia. 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 Contraindications and Precautions).

Simultaneous administration of rizatriptan and propranolol can cause an increased rizatriptan AUC and C_{max} by approximately 70-80%. 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.

Class I anti-arrhythmic drugs (e.g., disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

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

Combined use of beta-blockers 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 the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridine calcium channel blockers, e.g., nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant use of sympathomimetic agents eg, 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.

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.

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

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. 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.

Caution must be exercised if ergotamine, dihydroergotamine or related compounds are given in combination with Propranolol since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting drugs e.g., ibuprofen and indometacin, may decrease the hypotensive effects of Propranolol.

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.

Caution must be exercised when using anaesthetic agents with Propranolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers 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.

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 previously concerning the concomitant therapy with dihydropyridine calcium channel blockers.)

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 fetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia in the neonate and bradycardia in the fetus) may occur. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period.

Lactation
Most beta-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.

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

ADVERSE DRUG REACTIONS:
Propranolol is usually well tolerated. In clinical studies the possible adverse reactions reported are usually attributable to the pharmacological actions of propranolol.

The following possible adverse reactions, listed by body system, have been reported.

Common (1-9.9%):
General: Fatigue and/or lassitude (often transient).
Cardiovascular: Bradycardia, cold extremities, Raynaud's phenomenon.
CNS: Sleep disturbances, nightmares.

Uncommon (0.1-0.9%):
GI: Gastrointestinal disturbance, such as nausea, vomiting, diarrhea.

Rare (0.01-0.09%):
General: Dizziness.
Blood: Thrombocytopaenia.
Cardiovascular: Heart failure deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication.
CNS: Hallucinations, psychoses, mood changes, confusion, memory loss.
Skin: Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.
Neurological: Paraesthesia.
Eyes: Dry eyes, visual disturbances.
Respiratory: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome.

Very rare (<0.01%):
Endocrine system: 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.
Investigations: an increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.
Nervous system: Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.
Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the previously mentioned reactions. Cessation of therapy with a beta-blocker should be gradual. In the rare event of intolerance, manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment for overdosage instituted.

OVERDOSE AND TREATMENT:
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 to 2 mg intravenously 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 to 10 mg/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.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at a temperatures not exceeding 30°C.

Keep all medicines out of reach of children.

AVAILABILITY:
Alu /PVC Blister Pack x 10's (Box of 100's)

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