PROPRANOLOL HYDROCLORIDE

Rx

ASTEROL
10mg TABLET
NON-SELECTIVE BETA-BLOCKER

1. NAME OF THE MEDICINAL PRODUCT
Propranolol hydrochloride (ASTEROL) Tablet 10 mg

2. FORMULATION:
Each Tablet contains:
Propranolol Hydrochloride.....10 mg

3. PHARMACEUTICAL FORM
(White to off white , round, biconvex one side scored tablet)

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
a) Control of Hypertension
b) Management of angina pectoris
c) Long term prophylaxis after recovery from acute myocardial infarction
d) Control of cardiac arrhythmias
e) Prophylaxis of migraine
f) Management of essential tremor
g) Control of anxiety and anxiety tachycardia
h) Adjunctive management of thyrotoxicosis and thyrotoxic crisis
i) Management of hypertrophic obstructive cardiomyopathy
j) Management of pheochromocytoma [Propranolol (ASTEROL) should only be started in the presence of effective alpha blockade]

4.2 DOSAGE AND METHOD OF ADMINISTRATION:
The tablets should preferably be administered before meals.
Adult and children over 12 years old
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 to 320 mg per day and the maximum daily dose must not exceed 640 mg per day (see summary table below). 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 usual 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:
Most patients respond within the 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 be started between days 5 and 21 after myocardial infarction.

Phaeochromocytoma: [Propranolol (ASTEROL) is to be used only in the presence of effective alpha blockade].Pre-operatively; 60 mg daily for three days is recommended. Non-operable malignant cases, 30 mg daily.

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

	Min./Day	Max/Day
Hypertension	160 mg	320 mg
Angina pectoris	80 mg	320 mg
Arrhythmias	30 mg	160 mg
Migraine	80 mg	160 mg
Tremor	40 mg	160 mg
Anxiety	80 mg	160 mg
Anxiety Tachycardia	30 mg	160 mg
Portal hypertension/Esophageal varices	80 mg	320 mg
Thyrotoxicosis	30 mg	160 mg
Pheochromocytoma	60 mg (pre op)	60 mg
	30 mg (maintenance)	30 mg
Post-infarction	160 mg	160 mg

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

Children and Adolescent:
Dosage should be individually determined according to the cardiac status of the patient and the circumstances necessitating treatment. The doses given is intended only as guide.

Arrhythmias, pheochromocytoma , thyrotoxicosis:
Oral 0.25 - 0.5 mg/kg body weight three to 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.

4.3 Contraindications:
Propranolol (**ASTEROL**) 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 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 (**ASTEROL**) as with other beta - blockers must not be used in patients with any of the following: 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 pheochromocytoma; uncontrolled heart failure or Prinzmetal's angina.

Propranolol (**ASTEROL**) must not be used in patients prone to hypoglycemia, 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 hypoglycemia which includes glycogenolysis, gluconeogenesis and / or impaired modulation of insulin secretion. Patients at risk for an inadequate response to hypoglycemia 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
Propranolol (**ASTEROL**) as with other beta blockers:
- although contra - indicated in uncontrolled heart failure, (see Section 4.3 contraindication) 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 contra - indicated in severe peripheral arterial circulatory disturbances (see Section 4.3 contraindication), 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 hypoglycemia (especially tachycardia). Propranolol (**ASTEROL**) occasionally causes hypoglycemia, even in non - diabetic patients, e.g., neonates, infants, children, elderly patients, patients on hemodialysis or patients suffering from chronic liver disease and patients suffering from overdose. Severe hypoglycemia associated with Propranolol (**ASTEROL**) has rarely presented with seizures and / or coma in isolated patients. Caution must be exercised in the concurrent use of Propranol (**ASTEROL**) and hypoglycemic therapy in diabetic patients. Propranolol (**ASTEROL**) may prolong the hypoglycemic response to insulin. (see section 4.3 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 ischemic heart disease. Either the equivalent dosage of another beta-blocker may be substituted or the withdrawal of Propranolol (**ASTEROL**) should be gradual.
- Sudden withdrawal of beta-adrenoceptor blocking agents in patients with ischemic heart disease may result in the appearance of anginal attacks of increased frequency or severity of deterioration in cardiac state.
- 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 (**ASTEROL**) must not be used with caution in patients with decompensated cirrhosis (see section 4.2 Dosage and Method of administration)

In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop.
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4.5 Interaction with other medicinal products and other forms of interaction
ASTEROL modifies the tachycardia of hypoglycemia. Caution must be exercised in the concurrent use of ASTEROL and hypoglycemic therapy in diabetic patients. Asterol may prolong the hypoglycemic response to insulin (see Section 4.3 and 4.4 Contraindication and Special warning and special precaution for use).

Simultaneous administration of rizatriptan and propranolol can cause an increased rizatriptan AUC and C 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 betablocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridines 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 e.g. adrenaline, may counteract the effect of beta-blockers.

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Administration of Propranolol (**ASTEROL**) 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 (**ASTEROL**).

Concomitant administration of Propranolol (**ASTEROL**) 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 (**ASTEROL**).

Caution must be exercised when using anesthetic agents with Propranolol (**ASTEROL**). The anesthetist should be informed and the choice of anesthetic should be an agent with as little negative inotropic activity as possible. Use of beta - blockers with anesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anesthetic 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 metabolize 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
Pregnancy
As with all other drugs, propranolol should not be given in pregnancy or lactation unless its use is essential.There is no evidence of teratogenicity with propranolol. However, beta-adrenoceptor blocking drugs reduce the placental perfusion, which may result in intra-uterine fetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycemia 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 - 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
The use of propranolol is unlikely to result in any significant impairment of the ability of patients to drive or operate machinery. However, patients should be warned that visual disturbances, hallucinations, mental confusion, dizziness, drowsiness or fatigue may occur and they should not drive or operate machinery if they feel affected.

4.8 Possible Adverse effects reactions
Tabulated list of adverse reaction:
Propranolol (**ASTEROL**) is usually well tolerated. In clinical studies the possible adverse reactions reported are usually attributable to the pharmacological actions of propranolol.
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
Endocrine disorders	Not Known	Hypoglycemia in neonates, infants, children, elderly patients, patients on hemodialysis, patients concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported, seizure linked to hypoglycemia
Nervous system disorders	Common	Sleep disturbances, nightmares
	Rare	Paraesthesia
	Rare	Hallucinations, psychosis, mood changes, confusion, memory loss.
	Very rare	Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported
Eye disorders	Eye disorders	Dry eyes, visual disturbances
Cardiac disorders	Common	Bradycardia, cold extremities, Raynaud's phenomenon
	Rare	Heart failure deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome
Gastrointestinal disorders	Uncommon	Gastrointestinal disturbance, such as nausea, vomiting, diarrhea
Skin and subcutaneous tissue disorders	Rare	Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes
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, however the clinical relevance of this is not clear

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 above 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.

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/ risk balance of the medicinal product.
Reporting of suspected adverse reactions Healthcare professionals are asked to report any suspected adverse reactions via:
Tel no. : (2) 711-16-16 / (2) 731-04-08 / email: sanmarinolaboratories@ yahoo.com.ph

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. 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 this dose would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine or isoprenaline 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 (**ASTEROL**) hydrochloride is a beta-adrenoceptor blocking agent.
Mode of Action
Propranolol is a competitive antagonist at both beta1 and beta2-adrenoceptor, but has membrane stabilizing activity at concentrations exceeding 1-3mg / liter, though such concentrations are rarely achieved during oral therapy. Competitive beta - blockade has been demonstrated in man by 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 (**ASTEROL**) is a racemic mixture and the active form is the S (-) isomer of propranolol. With the exception of inhibitor 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 (**ASTEROL**) is effective and well tolerated in the 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%).

6. PHARMACEUTICALS PARTICULARS
6.1. STORAGE CONDITION :
Store at temperatures not exceeding 30'C. Protect from light and moisture
6.2. SHELF - LIFE - 36 Months
6.3 AVAILABILITY :
Propranolol (ASTEROL) 10 mg Tablet - Alu / PVC Clear Blister Pack of 20's , Box of 100's Tablets

ADR REPORTING STATEMENT:
"For suspected adverses drug reaction, report to the FDA: www.fda.gov.ph" Patient must seek medical attention immediately at the first sign of any adverse drug reaction.

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

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Based on Innovator drug Propranolol Hydrochloride 10 mg Tablet

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