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Directions for Use **Please Read Carefully!**

ANTAROL TABLET 20MG & ANTAROL TABLET 40MG

DESCRIPTION

Antarol Tablet 20mg & Antarol Tablet 40mg:
Dark-purple, film- coated, round and embossed with "P/20" or "P/40" and the "a" in italics. Each **Antarol Tablet 20mg & Antarol Tablet 40mg** contains propranolol HCl 20 mg and 40 mg respectively.

PHARMACODYNAMICS

Pharmacotherapeutic group: Beta blocking agents, non-selective
ATC code: C07AA05
Propranolol is a competitive antagonist at both beta-1 and beta-2 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.
Propanolol, 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 therapeutics effects.
Propranolol is effective and well-tolerated in most ethnic populations, although the response may be less in black patients.

PHARMACOKINETICS

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%).

INDICATIONS

Antarol is indicated in the management of angina pectoris, hypertension, cardiac dysrhythmias, hypertrophic obstructive cardiomyopathy and in the long-term prophylaxis following recovery from myocardial infarction. As an adjunct in the control of symptoms of anxiety, essential tremor, tachycardia (including that with thyrotoxicosis) and in the management of phaeochromocytoma (only if co-administered with an alpha-adrenoceptor blocker). It is also indicated in the prophylactic management of migraine.

RECOMMENDED DOSE

Adults:

- Angina pectoris and control of essential tremor: The usual total daily dose initially is 40 mg given 2 to 3 times daily with a maintenance dose of 80 to 320 mg daily, reached by weekly increments.
- Hypertension: The usual dose is 80 mg twice daily initially with slow increments to the level of optimal control, usually 160 to 320 mg daily in single or divided doses. Some patients may require up to a maximum dose of 640 mg daily. Diuretics and other antihypertensive agents may be used concurrently if necessary.
- Post myocardial infarction: 40 mg 4 times daily for 2 or 3 days followed by 80 mg twice daily, commencing between 5 and 21 days after infarction.
- Cardiac dysrhythmia, tachycardia and hypertrophic obstructive cardiomyopathy: The usual dose is 10 to 40 mg 3 or 4 times daily.
- Phaeochromocytoma: Pre-operatively, 60 mg daily for 3 days. For inoperable cases, 30 mg daily. (Propranolol should only be used with an alpha-receptor blocker).
- Anxiety: 40 mg daily, this may be increased to 40 mg 2 or 3 times daily if necessary.
- Migraine: The initial dose is 40 mg 2 or 3 times daily with weekly increments of these amounts depending upon the patient's response.

Children:

- Arrythmias, phaeochromocytoma and thyrotoxicosis: 0.25 – 0.5 mg/kg 3 or 4 times daily as required.
- Migraine: Children under 12 years age may be given 20 mg 2 or 3 times daily for the prophylactic purpose.

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.

ROUTE OF ADMINISTRATION

Oral

CONTRAINDICATION

Antarol 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: 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 (with an alpha-adrenoceptor antagonist) phaeochromocytoma; uncontrolled heart failure; prinzmetal 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

Antarol as with other beta-blockers:

- although contraindicated in uncontrolled heart failure 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, 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). **Antarol** 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 patient suffering from overdose. Severe hypoglycaemia associated with **Antarol** has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of **Antarol** and hypoglycaemic therapy in diabetic patients. **Antarol** may prolong the hypoglycaemic response to insulin.
- 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 **Antarol** 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 adrenalin used to treat the allergic reactions.

Prinzmetal angina: There is a risk of exacerbating coronary artery spasm if patients with prinzmetal or variant angina are treated with a beta-blocker. If this treatment is essential, it should only be undertaken in a coronary or intensive care unit.

Euthyroid hyperthyroxinaemia: The effects of beta-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.

Other metabolic effects: Beta-adrenoceptors 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.

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

Hyperthyroidism: Because beta-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 beta-blockers.

Antarol 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.

INTERACTIONS WITH OTHER MEDICAMENTS

- **Antarol** modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of **Antarol** and hypoglycaemic therapy in diabetic patients. **Antarol** may prolong the hypoglycaemic response to insulin.
- Simultaneous administration of rizatriptan and propranolol can cause an increased rizatriptan AUC and Cmax 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.

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- Concomitant use of sympathomimetic agents e.g., adrenaline, may counteract the effect of beta-blockers. Caution must be exercised in the parenteral administration of preparations containing adrenaline to patients taking beta-blockers as, in rare cases, vasoconstriction, hypertension and bradycardia may result.
- Administration of **Antarol** during infusion of lignocaine may increase the plasma concentration of lignocaine by approximately 30 %. Patients already receiving **Antarol** tend to have higher lignocaine 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 **Antarol** 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 **Antarol**.
- Concomitant administration of **Antarol** 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 **Antarol**.
- Caution must be exercised when using anaesthetic agents with **Antarol**. 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.
- ***Imipramine:*** Propranolol may cause plasma concentrations of imipramine to increase.
- ***Monoamine-oxidase Inhibitors (MAOIs):*** The hypotensive effects of beta-blockers may be enhanced by MAOIs.
- ***Selective Serotonin Re-uptake Inhibitors:*** Fluvoxamine inhibits oxidative metabolism and increases plasma concentrations of propranolol. This may result in severe bradycardia.
- ***Tobacco:*** Smoking tobacco may oppose the effects of beta-blockers in the treatment of angina or hypotension. Patients should be encouraged to stop smoking, apart from its other toxic effects, it aggravates myocardial ischaemia, increases heart rate and can impair blood pressure control. If patient continues to smoke, dosage of the beta-blocker may need to be increased or a cardio-selective beta-blocker may be more appropriate.
- ***Laboratory tests:*** Interference with laboratory tests - Propranolol has been reported to interfere with the estimation of serum bilirubin by the diazo method and with the determination of catecholamines by methods using fluorescence.

PREGNANCY AND LACTATION

Pregnancy

Antarol should not be administered during pregnancy unless it considered essential by the physician.
Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. In addition, there is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

Lactation

Most beta-blockers including propranolol is excreted into human milk. Breast-feeding is therefore not recommended following administration of these compounds.

SIDE EFFECTS

Antarol is usually well tolerated. In published 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.

System Organ Class	Frequency	Adverse Reaction
Blood and lymphatic disorders	Rare	Thrombocytopenia
Endocrine disorders	Very rare	Hypoglycaemia in neonates, infants, children, elderly, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease
Nervous system disorders	Common	Sleep disturbance, nightmares
	Rare	Hallucinations, psychoses, mood changes, confusion, memory loss, paraesthesia
	Very rare	Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis
	Not known	Depression
Eye disorders	Rare	Dry eyes, visual disturbance
Cardiovascular 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, diarrhoea
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.

SYMPTOMS AND TREATMENT OF OVERDOSE

Propranolol is known to cause severe toxicity when used in overdose. Patients should be informed of the signs of overdose and advised to seek urgent medical assistance if an overdose of propranolol has been taken.

Clinical features:
Cardiac: Bradycardia, hypotension, and cardiogenic shock may develop QRS complex prolongation, ventricular tachycardia, first to third degree AV block, ventricular fibrillation or asystole may also occur. Development of cardiovascular complications is more likely if other cardioactive drugs, especially calcium channel blockers, digoxin, cyclic antidepressants or neuroleptics have also been ingested.
CNS: Drowsiness, seizures, and in severe cases coma may occur.
Other features: Bronchospasm, hyperkalaemia and occasionally CNS-mediated respiratory depression may occur.

Management

- 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 1-2 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 1-10 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.
- Bronchospasm may be treated by aminophylline intravenously or by isoprenaline/salbutamol by inhalation or intravenous injection. Heart failure should be treated by digitalis and diuretic therapy.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Propranolol has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that occasionally dizziness or fatigue may occur.

STORAGE CONDITION

Store in a cool dry place, below 30° C. Protect from light.
Keep out of reach of children.
Jauhi ubat daripada kanak-kanak.

SHELF LIFE: Please refer to the outer label.

PACKING

Antarol Tablet 20mg: Bottle of 250 tablets.
Antarol Tablet 40mg : Bottle of 250 tablets, blister pack 100 X 10

MANUFACTURED BY

GoodScience Sdn. Bhd.
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PRODUCT REGISTRATION HOLDER

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