Atenolol

Therabloc®

25 mg, 50 mg & 100 mg Tablet

℞

Beta-Adrenoceptor Blocker / Antihypertensive

FORMULATION
Each tablet contains:
Atenolol …….....25 mg, 50 mg or 100 mg

PRODUCT DESCRIPTIONS
Therabloc® 25 mg Tablet
White to off-white, round 1/4" diameter, biconvex tablet, plain on both sides
Therabloc® 50 mg Tablet
White to off-white, flat, round 5/16" diameter, bisected on one side and plain on the other side of the tablet
Therabloc® 100 mg Tablet
White to off-white, round 3/8" diameter, with Therapharma insignia on one side, flat plain on the other side of the tablet

CLINICAL PHARMACOLOGY
• PHARMACODYNAMICS
Atenolol is a $beta_1$-selective beta-adrenergic receptor blocker without membrane stabilizing or intrinsic sympathomimetic activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits $beta_2$-adrenergic receptors particularly located in the bronchial and vascular musculature. Atenolol is a racemic mixture and its activity resides in the S(-) enantiomer.

In studies, atenolol's beta-adrenoceptor blocking activity has been demonstrated by reduction in resting and exercise heart rate and cardiac output, reduction of systolic and diastolic blood pressure at rest and on exercise, inhibition of isoproterenol-induced tachycardia, and reduction in reflex orthostatic tachycardia.

Atenolol's significant beta-blocking effect is apparent within one hour after oral administration of a single dose, as measured by reduction of exercise tachycardia. This effect is maximal at about 2 to 4 hours and persists for at least 24 hours.

The $beta_1$ selectivity of atenolol is demonstrated by its reduced ability to reverse the $beta_2$-mediated vasodilating effect of isoproterenol compared with equivalent beta-blocking doses of propranolol in normal subjects. A dose of atenolol producing a greater effect on resting heart rate than propranolol resulted in an adequate increase in airway resistance in patients with asthma. In a placebo-controlled comparison of approximately equipotent oral doses of several beta-blockers, atenolol produced a significantly smaller decrease of forced expiratory volume in 1 second (FEV1) compared with nonselective beta-blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the sinoatrial node, atenolol increases sinus cycle length and sinus node recovery time. Also, conduction in the atrioventricular node is prolonged. Atenolol is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Studies have shown a moderate (about 10%) increase in stroke volume at rest and during exercise.

In studies, atenolol, given as a single daily oral dose, provided 24-hour reduction in blood pressure. Atenolol's dose range is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effects. The mechanisms of the antihypertensive effects of beta-blockers have not been established. Several possible mechanisms have been proposed and include competitive antagonism of catecholamines at peripheral (particularly cardiac) adrenergic neuron sites resulting in reduced cardiac output, a central effect leading to reduced sympathetic outflow to the periphery, and suppression of renin activity. Atenolol has not shown diminution of the antihypertensive effect with prolonged use.

Atenolol's anti-anginal activity appears to be due to a reduction in left ventricular work and oxygen utilization resulting (mainly) from the decrease in heart rate and contractility. On the other hand, atenolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

• PHARMACOKINETICS
About 50% of an oral atenolol dose is rapidly absorbed.

Atenolol is distributed throughout the body and into breast milk. It also crosses the placenta, with fetal serum atenolol concentrations approaching those of the mother. Unlike propranolol, only a small portion of atenolol is distributed in the central nervous system. About 6 to 16% of atenolol is bound to plasma protein.

The serum half-life of atenolol in patients with normal renal function is 6 to 7 hours; half-life increases progressively as renal function worsens. Atenolol undergoes little or no metabolism by the liver. About 40 to 50% of an oral dose of atenolol is excreted in urine unchanged. The remainder is excreted unchanged in feces, principally as unabsorbed drug.

INDICATIONS
- Long term management of angina pectoris due to coronary atherosclerosis.
- Management of hypertension; may be used alone or in combination with other antihypertensive drugs particularly with a thiazide-type diuretic.
- Acute myocardial infarction.

DOSAGE AND ADMINISTRATION
Adult dose: Initially, 50mg orally once daily. Maintenance dose varies from 25 to 100 mg daily.

Hypertension
Atenolol is administered orally; most patients respond to 50-100 mg daily. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining therapy with other antihypertensive agents.

Angina Pectoris
Effective oral dose to most patients with angina pectoris is 100 mg daily as a single or divided dose. Some patients require a dosage of 200 mg once a day for optimal effect. It is unlikely that an additional benefit will be gained by increasing the dose.

A dose of 25 mg is useful in patients with hypertension or angina who are overly sensitive to the negative chronotropic effect of higher doses (50 to 100 mg) of Atenolol. A 25 mg dose of Atenolol may keep the heart rate within normal levels particularly at night and still produce the desired antihypertensive and antianginal action alone or in combination with other drugs.

Myocardial Infarction
Atenolol 5 mg, by slow intravenous injection (1mg/min), should be given to a patient within 12 hours of the onset of chest pain, followed by another 5 mg I.V. Atenolol 10 minutes later. In patients who tolerate the full intravenous dose (10 mg), Atenolol 50 mg should be initiated 10 minutes after the last I.V. dose followed by another 50 mg oral dose 12 hours later. Thereafter, Atenolol can be given orally either 100mg once daily or 50 mg twice daily for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any untoward effects occur, Atenolol therapy should be discontinued. An oral dose of 100 mg daily is recommended for long-term prophylaxis.

Pediatric Dose
There is no pediatric experience with Atenolol and for this reason, it is not recommended for pediatric use.

CONTRAINDICATIONS
- Severe peripheral arterial circulatory disturbances / Shock (including cardiogenic and hypovolemic shock)
- Congestive heart failure
- Hypotension
- Second- or third-degree heart block
- Sick sinus syndrome
- Sinus bradycardia (<45 beats per minute)
- Significant right ventricular hypertrophy
- Right ventricular failure secondary to pulmonary hypertension
- Hypersensitivity to any component of the product
- Bronchospasm / Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm
- Untreated pheochromocytoma
- Metabolic acidosis
- Anesthesia with agents that produce myocardial depression (e.g., ether, chloroform, cyclopropane)

WARNINGS AND PRECAUTIONS

Cessation of Therapy with Atenolol: Patients with coronary artery disease, who are being treated with atenolol, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients after abrupt discontinuation of therapy with beta-blockers. As with other beta-blockers, when abrupt discontinuation of atenolol is planned, carefully observe the patient and advise to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that atenolol be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol therapy abruptly even in patients treated only for hypertension.

Cardiac failure: Beta-blockade carries the potential hazard of depressing myocardial contractility and precipitating more severe heart failure. Cautiously administer atenolol in patients with congestive heart failure controlled by digitalis and/or diuretics, since both digitalis and atenolol slow AV conduction.

Cardiac failure which is not promptly and effectively controlled by IV furosemide 80 mg or equivalent therapy is a contraindication to beta-blocker treatment in patients with acute myocardial infarction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blockers over the period of time may, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, appropriately treat patients according to currently recommended guidelines and closely observe patients' response. Discontinue atenolol if cardiac failure continues despite adequate treatment.

Concomitant Use of Calcium channel Blockers: (see **Interactions with Other Medicaments)**

Bronchospastic Diseases: **In general, patients with bronchospastic diseases should not receive beta-blockers. Because of its relative $beta_1$ selectivity, however, atenolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta1 selectivity is not absolute, the lowest possible atenolol dose should be used with therapy initiated at 50 mg and a $beta_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, consider dividing the dose to achieve lower peak blood levels.**

Anesthesia and Major Surgery: During anesthesia and post-operative period, beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischemia. It is recommended that maintenance of beta-blockade be continued peri-operatively. The anesthetist must be aware of beta-blockade because of the potential for interactions with other medication, resulting in severe bradyarrhythmias and hypotension, decreased reflex ability to compensate for blood loss, hypovolemia and regional sympathetic blockade, and increased propensity for vagal-induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anesthesia have been observed. Modern inhalational anesthetics are generally well tolerated, although older agents (e.g., ether, cyclopropane, methoxyflurane, trichloroethylene) are sometimes associated with severe circulatory depression in the presence of beta-blockade.

Diabetes and Hypoglycemia: Beta-blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycemia (i.e., tachycardia).

In patients with insulin or non-insulin dependent diabetes, particularly labile diabetes, or with a history of spontaneous hypoglycemia, beta-blockade may result in the loss of diabetic control and delayed recovery from hypoglycemia. The dose of insulin or oral hypoglycemic agent may need adjustment.

Thyrotoxicosis: The effect of beta-blockers on thyroid hormone metabolism may result in increased 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. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; thus, closely monitor patients suspected of developing thyrotoxicosis from whom atenolol is to be withdrawn.

Pheochromocytoma: In patients with this condition, an alpha-blocking agent (e.g, phentolamine/phenoxybenzamine) must be administered before a beta-blocker to avoid exacerbation of hypertension.

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

Peripheral Circulation: Beta blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease.

First Degree Heart Block: Use with caution in patients with first degree heart block due to its negative effect on conduction time.

Renal Disease: Hemodynamic changes following beta-blockade may impair renal function further in patients with severe renal disease.

Use in Myocardial Infarction: Patients with the following conditions are not suitable for atenolol treatment:
- Systolic blood pressure <120 mmHg (systolic blood pressure <120 mmHg in combination with a heart rate >90 beats/min has a particularly poor prognosis)
- First degree AV block. After atenolol use, an increased incidence of cardiogenic shock (and need for inotropes), complete heart block and cardiovascular death has been observed in these patients.

Patients with atrial fibrillation after myocardial infarction, who were treated with atenolol, also had increased cardiovascular mortality compared with those not treated with atenolol. Patients may be digitalized before therapy with atenolol is resumed.

Bradycardia: Reduce dosage if patients treated with atenolol develop symptoms which may be attributable to slow heart rate.

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

History of Anaphylactic Reaction: While taking beta-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 epinephrine used to treat the allergic reactions.

Allergic Conditions: Allergy may be exaggerated by beta-blockade (e.g., allergic rhinitis during pollen season and allergic reactions to bee and wasp stings). Avoid beta-blockers if there is a risk of bronchospasm.

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

INTERACTIONS WITH OTHER MEDICAMENTS
Concomitant use of calcium channel blockers:
- Verapamil, diltiazem: Bradycardia and heart block may occur and left ventricular end diastolic pressure may increase. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible.
- Dihydropyridine calcium antagonists (e.g., nifedipine) may be administered cautiously with beta-blockers. Reduce dosage or discontinue calcium channel blocker if excessive hypotension develops.

Anti-arrhythmic agents: Class I anti-arrhythmic agents (e.g., disopyramide) and the Class III agent amiodarone may have potentiating effect on atrial conduction time and induce negative inotropic effect. This is seen less frequently with quinidine, class IB agents (e.g., tocainide, mexiletine, lignocaine), class IC agents (e.g., flecainide, propaferone), and the class IV anti-arrhythmic agents.

Use of catecholamine-depleting agents (e.g., reserpine): Observe closely for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Clonidine: Beta-blockers may exacerbate the rebound hypertension that may follow after withdrawal from clonidine. If the two drugs are concomitantly administered, the beta-blocker should be withdrawn several days before the gradual withdrawal of clonidine. In replacing clonidine with beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Anesthetics (e.g., methoxyflurane): Contraindicated with atenolol

Digitalis/digitalis glycosides: There have been reports of excessive bradycardia when beta-blockers are used to treat digitalis intoxication.

Sympathomimetic agents (e.g., epinephrine): Sympathomimetic agents may counteract the effect of beta-blockers

Prostaglandin synthetase inhibitors (e.g., ibuprofen, indomethacin): May decrease the hypotensive effects of beta-blockers

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: Pregnancy Category C. Beta-blockers may cause bradycardia in the fetus and newborn infant. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. Chronic administration of atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intrauterine growth retardation. The use of atenolol in women who are, or may become pregnant requires that the anticipated benefit justify the potential risks to the fetus, particularly in the first and second trimesters, since beta-blockers, in general, have been associated with decreased in placental perfusion resulting in intrauterine deaths, immature and premature deliveries.
Lactation: Exercise caution when atenolol is administered to a breastfeeding woman as it can be excreted in human milk. Neonates of mothers who receive atenolol during breastfeeding may be at risk of hypoglycemia and bradycardia.
Infants and Children: There is no experience with atenolol in children.
Geriatrics: Dosage requirements may be reduced particularly in patients with renal impairment.

UNDESIRABLE EFFECTS
Body as a Whole: Fever combined with aching and sore throat, laryngospasm, and respiratory distress; fatigue; malaise; lupus syndrome; sclerosing serositis
Cardiovascular: Bradycardia, postural hypotension which may be associated with syncope, hypotension, heart failure, heart block, supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia, cardiac reinfarction, total cardiac arrest, nonfatal cardiac arrest, cardiogenic shock, development of ventricular septal defect, development of mitral regurgitation, sick sinus syndrome, left ventricular insufficiency, intermittent claudication, Raynaud's phenomenon, cold extremities, deterioration in heart failure, increase in early death secondary to bradycardia and shock
Gastrointestinal: Diarrhea, nausea, dry mouth, mesenteric arterial thrombosis, ischemic colitis, gastrointestinal disturbance including indigestion, constipation, hepatic toxicity including intrahepatic cholestasis
Hematologic: Purpura, thrombocytopenia, agranulocytosis, increased antinuclear antibodies (ANA)
Metabolic and Nutritional: Elevated liver enzymes, aspartate aminotransferase (AST), blood urea, serum creatinine, bilirubin, hypoglycemia
Musculoskeletal: Ataxia, leg pain
***Nervous*:** Dizziness, vertigo, light-headedness, tiredness, fatigue, lethargy, drowsiness, depression, vivid dreams, hallucination, headache, psychoses, reversible mental depression progressing to catatonia (acute reversible syndrome characterized by disorientation of time and place), short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics, confusion, mood changes, nightmares, paresthesia, vertigo, insomnia, sleep disturbance
Reproductive: Impotence, Peyronie's disease
Respiratory: Wheezing, dyspnea, bronchospasm, pulmonary emboli, asthma, nasal congestion
Skin and Appendages: Psoriasiform skin reactions, exacerbation of psoriasis, reversible alopecia, skin rash, erythematous rash
Special Senses: Visual disturbance, dry eyes, conjunctivitis, tinnitus, otitis
Urogenital: Renal failure

OVERDOSE AND TREATMENT
Manifestation: Overdosage of atenolol may be expected to produce effects that are mainly extensions of pharmacologic effects, including symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. Hypoglycemia may also occur.
Treatment: Empty the stomach immediately by gastric lavage. Initiate symptomatic treatment. For severe bradycardia, IV atropine 1 to 2 mg may be given to induce vagal blockade. If bradycardia persists, an inotrope, IV isoprenaline (25 mcg initially) may be given. The use of cardiac pacemaker may be used in refractory cases. A vasopressor (e.g., dobutamine, dopamine, epinephrine, norepinephrine) may be given for severe hypotension. IV glucagon may be useful if hypotension is refractory to vasopressors. A $beta_2$-stimulant (e.g., salbutamol, tebutaline) or therapy with aminophylline may be given for bronchospasm. For acute cardiac failure, a cardiac glycoside, diuretic, and oxygen should be used. In refractory cases, IV isoprenaline followed, if necessary, by glucagon or IV aminophylline may be useful. Hypoglycemia should be treated with IV dextrose. Hemodialysis may be useful in enhancing elimination of atenolol in patients with severe overdosage.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632)858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITION
Store at temperatures not exceeding 30°C
Keep the product out of sight and reach of children
Protect from light

AVAILABILITY
Atenolol (Therabloc®) 25 mg Tablet, in bister pack of 20's (box of 60's)
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CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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Manufactured by **AMHERST LABORATORIES, INC.**
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Trusted Quality Healthcare

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