PRODUCT MONOGRAPH

Pr APO-ATENIDONE

Atenolol/Chlorthalidone Tablets

100/25mg

Antihypertensive Agent

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T9

Date of Revision:
February 12, 2019

Control # 224199

PRODUCT MONOGRAPH

Pr APO-ATENIDONE

Atenolol/chlorthalidone Tablets

100/25 mg

THERAPEUTIC CLASSIFICATION
Antihypertensive Agent

ACTIONS AND CLINICAL PHARMACOLOGY

APO-ATENIDONE (atenolol/chlorthalidone) combines the antihypertensive activity of two agents, a beta-adrenergic receptor blocking agent (atenolol) and a diuretic (chlorthalidone).
Atenolol is a $beta_1$-selective, beta adrenergic blocking agent, devoid of membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. It is a racemic mixture and the $beta_1$ properties reside in the S(-) enantiomer. $Beta_1$-selectivity decreases with increasing dose.
The mechanism of the antihypertensive effect of atenolol has not been established. Among the factors that may be involved are:

a) competitive ability to antagonize catecholamine-induced tachycardia at the beta receptor sites in the heart, thus decreasing cardiac output.

b) inhibition of renin release by the kidneys.

c) inhibition of the vasomotor centres.

In man atenolol reduces both isoproterenol- and exercise-induced increases in heart rate over the dose range of 50 to 200 mg. At an oral dose of 100 mg the $beta_1$ blocking effects persist for at least 24 hours; the reduction in exercise-induced heart rate increase being about 32% and 13%, 2 and 24 hours after dosing, respectively. The logarithm of the plasma atenolol level correlates with the degree of $beta_1$ blockade but not with the antihypertensive effect.

Chlorthalidone, a monosulfonamyl diuretic, increases excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The mechanism by which chlorthalidone reduces blood pressure is not fully known but may be related to the excretion and redistribution of body sodium. Chlorthalidone usually does not decrease normal blood pressure.

The combination of atenolol with thiazide-like diuretics has been shown to be compatible and generally more effective than either drug used alone as an antihypertensive agent.

Pharmacokinetics

Approximately 40 to 50% of an oral dose of atenolol is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak plasma concentrations occur 2 to 4 hours after dosing and are subject to a 4-fold variability. The plasma levels are proportional to dose over the range 50 to 400 mg and 6 to 16% of atenolol is bound to plasma proteins. The plasma half-life is approximately

6 to 7 hours.

Approximately 60% of an oral dose of chlorthalidone is absorbed from the gastrointestinal tract and excreted unchanged in the urine. Following a single dose, the peak blood concentration of chlorthalidone occurs after approximately 12 hours and decreases thereafter according to first-order kinetics; the disposition half-life is approximately 50 hours. Approximately 75% of chlorthalidone is bound in plasma.

Comparative Bioavailability

A comparative bioavailability study was performed on healthy human volunteers under fasting conditions. The rate and extent of absorption of atenolol and chlorthalidone was measured and compared following a single oral 100 mg/25 mg dose of APO-ATENIDONE (atenolol/chlorthalidone) or TENORETIC® tablets. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Atenolol/Chlorthalidone (Dose: 1 x 100/25 mg) From Measured Data - Under Fasting Conditions
Based on Atenolol

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Apo-Atenidone	Tenoretic®□	
AUC_T (ng.h/mL)	5149 5391 (31)	5224 5391 (25)	98.6
AUC_I (ng.h/mL)	5540 5753 (29)	5601 5750 (23)	98.9
C_{MAX} (ng/mL)	580 610 (30)	594 621 (29)	97.7
T_{MAX}* (h)	3.06 (29)	2.97 (45)	
$T_{½}$* (h)	8.17 (27)	7.88 (20)	

* Arithmetic means (CV%).

** Based on the least squares estimate.

□ Tenoretic® is manufactured by Zeneca Pharma (currently AstraZeneca) and was purchased in Canada.

Summary Table of the Comparative Bioavailability Data
Atenolol/Chlorthalidone (Dose: 1 x 100/25 mg) From Measured Data - Under Fasting Conditions
Based on Chlorthalidone

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Apo-Atenidone	Tenoretic®□	
AUC_{72} (ng.h/mL)	77270 78025 (14)	76427 77292 (15)	100.9
AUC_{I} (ng.h/mL)	128123 131344 (23)	119788 122703 (23)	104.4
C_{MAX} (ng/mL)	1533 1554 (17)	1562 1575 (13)	98.1
T_{MAX}* (h)	12.1 (42)	11.6 (35)	
$T_{½}^{*}$ (h)	52.7 (26)	47.8 (26)	

* Arithmetic means (CV%).

** Based on the least squares estimate.

□ Tenoretic® is manufactured by Zeneca Pharma (currently AstraZeneca) and was purchased in Canada.

INDICATIONS AND CLINICAL USE

This fixed combination is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. It is always better to adjust the dosage of each antihypertensive drug separately, but when the fixed combination corresponds to the optimum drug and dose requirements of the patient, its use may be more convenient in patient management. For further adjustment of dosage, however, it is best to use the individual drugs again. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

APO-ATENIDONE (atenolol/chlorthalidone) is indicated for the maintenance therapy of patients with hypertension who require atenolol and chlorthalidone in the dosage and ratios present in APO-ATENIDONE.

CONTRAINDICATIONS

APO-ATENIDONE (atenolol/chlorthalidone) should not be used in the presence of:

- sinus bradycardia, or bradycardia of other origin
- second and third degree A-V block
- sick sinus syndrome
- right ventricular failure secondary to pulmonary hypertension
- uncontrolled heart failure
- cardiogenic shock
- hypotension
- severe peripheral arterial disorders
- anesthesia with agents that produce myocardial depression
- pheochromocytoma, in the absence of alpha-blockade
- metabolic acidosis
- anuria
- hypersensitivity to atenolol, chlorthalidone or to sulfonamide-derived drugs
- pregnancy or lactation (see WARNINGS, Pregnancy and Use in Lactating Women)

WARNINGS

a) Cardiac Failure

Special caution should be exercised when administering APO-ATENIDONE (atenolol/ chlorthalidone) to patients with a history of cardiac failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure and inhibition with beta blockade always carries the

potential hazard of further depressing myocardial contractility and precipitating cardiac failure.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalised and/or given additional diuretic and the response observed closely.

Atenolol acts selectively without blocking the inotropic action of digitalis on the heart muscle. However, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of atenolol when the two drugs are used concomitantly. The effects of beta blockers and digitalis are additive in depressing A-V conduction. If cardiac failure continues, despite adequate digitalisation, atenolol/ chlorthalidone therapy should be withdrawn immediately and diuretic therapy maintained (see below).

b) Abrupt Cessation of Therapy with APO-ATENIDONE

Patients with angina should be warned against abrupt discontinuation of APO-ATENIDONE. There have been reports of severe exacerbation of angina and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of beta-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of APO-ATENIDONE is planned in patients with angina pectoris, the drug should be stopped and immediately replaced with atenolol and a diuretic given separately, so that the dose of atenolol may be gradually reduced over a period of about two weeks while the dose of diuretic is maintained. The same frequency of administration of both drugs should be maintained. The patients should be carefully observed.

In situations of greater urgency, APO-ATENIDONE should be discontinued stepwise over a shorter time and under closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with APO-ATENIDONE be reinstituted promptly, at least temporarily.

Since ischemic heart disease may be unrecognized, the above advice should be followed in patients considered to be at risk of having asymptomatic ischemic heart disease.

c) Oculomucocutaneous Syndrome

Various skin rashes and conjunctival xerosis have been reported with beta blockers, including atenolol. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic blocking agent (practolol). This syndrome has not been observed with atenolol or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment with APO-ATENIDONE in the event that they occur.

d) Prinzmetal's Angina

Atenolol may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. APO-ATENIDONE therefore, should only be used in these patients with the utmost care.

e) Sinus Bradycardia

Severe sinus bradycardia may occur with the use of atenolol from unopposed vagal activity remaining after blockade of $beta_1$-adrenergic receptors; in such cases, the dose should be reduced.

f) Thyrotoxicosis

In patients with thyrotoxicosis, possible deleterious effects from long-term use of atenolol have not been adequately appraised. Beta blockade may mask the clinical signs of continuing hyperthyroidism or its complications and give a false impression of improvement. Therefore, abrupt withdrawal of atenolol may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm. Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

g) Impaired Renal Function

APO-ATENIDONE should be used with caution since chlorthalidone may precipitate or increase azotemia. Cumulative effects may develop since both components of APO-ATENIDONE are excreted by the kidney. If progressive renal impairment becomes evident, APO-ATENIDONE should be discontinued.

When renal function is impaired, clearance of atenolol is closely related to the glomerular filtration rate. However, significant accumulation does not occur until the creatinine clearance falls below 35 mL/min/1.73m^2.

h) Impaired Hepatic Function

In patients with impaired hepatic function or progressive liver disease, even minor alterations in fluid and electrolyte balance may precipitate hepatic coma. Hepatic encephalopathy, manifested by tremors, confusion and coma, has been reported in association with diuretic therapy, including chlorthalidone.

i) Hypersensitivity Reactions

In patients receiving chlorthalidone, sensitivity reactions may occur with or without a history of allergy or bronchial asthma.

j) Systemic Lupus Erythmatosus

Possible exacerbation of Systemic Lupus Erythmatosus has been reported with thiazide-like diuretics.

k) **Pregnancy**

Use of APO-ATENIDONE is contraindicated during pregnancy.

Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in the cord blood.

No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age.

In a limited number of patients who were given atenolol during the last trimester of pregnancy, low birth weight, neonatal hypoglycemia, bradycardia in the fetus/newborn, and placental insufficiency were observed.

Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia.

Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human dose.

Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone during pregnancy may cause fetal or neonatal jaundice, thrombocytopenia and, possibly, other adverse reactions, which have occurred in the adult.

l) **Use in Lactating Women**

APO-ATENIDONE is contraindicated in lactating women.

There is a significant accumulation of atenolol in breast milk.

Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia.

PRECAUTIONS

a) Bronchospastic Disorders

Patients with bronchospastic diseases should, in general, not receive beta-blockers. Due to the relative $beta_1$-selectivity of atenolol, atenolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$-selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly and the lowest possible dose of atenolol should be used. Despite these precautions, the respiratory status of some patients may worsen, and, in such cases, APO-ATENIDONE (atenolol/chlorthalidone) should be withdrawn.

b) First Degree Heart Block

Due to atenolol's negative effect on A-V conduction time, APO-ATENIDONE should be used with caution in patients with first degree block.

c) Peripheral Arterial Circulatory Disorders

APO-ATENIDONE may aggravate less severe peripheral arterial circulatory disorders (see CONTRAINDICATIONS).

d) Anaphylaxis - Epinephrine and Beta-Blockers

There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacological effects of beta- blockers

and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of brochospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

e) Diabetes and Patients Subject to Hypoglycemia

APO-ATENIDONE should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the premonitory signs (e.g. tachycardia) and symptoms of acute hypoglycemia. Insulin requirements in diabetic patients may be increased, decreased, or unchanged by chlorthalidone. Diabetes mellitus which has been latent may become manifest during chlorthalidone administration.

f) Elective or Emergency Surgery

It is not advisable to withdraw beta-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using APO-ATENIDONE with anaesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg i.v.).

Some patients receiving beta-adrenergic blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

In emergency surgery, since atenolol is a competitive inhibitor of beta-adrenergic receptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or norepinephrine.

g) Fluid or Electrolyte Imbalance

Patients receiving chlorthalidone should be carefully observed for clinical signs of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis and hypokalemia). Periodic determination of serum electrolytes should be performed at appropriate intervals. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, potassium-sparing agents or foods with a high potassium content.

Any chloride deficit during chlorthalidone therapy is generally mild and usually does not require

specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Because calcium excretion is decreased by chlorthalidone, APO-ATENIDONE should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption and peptic ulceration have not been seen.

h) Post-Sympathectomy Patients

The antihypertensive effects of thiazides may be enhanced in the post-sympathectomy patient.

i) Hyperuricemia

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving chlorthalidone.

j) Ethnic Populations

Atenolol appears to be effective and well-tolerated in most ethnic populations, although the response may be less in black patients than in Caucasians.

k) Use in Children

The safety of use of atenolol in children has not been established; therefore, APO-ATENIDONE is not recommended in the pediatric age group.

l) Activities Requiring Mental Alertness

Use of APO-ATENIDONE 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 dizziness or fatigue may occur.

m) Geriatric Use

Clinical studies of APO-ATENIDONE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic renal, or cardiac function, and concomitant diseases or other drug therapy.

n) Drug Interactions

Clonidine

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. (Also see prescribing

information for clonidine).

Reserpine or Guanethidine

Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored because the added beta-adrenergic blocking action of atenolol may produce an excessive reduction of sympathetic activity. APO-ATENIDONE should not be combined with other drugs containing beta blockers.

Antihypertensive Peripheral Vasodilator

The combination of APO-ATENIDONE with an antihypertensive peripheral vasodilator produces a greater fall in blood pressure than either drug alone. The same degree of blood pressure control can be achieved by lower than usual doses of each drug. Therefore, when using such concomitant therapy, careful monitoring of the doses is required until the patient is stabilized.

Norepinephrine

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of the pressor agent in therapy.

Tubocurarine

Thiazide diuretics may increase the responsiveness to tubocurarine.

Lithium

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. The Prescribing Information for lithium preparations should be read before use of such preparations with APO-ATENIDONE.

Alcohol, Barbiturates or Narcotics

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates or narcotics.

Antiarrhythmic Agents

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

Calcium Channel Blockers

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects can lead to prolongation of S-A and A-V conduction, particularly in patients with impaired ventricular function, conduction abnormalities, or diminished cardiac output. This may result in severe hypotension, bradycardia and cardiac failure. Concomitant therapy with dihydropyridines, e.g., nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency. On rare occasions the concomitant administration of intravenous beta adrenergic blocking agents with intravenous verapamil has resulted in serious adverse effects, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Digitalis Glycosides

Digitalis glycosides may potentiate the bradycardia of beta blockade.

Non-Steroidal Anti-Inflammatory Agents

The concomitant use of non-steroidal anti-inflammatory agents may blunt the antihypertensive effects of beta-blockers.

Anaesthetic Agents

Anaesthetics can produce a hypotensive state with associated reflex tachycardia. Since beta blockade will inhibit reflex tachycardia, the hypotensive potential of anaesthetic agents is increased with concomitant use of APO-ATENIDONE, thus the anaesthetic used should be an agent with as little negative inotropic activity as possible (see CONTRAINDICATIONS and PRECAUTIONS, Emergency or Elective Surgery).

Fingolimod

Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is not recommended. Where such co-administration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.

ADVERSE REACTIONS

Adverse reactions that have been reported with the individual components are listed below:

ATENOLOL

The most serious adverse reactions encountered are congestive heart failure, A-V block and bronchospasm. Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

The most common adverse reactions reported in clinical trials with atenolol in 2500 patients are bradycardia (3%), dizziness (3%), vertigo (2%), fatigue (3%), diarrhea (2%) and nausea (3%).

Adverse reactions, occurring with an incidence of less than 1%, grouped by system, are as follows:

Cardiovascular

Heart failure deterioration (see WARNINGS)

Heart block

Palpitations

Lengthening of P-R interval

Chest pain

Lightheadedness

Postural hypotension which may be associated with syncope

Raynaud's phenomenon

Intermittent claudication, or worsening of pre-existing intermittent claudication

Leg pain and cold extremities

Edema

Respiratory

Dyspnea, wheeziness

Cough

Bronchospasm

Central Nervous System

Faintness

Ataxia

Tiredness

Lethargy

Nervousness

Depression

Drowsiness

Vivid dreams

Insomnia

Paresthesia

Headache

Tinnitus

Mood changes

Visual disturbances

Psychoses and hallucinations

Gastrointestinal

Abdominal discomfort, indigestion
Constipation
Anorexia

Miscellaneous

Skin rash

Itchy and/or dry eyes

Psoriasiform skin reactions

Exacerbation of psoriasis

Decreased exercise tolerance

Alopecia

Epistaxis

Flushes

Impotence, decreased libido

Sweating

General body aches

Thrombocytopenia and purpura

POST MARKETING EXPERIENCE

During postmarketing experience with atenolol, cold extremeties, gastrointestinal disturbances and fatigue were commonly reported. The following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, headache, confusion, nightmares, impotence, Peyronie's disease, psoriasiform rash or exacerbation of psoriasis, purpura, reversible alopecia and thrombocytopenia. Rare cases of hepatic toxicity including intrahepatic cholestasis have been reported. Atenolol, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

In a long-term, well controlled trial of 1,627 elderly patients with systolic hypertension, the incidence of dry mouth was significantly higher in patients taking atenolol (12.2%).

Potential adverse reactions

The following adverse reactions have occurred with other beta-blockers but have not been reported with atenolol:

Cardiovascular:	pulmonary edema, cardiac enlargement, hot flushes and sinus arrest
Central Nervous System:	aggressiveness, anxiety, short term memory loss, and emotional lability with slightly clouded sensorium
Allergic:	laryngospasm, status asthmaticus and fever combined with aching and sore throat
Dermatological:	exfoliative dermatitis
Ophthalmological:	blurred vision, burning, and grittiness.
Hematological:	agranulocytosis
Gastrointestinal:	mesenteric arterial thrombosis and ischemic colitis

CHLORTHALIDONE

The following adverse reactions have been reported:

Gastrointestinal Reactions

- Anorexia
- Gastric irritation
- Nausea
- Vomiting
- Cramping
- Diarrhea
- Constipation
- Jaundice (intrahepatic cholestatic jaundice)
- Pancreatitis

Central Nervous System Reactions

- Dizziness
- Vertigo
- Paresthesias
- Headache
- Xanthopsia

Hematologic Reactions

- Leukopenia
- Agranulocytosis
- Thrombocytopenia
- Aplastic anemia

Dermatologic-Hypersensitivity Reactions

- Purpura
- Photosensitivity
- Rash
- Urticaria
- Necrotizing angiitis (vasculitis) (cutaneous vasculitis)
- Lyell's syndrome (toxic epidermal necrolysis)

Cardiovascular Reactions

Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics.

Other Adverse Reactions

- Hyperglycemia
- Glycosuria
- Hyperuricemia
- HyponatremIa
- Muscle spasm
- Weakness
- Restlessness
- Impotence
- Hypokalemia

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific information is available with regard to overdosage of APO-ATENIDONE in humans.

Atenolol: Overdosage with atenolol has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following atenolol overdosage are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia.

Treatment should be symptomatic and supportive and directed to the removal of any unabsorbed drug by induced emesis, or administration of activated charcoal. Atenolol can be removed from the general circulation by hemodialysis. Further consideration should be given to dehydration, electrolyte imbalance and hypotension by established procedures.

Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA:	Atropine 1 to *2* mg intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated. Glucagon in a 10 mg intravenous bolus has been reported to be useful. If required, this may be repeated or followed by an intravenous infusion of glucagon 1 to 10 mg/h 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 or isoproterenol 10 to 25 micrograms given as an infusion at a rate not exceeding 5 micrograms/minute may be given, although larger doses may be required.
HEART BLOCK: (second or third degree)	Isoproterenol, transvenous pacemaker.
CONGESTIVE HEART FAILURE:	Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.
HYPOTENSION:	Vasopressors such as dopamine or norepinephrine. Monitor blood pressure continuously.
BRONCHOSPASM:	A $beta_2$-stimulant such as isoproterenol or terbutaline and/or intravenous aminophylline.
HYPOGLYCEMIA:	Intravenous glucose.
ELECTROLYTE DISTURBANCE:	Monitor electrolyte levels and renal function.

	Institute measures to maintain hydration and electrolytes.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

Chlorthalidone: Symptoms of chlorthalidone overdose include nausea, weakness, dizziness and disturbances of electrolyte balance.

DOSAGE AND ADMINISTRATION

Dosage must be determined for individual patients by titration of each component separately. Where the fixed combination in APO-ATENIDONE (atenolol/chlorthalidone) supplies the dosage so determined, the combination product may be used for maintenance therapy.

One APO-ATENIDONE tablet once daily can be used to administer up to 100 mg of atenolol and 25 mg of chlorthalidone.

If further lowering of the blood pressure is required, another antihypertensive agent may be added to the regimen.

In patients with renal impairment, the dose of the components should be carefully individualized. Recommendations for dosage adjustments for atenolol and chlorthalidone in renal disease are found in the Atenolol prescribing information and Chlorthalidone prescribing information.

If dosage adjustment is necessary during maintenance therapy, it is advisable to use the individual drugs.

PHARMACEUTICAL INFORMATION

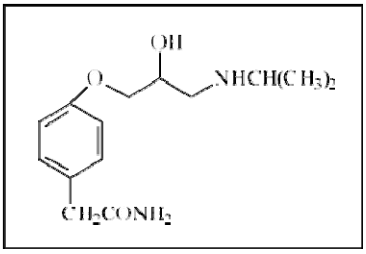
i) Drug Substances

ATENOLOL:

Proper Name: atenolol

Chemical Name: 4-[2'-hydroxy-3'-[(1 -methyl-ethyl) amino]propoxy]-benzeneacetamide

Structural Formula:



Molecular Weight: 266.34 g/mol

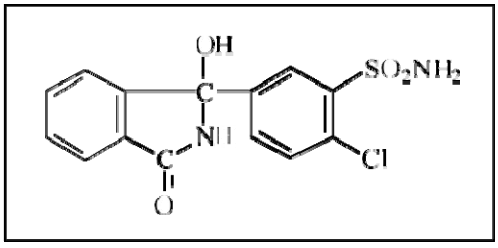
Description: White or almost white crystalline powder. A relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37^0C and a distribution coefficient (n-octanol/buffer) of 0.015 at pH 7.4 and 37^0C; freely soluble in *1* N HCl (300 mg/mL at 25^0C) and less soluble in chloroform (3 mg/mL at 25^0C).

CHLORTHALIDONE:

Proper Name: chlorthalidone

Chemical Name: 2-chloro-5-(1 -hydroxy-3-oxo- 1 -isoindolinyl) benzenesulphonamide

Structural Formula:



Molecular Weight: 338.73 g/mol

Description: White to yellowish-white powder. Water solubility of 0.27 mg/mL at 37^0C.

ii) Composition:

APO-ATENIDONE (atenolol/chlorthalidone 100/25) tablets contain 100 mg atenolol and 25 mg chlorthalidone.

In addition to atenolol and chlorthalidone, each tablet contains the following non-medicinal ingredients: microcrystalline cellulose, crospovidone, magnesium stearate, colloidal silicon dioxide.

iii) Stability and Storage Recommendations:

APO-ATENIDONE tablets should be protected from light and moisture. Store at room temperature (15°C to 30°C).

AVAILABILITY

APO-ATENIDONE 100/25 tablets: white, round, biconvex tablets. Scored and engraved “100” over “25” on one side and engraved “APO” on the other. Available in blisters of 30 and bottles of 100 tablets.

PHARMACOLOGY

ATENOLOL/CHLORTHALIDONE Combination

In rats, atenolol administered in combination with chlorthalidone does not interfere with the diuretic action of chlorthalidone or with beta-blocking activity of atenolol.

ATENOLOL

Animal Studies

Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner’s glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and an increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

Effects on the Cardiovascular System

In anesthetized cats, atenolol infusion reduces the chronotropic response to isoproterenol and right cardiac sympathetic nerve stimulation.

In anesthetized dogs, atenolol 0.03 mg/kg i.v. depresses the heart rate by 22%, cardiac contractile force by 16% and diastolic blood pressure by 11%.

Studies in rats showed that atenolol was devoid of intrinsic sympathomimetic activity.

Atenolol in concentrations up to 10 mg/mL had no local anesthetic effect on the isolated sciatic nerve of the frog.

Atenolol (5 to 20 mg/kg i.v.) was without effect on the ventricular tachycardia produced by toxic levels of ouabain in anesthetized dogs. Atenolol (0.2 mg/kg i.v.) protected coronary ligated dogs from the arrhythmogenic activity of adrenaline on the fourth day after ligation (when the cardiac rhythm was predominantly sinus).

Single oral doses of 100 mg atenolol given to volunteers reduced exercise-induced tachycardia by 31 % at 4 hours and by 15% at 24 hours after administration. The maximal suppression of the systolic blood pressure response to exercise was 21 % at 4 hours.

Effects on Plasma Renin Activity

Studies in hypertensive patients have shown that the antihypertensive effect of atenolol is associated with a decrease in plasma renin activity.

Effects on Pulmonary Function

The effects of a single 100 mg dose of atenolol on forced expiratory volume (FEV_1) and airways resistance (AWR) were assessed in 10 patients with labile asthma. The cardioselective agents tested in this comparative trial, including atenolol, usually had a lesser dose-related effect on airway function than non-selective beta-blockers. Atenolol produced a smaller decrease in FEV_1 than did the non-selective agents and did not inhibit the bronchodilator response to isoprenaline. The decrease in FEV_1 was 8 to 9%.

Other studies in asthmatic patients have reported similar decreases in FEV_1 with atenolol. Dose-effect comparisons with cardioselective agents have shown a fall in FEV_1 values at the higher doses, indicating some $beta_2$-blocking effect.

Metabolic Effects

Atenolol did not potentiate the hypoglycemic effects of insulin in 12 patients with diabetes.

CHLORTHALIDONE

Chlorthalidone has been shown to reduce mean diastolic blood pressure in the genetically hypertensive rat and has an effect on norepinephrine vasoconstriction in animal studies.

Hypertension studies with chlorthalidone 12.5 to 100 mg once daily have shown that the dose-response curve is very flat for all doses above 25 mg. Adequate 24-hour reduction in blood pressure was obtained with the 25 mg dose.

In vivo and in vitro studies in rats have shown that chlorthalidone produces an increased excretion of water, sodium, chloride and to a lesser extent, potassium and bicarbonate.

Chlorthalidone has been reported to produce hyperglycemia in the rat following single large doses of the drug.

Chlorthalidone has no effect on renal circulation or glomerular filtration rate.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	LD_{50} mg/kg Chlorthalidone	LD_{50} mg/kg Atenolol	LD_{50} mg atenolol/kg Fixed Combination*
Mouse	M&F	Oral i.p. oral		>2,500	>3,125
	M&F			525	655
Rat	M&F		>10,000	>5,000	>5,000
	M	i.p.	6,520	268	122
	F	i.p.	3,025	268	233

*The fixed combination contained at 4:1 ratio of atenolol to chlorthalidone.

Six-Month Oral Administration Study in Rats

Atenolol and chlorthalidone alone and in combination were administered by gavage, to groups of 20 male and 20 female CD rats, once a day, 7 days a week for 6 months. Doses per group were 0, atenolol 10, chlorthalidone 2.5, and combination atenolol/chlorthalidone 10/2.5 mg/kg/day.

Results Increased urine volume for combination treated rats; slight decrease in growth rate for rats treated with atenolol or chlorthalidone alone.

Six Month Oral Administration Study in Dogs

Atenolol and chlorthalidone alone and in combination were administered as tablets in gelatine capsules to groups of 32 female and 32 male beagle dogs, once daily, 7 days a week for 6 months. Same doses as used in the rat study.

Results Atenolol caused a reduction in heart rate and blood pressure in dogs receiving atenolol alone or in combination. Chlorthalidone alone or in combination was associated with a decrease in serum potassium levels. In dogs dosed with the combination a lower mean prostate weight was observed.

Chronic Toxicity Studies (1 year)

No 12 month studies have been conducted for chlorthalidone alone or in combination with atenolol.

ATENOLOL

Species	Strain	Sex		Dose mg/kg/day	Route	Duration (mo)	Effects
		M	F				

Dog	Beagle	20	20	0, 50, 100, 200	oral	12	Decreased heart rate. Prolongation of PR interval on ECG. Vacuolation of epithelial cells of duodenal Brunner's glands: 5/10 low dose, 2/10 middose, 7/10 high dose. One high dose female died.
Dog	Beagle	15	15	0, 15	oral	12	Vacuolation of epithelium 200 of Brunner's glands 9/10 high dose; 1/10 low dose.

Teratology and Reproduction Studies

Combination (Atenolol/Chlorthalidone)

Species	Free combination dosage	Period of administration	Signs of toxicity
Rats	up to 300 mg/kg/day (4:1 atenolol:CHT)	days 6-15 of pregnancy	nervousness, decreased weight gain,decreased food consumption, two deaths (at high dose level only).
Rabbits	up to 25 mg/kg/day (4:1 atenolol:CHT)	days 6-18 of pregnancy	no observed malformations
Rabbits	up to 200 mg/kg/day (4:1 atenolol:CHT)	days 6-18 of pregnancy	slight decrease in weight gain; dose-related increase in the numbers of embryonic resorptions.

Atenolol

Atenolol associated malformations were not observed when atenolol was administered at oral doses of up to 200 mg/kg/day, days 6 to 15 of gestation in rats or at doses of up to 25 mg/kg/day, days 6 to 18 of gestation in rabbits. Dose levels of 50 or more mg/kg/day were, however, associated with an increased incidence of resorptions in rats. Although a similar effect was not seen in rabbits, it should be noted that the compound was not evaluated in rabbits at doses above 25 mg/kg/day. Atenolol, administered at doses of up to 200 mg/kg/day, for 11 weeks prior to mating in males or 2 weeks prior to mating in females, did not adversely affect fertility of male or female rats. Growth or survival of offspring were not affected when pregnant females were exposed at 200 mg/kg/day from day 15 of gestation to day 21 post partum.

Chlorthalidone

Administration of various doses of chlorthalidone to pregnant mice, rats, hamsters and rabbits did not affect litter size, fetal body weight or the number of resorptions.

Carcinogenicity Studies

Carcinogenicity studies have not been carried out with the combination or chlorthalidone alone.

Atenolol was administered to 3 groups of 65 male and 65 female CR7B1/1OJ mice at dietary levels of 0,150 and 300 mg/kg/day for 18 months followed by the control diet for an additional three months. A fourth group received 2-AAF (positive control) and a fifth was the negative control group. Retardation in weight gain was observed. There was no statistically significant difference in mortality, number of tumor bearers, number of tumors in each animal or the total number of tumors in treated and negative control animals.

Two studies were conducted in Alderley Park Strain I rats. One study employed doses of 150 and 300 mg/kg/day for 18 months followed by the control diet for an additional 6 months, while the second study used doses of 75, 150 and 300 mg/kg/day for 24 months. Results from the two studies showed no significant difference in mortality for treated and control groups. No apparent carcinogenic potential was observed.