PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr AA-ATENIDONE

Atenolol and Chlorthalidone Tablets

Tablets, 50/25 mg and 100/25 mg, Oral

USP

Antihypertensive Agent

AA Pharma Inc.
1165 Creditstone Road Unit #1
Vaughan, Ontario
L4K 4N7
www.aapharma.ca

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AA-ATENIDONE (atenolol and chlorthalidone tablets) is indicated for:

- Treatment of hypertension for patients for whom combination therapy with atenolol and chlorthalidone is required.

This fixed combination is not indicated for initial therapy of hypertension. See 4.2 Recommended Dose and Dosage Adjustment.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AA-ATENIDONE in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

AA-ATENIDONE (atenolol and chlorthalidone) is contraindicated in

- Patients with known hypersensitivity to atenolol, chlorthalidone or to sulfonamide-derived drugs or to any ingredient in the formulation, including any non-medical ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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.
- Pregnancy or breast-feeding. See 7.1.1 Pregnant Women and 7.1.2 Breast-feeding.
- Severe renal failure (creatinine clearance lower than 30 ml/min) severe hepatic failure, refractory hypokalemia or conditions involving enhanced potassium loss, hyponatremia, hypercalcemia, hyperuricemia (history of gout or uric acid calculi), untreated Addison's Disease and concomitant lithium therapy.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

One AA-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.

Pediatrics

Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics.

4.4 Administration

AA-ATENIDONE tablets should be taken whole with a glass of water at the same time each day.

4.5 Missed Dose

If the patient misses a dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule. Do not double dose.

5 OVERDOSAGE

No specific information is available with regard to overdosage of AA-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)	lsoproterenol, 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 50/25 contains 50 mg atenolol and 25 mg chlorthalidone, 100/25 contains 100 mg atenolol and 25 mg chlorthalidone	colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose.

AA-ATENIDONE 50/25 tablets: white, round, biconvex tablets. Scored and engraved “50” over “25” on one side and engraved “APO” on the other. Available in bottles of 100 tablets.

AA-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 bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity.

Cardiovascular

Cardiac Failure: Special caution should be exercised when administering AA-ATENIDONE (atenolol and 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).

Abrupt Cessation of Therapy with AA-ATENIDONE: Patients with angina should be warned against abrupt discontinuation of AA-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 AA-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, AA-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 AA-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.

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. AA-ATENIDONE therefore, should only be used in these patients with the utmost care.

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.

First Degree Heart Block: Due to atenolol's negative effect on A-V conduction time, AA-ATENIDONE should be used with caution in patients with first degree block.

Peripheral Arterial Circulatory Disorders: AA-ATENIDONE may aggravate less severe peripheral arterial circulatory disorders. See 2 CONTRAINDICATIONS.

Driving and Operating Machinery

Activities Requiring Mental Alertness: Use of AA-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.

Endocrine and Metabolism

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.

Diabetes and Patients Subject to Hypoglycemia: AA-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.

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

Hypercholesterolemia: Small and partially reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is equivocal. Chlortalidone should not be used as a first-line drug for long-term treatment in patients with hypercholesterolemia. If chlortalidone must be used, serum lipids should be regularly monitored. If there is a rise in lipid levels, withdrawal of chlortalidone should be considered.

Hepatic/Biliary/Pancreatic

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.

Immune

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

Monitoring and Laboratory Tests

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, AA-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.

Serum glucose levels may increase with chronic use.

Ophthalmologic

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 AA-ATENIDONE in the event that they occur.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma related to chlorthialidone: Chlorthialidone, a thiazide-like diuretic, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity, blurred vision or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue "**AA-ATENIDONE"** as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Peri-Operative Considerations

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 AA-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.

Post-Sympathectomy Patients: The antihypertensive effects of thiazides may be enhanced in the post-sympathectomy patient.

Renal

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

Respiratory

Bronchospastic Disorders: Patients with bronchospastic diseases should, in general, not receive beta-blockers. Due to the relative beta1-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 beta1-selectivity is not absolute, a beta2-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, AA-ATENIDONE (atenolol/chlorthalidone) should be withdrawn.

Sensitivity/Resistance

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

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.

7.1 Special Populations

7.1.1 Pregnant Women

Use of AA-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.

Chlortalidone, like other diuretics, can cause placental hypoperfusion. Since they do not prevent or alter the course of EPH (edema, proteinuria, hypertension)-gestosis (pre-eclampsia), these drugs must not be used to treat hypertension in pregnant women. 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. See 2 CONTRAINDICATIONS; 10.3 Pharmacokinetics, Special Populations and Conditions, Pregnancy and 10.3 Pharmacokinetics, Special Populations and Conditions, Breast-feeding.

7.1.2 Breast-feeding

AA-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.

Thiazide-like diuretics, like chlorthalidone, are excreted in human milk. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, use in lactating mothers is contraindicated. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. See 2 CONTRAINDICATIONS and 10.3 Pharmacokinetics, Special Populations and Conditions, Breast-feeding.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety of use of atenolol in children has not been established; therefore, AA-ATENIDONE is not recommended in the pediatric age group.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Clinical studies of AA-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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

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%).

The most serious adverse reactions encountered with atenolol 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%).

Serious adverse reactions reported with chlorthalidone include cardiac arrhythmia, dyspnea, aplastic anemia and agranulocytosis. Most frequent adverse reactions (≥10%) include hypokalemia, hyperuricemia, and hyperlipidemia.

Chlorthalidone:

The following adverse reactions have been reported:

Blood and lymphatic system disorders:

Rare: Leukopenia, thrombocytopenia.

Not known: Agranulocytosis, aplastic anemia.

Eye disorders:

Not known: Xanthopsia.

Gastrointestinal disorders:

Rare: Nausea, vomiting, diarrhea, constipation.

Very rare: Pancreatitis.

Not known: Gastric irritation, cramping.

General disorders and administration site conditions:

Not known: Weakness.

Hepatobiliary disorders:

Rare: Jaundice (intrahepatic cholestatic jaundice).

Immune system disorders:

Very rare: Necrotizing angiitis (vasculitis) (cutaneous vasculitis).

Not known: Lyell's syndrome (toxic epidermal necrolysis).

Metabolism and nutrition disorders:

Common: Anorexia, hyperglycemia, hyponatremia.

Uncommon: Hyperuricemia.

Not known: Hypokalemia.

Musculoskeletal and connective tissue disorders:

Not known: Muscle spasm.

Nervous system disorders:

Common: Dizziness.

Rare: Paresthesias, headache.

Not known: Vertigo, restlessness

Renal and urinary disorders:

Rare: Glycosuria.

Reproductive system and breast disorders:

Common: Impotence.

Skin and subcutaneous tissue disorders:

Common: Rash, urticaria.

Rare: Photosensitivity.

Not known: Purpura.

Vascular disorders:

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

Potential adverse reactions

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

Blood and lymphatic system disorders:	Agranulocytosis.
Cardiac disorders:	Pulmonary edema, cardiac enlargement, and sinus arrest.
Eye disorders:	Blurred vision, burning, and grittiness.
Gastrointestinal disorders:	Mesenteric arterial thrombosis and ischemic colitis.
Nervous system disorders:	Short term memory loss.
Psychiatric disorders:	Aggressiveness, anxiety, emotional lability with slightly clouded sensorium.
Respiratory, thoracic, and mediastinal disorders:	Laryngospasm, status asthmaticus, and fever combined with aching and sore throat.
Skin and subcutaneous tissue disorders:	Exfoliative dermatitis.
Vascular disorders:	Hot flushes.

8.2 Clinical Trial Adverse Reactions

No information is available.

8.3 Less Common Clinical Trial Adverse Reactions

Atenolol:

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

Blood and lymphatic system disorders:	Thrombocytopenia
Cardiac disorders:	Heart failure deterioration (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular) Heart block, Palpitations, Chest pain, Lightheadedness

Eye disorders:	Visual disturbances, Ichy and/or dry eyes.
Gastrointestinal disorders:	Abdominal discomfort, Indigestion, Constipation.
General disorders and administration site conditions:	Edema, Tiredness, Flushes, General body aches, Decreased exercise tolerance.
Investigations:	Lengthening of P-R interval.
Metabolism and nutrition disorders:	Anorexia.
Musculoskeletal and connective tissue disorders:	Leg pain.
Nervous System disorders:	Faintness, Ataxia, Drowsiness, Vivid dreams, Paresthesia, Headache, Tinnitus
Psychiatric disorders:	Lethargy, Nervousness, Depression, Insomnia, Mood changes, Psychoses and hallucinations
Reproductive system and breast disorders:	Impotence, Decreased libido.
Respiratory, thoracic, and mediastinal disorders:	Dyspnea, Wheeziness, Cough, Bronchospasm, Epistaxis.
Skin and subcutaneous tissue disorders:	Skin rash, Psoriasiform skin reactions, Exacerbation of psoriasis, Alopecia, Sweating, Purpura
Vascular disorders:	Postural hypotension which may be associated with syncope, Raynaud's phenomenon, Intermittent claudication, or worsening of pre-existing intermittent claudication, cold extremities.

8.5 Post-Market Adverse Reactions

During post-marketing 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:

Blood and lymphatic system disorders:	Thrombocytopenia.
Eye disorders:	Choroidal effusion, acute myopia, acute angle-closure glaucoma (frequency unknown).
Investigations:	Elevated liver enzymes and/or bilirubin.
Nervous system disorders:	Headache, confusion.
Psychiatric disorders:	Nightmares, impotence.

Reproductive system and breast disorders:	Peyronie's disease.
Skin and subcutaneous tissue disorders:	Psoriasiform rash or exacerbation of psoriasis, purpura, reversible alopecia.

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.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Consuming alcohol may modify the effect of this product. Limit alcohol consumption during treatment. Patients should also be cautioned that taking alcohol can increase the chance of dizziness and cause the blood pressure to fall even more.
Orthostatic hypotension may occur when taking CHLORTHALIDONE and may be aggravated by alcohol, anesthetics or sedatives

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions for Atenolol

Proper/Common name	Effect	Clinical comment
Alcohol, Barbiturates or Narcotics	↑Orthostatic hypotension	Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates or narcotics.
Anaesthetic Agents	↑Hypotensive potential	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 AA-ATENIDONE, thus the anaesthetic used should be an agent with as little negative inotropic activity as possible. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Peri-Operative Considerations.
Antiarrhythmic Agents	↑Atrial-conduction time	Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Proper/Common name	Effect	Clinical comment
Antihypertensive Peripheral Vasodilator	↓Blood pressure	The combination of AA-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.
Calcium Channel Blockers	↑Severe hypotension, bradycardia and cardiac failure	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.
Clonidine	↑Hypertension	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)
Digitalis Glycosides	↑Bradycardia	Digitalis glycosides may potentiate the bradycardia of beta blockade.

Proper/Common name	Effect	Clinical comment
Fingolimod	↑Bradycardic effects	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.
Lithium	↓Renal clearance ↑Lithium toxicity.	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 AA-ATENIDONE.
Non-Steroidal Anti-Inflammatory Agents	↓Antihypertensive effects	The concomitant use of non-steroidal anti-inflammatory agents may blunt the antihypertensive effects of beta-blockers.
Norepinephrine	↓Norepinephrine	Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of the pressor agent in therapy.
Reserpine or Guanethidine	↓Sympathetic activity	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. AA-ATENIDONE should not be combined with other drugs containing beta blockers.

Table 3 - Established or Potential Drug-Drug Interactions for Chlorthalidone

Common name	Source of Evidence	Effect	Clinical comment
ACE inhibitors	T	The antihypertensive effect of ACE inhibitors is potentiated in the presence of agents that increase plasma renin activity (diuretics).	A cautious dosage schedule should therefore be adopted when an ACE inhibitor is added to a diuretic agent.

Common name	Source of Evidence	Effect	Clinical comment
Alcohol, barbiturates and narcotics	C	Potentiation of orthostatic hypotension may occur	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Allopurinol	T	Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.	Dosage adjustment of allopurinol may be required.
Amantadine	T	Co-administration of thiazide diuretics may increase the risk of adverse effects from amantadine.	
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor serum potassium level.
Anticholinergics (e.g., atropine, biperiden)	T	The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and rate of gastric emptying.	Dose adjustment of thiazide may be required.
Antineoplastic Agents (e.g., cyclophosphamide, methotrexate)	T, C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance the myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestrants, e.g. Cholestyramine and colestipol resins	T	Absorption of thiazide diuretics is decreased by cholestyramine because Bile acid sequestrants bind thiazide diuretics in the gut and impair	Give thiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor

Common name	Source of Evidence	Effect	Clinical comment
		gastrointestinal absorption by 43- 85%., A decrease in pharmacological effect may be expected.	blood pressure, and increase dose of thiazide, if necessary.
Calcium or Vitamin D supplements	T C	Concomitant use of thiazide diuretics may decrease urinary excretion of calcium, and coadministration of Vitamin D may potentiate the increase in serum calcium. Concomitant use of thiazide-type diuretics may cause hypercalcemia by increasing tubular calcium reabsorption.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements, and signs of hypercalcemia. Dose reduction and/or withdrawal of calcium and/or Vitamin D supplements may be necessary.
Corticosteroids and Adrenocorticotropic hormone (ACTH)	T	The hypokalemic effects of diuretic may be increased by corticosteroids, ACTH and amphotericin.	Monitor serum potassium, and adjust medications, as required.
Curare Derivatives and Ganglionic Blocking Agents	T	Thiazides may increase responsiveness to curare derivatives and ganglionic blocking agents.	
Cyclosporin	T	Concomitant treatment with diuretics may increase the risk of hyperuricemia and gout-type complications.	
Diazoxide	T	Thiazide diuretics may enhance the hyperglycemic effect of diazoxide.	
Digitalis	CT, T	Thiazide-induced electrolyte disturbances, i.e. hypokalemia,	Concomitant administration of chlorthalidone and

Common name	Source of Evidence	Effect	Clinical comment
		hypomagnesemia, increase the risk of digitalis-induced toxicity, which may lead to fatal arrhythmic events. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.	digitalis requires caution. Monitor electrolytes and digitalis levels closely. Supplement potassium or adjust doses of digitalis or chlorthalidone, as required.
Insulin and Oral Antidiabetic Agents	CT T	Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required. It may be necessary to adjust the dosage of insulin or oral antidiabetic agents in response to changes in glucose tolerance that chlortalidone may produce. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.
Lithium	T	Diuretics enhance the cardiotoxic (manifested in ECG changes) and neurotoxic (manifested by ataxia, confusion, and mental disorientation) effects of lithium and these drugs should not be administered concurrently.	In those rare instances when these drugs must be given together, patients should be observed closely for signs and symptoms of lithium toxicity. Close monitoring of serum electrolytes and lithium concentrations and maintenance of adequate fluid, potassium and sodium intake are also necessary.
NSAIDs	CT	Concomitant administration of certain	If combination use is necessary, monitor renal

Common name	Source of Evidence	Effect	Clinical comment
		NSAIDs (e.g., indomethacin) may weaken the diuretic and antihypertensive activity of thiazides, and there have been isolated reports of a deterioration of renal function in predisposed patients.	function, serum potassium, and blood pressure closely. Dose adjustments may be required.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

AA-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 thus promoting water loss. 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.

10.2 Pharmacodynamics

Atenolol and 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

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 (FEV1) 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 FEV1 than did the non-selective agents and did not inhibit the bronchodilator response to isoprenaline. The decrease in FEV1 was 8 to 9%.

Other studies in asthmatic patients have reported similar decreases in FEV1 with atenolol. Dose- effect comparisons with cardioselective agents have shown a fall in FEV1 values at the higher doses, indicating some beta2-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.

10.3 Pharmacokinetics

Absorption

Atenolol: Approximately 40 to 50% of an oral dose of atenolol is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces.

Chlorthalidone: Approximately 60% of an oral dose of chlorthalidone is absorbed from the gastrointestinal tract and excreted unchanged in the urine.

Distribution

Atenolol: Peak plasma concentrations occur 2 to 4 hours after dosing and are subject to a 4 times 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.

Chlorthalidone: 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.

Metabolism

Atenolol: There is no significant hepatic metabolism of atenolol in man and more than 90% of the absorbed dose reaches the systemic circulation unaltered. Small quantities of a hydroxy metabolite and a glucuronide are produced but neither has major pharmacological activity. As a consequence no accumulation occurs in patients with liver disease and no dosage adjustment is required.

Chlorthalidone: Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and in the faeces, mainly in unchanged form.

Elimination

Atenolol: Approximately 47 and 53% of the oral dose is eliminated in the urine and feces, respectively. Recovery is complete after 72 hours.

Atenolol is primarily eliminated by the kidney, predominantly by glomerular filtration. The normal elimination half-life may increase in severe renal impairment, but no significant accumulation occurs in patients who have creatinine clearance greater than 35 mL/min. The oral dose should be reduced in patients with a creatinine clearance less than 35 mL/min.

Following intravenous administration, peak plasma levels were reached within 5 minutes. Declines from peak plasma levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Over 85% of an intravenous dose is excreted in urine within 24 hours.

Chlorthalidone: The major portion of an absorbed dose of chlortalidone from whole blood and plasma is excreted by the kidneys with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlortalidone is excreted by the kidneys, with a mean renal clearance of 60 ml/min. Metabolism and hepatic excretion into the bile constitute a minor way of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and in the feces, mainly in an unchanged form.

Special Populations and Conditions

- **Pediatrics:** The safety of use of atenolol in children has not been established; therefore, AA-ATENIDONE is not recommended in the pediatric age group.
- **Geriatrics:** Clinical studies of atenolol and chlorthalidone tablets 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. See 7.1.4 Geriatrics**.**
- **Sex:** There is no available information related to differences in sex.
- **Pregnancy:** Atenolol and chlorthalidone tablets are contraindicated during pregnancy and breastfeeding. See 7.1.1 Pregnant Women and 7.1.2 Breast-feeding.
- **Breast-feeding:** Atenolol and chlorthalidone tablets are contraindicated during pregnancy and breastfeeding. Chlorthalidone crosses the placental barrier and passes into the breast milk. in mothers treated with 50 mg chlorthalidone daily before and after delivery, chlorthalidone levels in foetal whole blood are about 15% of those found in maternal blood. See 7.1.2 Breast-feeding.
- **Genetic Polymorphism:** There is no available information related to differences in genetic polymorphism.

- **Ethnic Origin:** Atenolol appears to be effective and well-tolerated in most ethnic populations, although the response may be less in black patients than in Caucasians.
- **Hepatic Insufficiency:** Chlorthalidone should be used with caution in patients with impaired hepatic function of progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.
- **Renal Insufficiency:** 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. See 7 WARNINGS AND PRECAUTIONS, Renal.

  Renal dysfunction does not alter the pharmacokinetics of chlorthalidone, the rate limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes. No dosage adjustment is needed in patients with impaired renal function. Chlorthalidone may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
- **RenalObesity:** There is no available information related to differences due to obesity.

11 STORAGE, STABILITY AND DISPOSAL

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

AA-ATENIDONE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

PART II: SCIENTIFIC INFORMATION

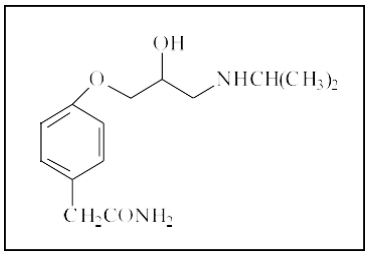
13 PHARMACEUTICAL INFORMATION

Drug Substances

Atenolol:

Proper name:	Atenolol
Chemical name:	4-[2'-hydroxy-3'-[(1 -methyl-ethyl)amino]propoxy]-benzeneacetamide
Molecular mass:	266.34 g/mol

Structural formula:



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

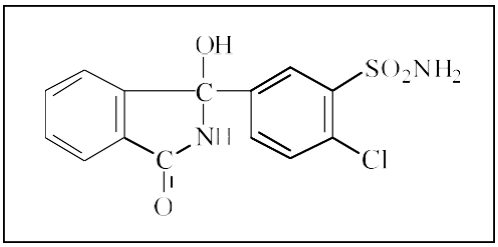
Chlorthalidone:

Proper name: Chlorthalidone

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

Molecular mass: 338.73 g/mol

Structural formula:



Physicochemical properties: White to yellowish-white powder. Water solubility of 0.27 mg/mL at 37°C.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

50/25 mg Tablets

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 double oral 50 mg/25 mg dose of AA-ATENIDONE (Atenolol and chlorthalidone Tablets) or TENORETIC® tablets.

The results from measured data are summarized as follows:

Table 4 - Summary Table of the Comparative Bioavailability Data Atenolol and Chlorthalidone Tablets (Dose: 2 x 50/25 mg) From Measured Data – Under Fasting Conditions Based on Atenolol

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	AA-Atenidone	Tenorectic®Y	
AUC_T (ng.h/mL)	4494 4822 (38)	4632 4775 (24)	97.1
AUC_I (ng.h/mL)	4794 5092 (36)	4939 5069 (22)	97.2
C_{MAX} (ng/mL)	532 578 (39)	581 600 (26)	91.4
T_{MAX}* (h)	2.96 (63)	2.83 (35)	-

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	AA-Atenidone	Tenorectic®ϒ	
$T_{1/2}$* (h)	7.45 (28)	7.61 (25)	-
* Arithmetic means (CV%) ** Based on the least square estimate. ϒ Tenorectic® is manufactured by Zeneca Pharma (currently AstraZeneca) and was purchased in Canada.)			

Table 5 - Summary Table of the Comparative Bioavailability Data Atenolol and Chlorthalidone Tablets (Dose: 2 x 50/25 mg) From Measured Data – Under Fasting Conditions Based on Chlorthalidone

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	AA-Atenidone	Tenorectic®ϒ	
AUC_T (ng.h/mL)	118198 122323 (25)	122054 124330 (20)	100.9
AUC_I (ng.h/mL)	204088 213693 (31)	219908 228253 (27)	104.4
C_{MAX} (ng/mL)	2501 2599 (27)	2574 2626 (21)	98.1
T_{MAX}* (h)	12.5 (51)	10.9 (39)	-
$T_{1/2}$* (h)	52.4 (27)	60.9 (33)	-
* Arithmetic means (CV%) ** Based on the least square estimate. ϒ Tenorectic® is manufactured by Zeneca Pharma (currently AstraZeneca) and was purchased in Canada.)			

<u>100/25 mg tablets</u>

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 AA-ATENIDONE (atenolol/chlorthalidone) or TENORETIC® tablets.

The results from measured data are summarized as follows:

Table 6 - Summary Table of the Comparative Bioavailability Data
Atenolol and Chlorthalidone Tablets (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 (%)**
	AA-Atenidone	Tenoretic®ϒ	
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 square estimate.
 Tenorectic® is manufactured by Zeneca Pharma (currently AstraZeneca) and was purchased in Canada.)

Table 7 - Summary Table of the Comparative Bioavailability Data Atenolol and Chlorthalidone Tablets (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 (%)**
	AA-Atenidone	Tenoretic®ϒ	
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 square estimate.
ϒ Tenorectic® is manufactured by Zeneca Pharma (currently AstraZeneca) and was purchased in Canada.)

15 MICROBIOLOGY

No microbiological information is available for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity:

Table 8 - Summary Table of Chlorthalidone and Atenolol Alone and In combination Acute Toxicity Study Data

Species	Sex	Route	LD_{50} mg/kg Chlorthalidone	LD_{50} mg/kg Atenolol	LD_{50} mg atenolol/kg Fixed Combination*
Mouse	M&F	Oral		>2,500	>3,125
	M&F	i.p.		525	655
Rat	M&F	Oral	>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.

Rats treated with 75, 150 and 300 mg/kg/day atenolol orally for 6 months showed reduction in heart rate. High and intermediate dose showed decreased blood pressure. Spleen and heart weights increased. Chronic myocarditis was seen in all groups including 3 controls. Three high dose and 2 mid-dose animals were killed in moribund state.

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

Chronic toxicity studies were conducted using atenolol only. No 12 month studies have been conducted for chlorthalidone alone or in combination with atenolol.

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).

Table 9 - Summary Table of Atenolol Chronic Toxicity Study Data

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.

Carcinogenicity

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.

Reproductive and Developmental Toxicology

Table 10 - Summary Table of Atenolol and Chlorthalidone Combination Reproductive and Developmental Toxicity Study Data

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. Chlorthalidone had no effect on fertility in rats. Reproduction studies have been performed in the rat and the rabbit at doses up to 420 times the human dose and have revealed no evidence of harm to the fetus due to chlorthalidone.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Pr TENORETIC® 50/25 mg and 100/25 mg Tablets. submission control 190685, Product Monograph, AstraZeneca Canada Inc. JUL 12, 2016

2. [Pr] CHLORTHALIDONE Tablets, 50mg, submission control 256341, Product Monograph, AA Pharma Inc. MAR 11, 2022

3. [Pr] APO-ATENOL Tablets, 50 mg and 100 mg, submission control 249096, Product Monograph, Apotex Inc. MAR 17, 2021

4. [Pr] EDARBYCLOR®, Tablets 40 mg/12.5 mg, 80 mg/12.5 mg and 40 mg/25 mg, submission control: 246568, Product Monograph, Bausch Health, Canada Inc. JUL 21, 2021

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **AA-ATENIDONE**

Atenolol and Chlorthalidone Tablets

Read this carefully before you start taking **AA-ATENIDONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about AA-ATENIDONE.

What is AA-ATENIDONE used for?

AA-ATENIDONE is used to treat high blood pressure (also known as hypertension) in adults.

How does AA-ATENIDONE work?

AA-ATENIDONE contains two active ingredients: atenolol and chlorthalidone. Each active ingredient reduces blood pressure in a different way.

Atenolol belongs to a group of drugs called “beta blockers”.

- It makes your heart beat more slowly and less forcefully.

Chlorthalidone is a diuretic.

- It increases the amount of urine produced by the kidneys.

This medicine does not cure your disease but helps to control it.

What are the ingredients in AA-ATENIDONE?

Medicinal ingredients: atenolol and chlorthalidone

Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose.

AA-ATENIDONE comes in the following dosage forms:

AA-ATENIDONE 50/25 tablets: 50 mg atenolol and 25 mg chlorthalidone

AA-ATENIDONE 100/25 tablets: 100 mg atenolol and 25 mg chlorthalidone

Do not use AA-ATENIDONE if:

- you are allergic to atenolol, chlorthalidone or sulfonamide-derived drugs or any of the ingredients in AA-ATENIDONE.
- you have slow or irregular heartbeats or if you have been told that you have heart block.

- you have severe heart damage and your heart is not able to pump enough blood to meet your body's needs.
- you have heart failure and you notice that your symptoms are getting worse. For example, you feel more tired, are out of breath more often, or have swelling of the ankles.
- you have a problem with your heart's electrical conduction (that causes you to have chest pain, difficulty breathing, nausea, fatigue and fainting).
- you have low blood pressure.
- you have serious problems with blood flow in your feet and legs (peripheral artery disease).
- you have loss of sensation with agents that cause heart failure.
- you have a condition called pheochromocytoma (a tumour of the adrenal gland).
- you have a condition called metabolic acidosis (abnormal levels of acids in your blood).
- you are unable to produce urine.
- you have severe kidney or liver problems.
- you have low blood levels of potassium or any conditions that cause you to lose potassium.
- you have low blood levels of sodium.
- you have high blood levels of calcium or uric acid.
- you have untreated Addison's Disease, a condition involving your adrenal glands (the glands located above your kidneys).
- you are taking lithium, used to treat bipolar disorder.
- you are pregnant, are trying or planning on becoming pregnant.
- you are breastfeeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AA-ATENIDONE. Talk about any health conditions or problems you may have, including if you:

- have a history of heart problems.
- have a history of fainting.
- have asthma or other lung problems (like bronchitis or emphysema).
- have thyroid problems.
- have high cholesterol levels.
- have liver or kidney problems.
- have circulation problems.
- have lupus or gout.
- have diabetes and take medicine to control your blood sugar or have low blood sugar (hypoglycemia).

- have ever been told that you suffer from a particular type of chest pain (angina), called Prinzmetal's angina.
- have had allergic reactions or have allergies.
- have had a surgery on a nerve (sympathectomy).
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- develop a skin rash while taking AA-ATENIDONE.

Other warnings you should know about:

Do not stop taking AA-ATENIDONE suddenly. This could cause chest pain or a heart attack. Follow your healthcare professional's advice to use it less and less before you stop the medication completely.

If you are going to the hospital for an operation, let the medical staff know and in particular the anaesthetist that you are taking AA-ATENIDONE.

Drinking alcohol: Drinking alcohol while taking AA-ATENIDONE may change the effect of the medicine and cause your blood pressure to drop when standing up after sitting or lying down. This may make you feel dizzy or lightheaded.

Driving and using machines: Atenolol in AA-ATENIDONE can cause dizziness and fatigue. Before doing tasks that require special attention, wait until you know how you respond to AA-ATENIDONE.

You may notice that your pulse rate becomes slower while taking AA-ATENIDONE. This is normal but if you are concerned, please talk to your healthcare professional about it.

Eye disorders: Chlorthialidone in AA-ATENIDONE can cause sudden eye disorders such as:

- Choroidal effusion: an abnormal buildup of liquid in your eye that may result in vision changes.
- Myopia: sudden nearsightedness or blurred vision.
- Glaucoma: an increased pressure in your eyes, eye pain. May lead to permanent vision loss if untreated.

If your vision changes, stop taking AA-ATENIDONE and seek medical help. These eye disorders are related and can develop within hours to weeks of starting AA-ATENIDONE.

Check-Ups: Your healthcare professional may do blood tests during your treatment with AA-ATENIDONE. These tests may be done to check your:

- Electrolyte levels, such as potassium, sodium, or chloride.
- Cholesterol levels.
- Glucose levels.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AA-ATENIDONE:

- drugs used for lowering blood pressure or treating angina:
  - alpha-blockers (such as clonidine)
  - calcium channel blockers (such as verapamil, diltiazem or nifedipine)
  - catecholamine-depleting drugs (such as reserpine or guanethidine)
  - vasodilators
- drugs used to treat irregular heartbeats (such as disopyramide or amiodarone)
- drugs used to treat heart failure (such as digoxin)
- non-steroidal anti-inflammatory agents (NSAIDs) (such as indomethacin or ibuprofen)
- anesthetic drugs used during surgery
- alcohol, sleeping pills (barbiturates) or strong pain medications (narcotics)
- norepinephrine, a heart stimulant
- lithium, a drug used to treat certain psychiatric disorders
- fingolimod, a drug used to treat multiple sclerosis
- allopurinol, a drug used to prevent gout
- amantadine, a drug used to treat Parkinson's disease
- amphotericin B, a drug used to treat fungal infections
- anticholinergic drugs (such as atropine or biperiden)
- drugs used to treat cancer (such as cyclophosphamide or methotrexate)
- drugs used to lower your cholesterol (such as cholestyramine or colestipol resins)
- calcium or vitamin D supplements
- corticosteroids, drugs used to reduce inflammation
- muscle relaxants
- cyclosporine, a drug used to suppress your immune system
- diazoxide, a drug used to treat low blood sugar
- digitalis, a drug used to treat heart conditions
- insulin and oral medications used to treat diabetes

How to take AA-ATENIDONE:

Take AA-ATENIDONE:

- exactly as prescribed by your healthcare professional.
- by swallowing the tablet whole with water.
- once a day, at the same time each day.

Your healthcare professional will decide how much AA-ATENIDONE you should take each day depending on your condition.

If you have the impression that the effect of AA-ATENIDONE is too strong or too weak, talk to your healthcare professional as soon as possible.

Do not stop taking AA-ATENIDONE or change your dose without consulting your healthcare professional. This can be dangerous.

Usual dose:

Adults: One tablet per day.

Overdose:

If you think you, or a person you are caring for, have taken too much AA-ATENIDONE, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take the dose as soon as you remember. Do NOT take a double dose to make up for the missed dose.

What are possible side effects from using AA-ATENIDONE?

These are not all the possible side effects you may have when taking AA-ATENIDONE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- cough
- cold fingers and toes
- constipation
- diarrhea
- dizziness
- dry mouth
- fatigue
- headache
- impotence (not able to have an erection)
- indigestion
- itchy or dry eyes
- joint and back pain
- leg pain
- nausea
- nosebleeds

- shortness of breath
- skin rash
- stomach discomfort
- sweating
- tiredness
- trouble sleeping
- vertigo

AA-ATENIDONE can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON:			
Chest pain or discomfort			√
Heart arrhythmia (irregular heartbeat): very fast (tachycardia) or unusually slow (bradycardia) heartbeat, dizziness, fainting		√	
Low levels of sodium or potassium in the blood: weakness, vomiting, cramps		√	
UNCOMMON			
Allergic reactions: rash, swelling of the lips, face or neck, difficulty breathing or speaking			√
Anorexia (a type of eating disorder): loss of appetite, not eating even if you are hungry, rapid or severe weight loss		√	
Blood conditions **- Anemia** (low red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness **- Leukopenia** (low white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms **- Thrombocytopenia** (low blood platelets): bruising or bleeding for longer		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
than usual if you hurt yourself, fatigue and weakness			
Bronchospasm (when there is a sudden narrowing of the airway): difficulty breathing with wheezing or coughing		√	
Heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise		√	
Skin disorders **- Photosensitivity** (sensitivity to sunlight): itchy, dry, red skin when exposed to sunlight **- Purpura** (bleeding under the skin): bruising, purple spots or patches on your skin **- Urticaria** (skin rash): rash, hives, itchy skin		√	
Toxic Epidermal Necrolysis (TEN) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			√
RARE			
Edema: unusual swelling of the arms, hands, legs, feet, ankles, face or airway passages.		√	
Heart conduction disorders: feeling lightheaded, dizzy or passing out			√
Hypotension (low blood pressure): dizziness or lightheadedness leading to fainting can occur when changing		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
positions, for example from lying down to standing up			
Liver disorder: yellowing of the skin or eyes, dark urine, pale stools, abdominal pain, nausea, vomiting, loss of appetite		√	
Memory problems		√	
Palpitations: fluttering or pounding heart, heart is beating fast, skipping beats		√	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea, vomiting, tenderness when touching the abdomen		√	
UNKNOWN FREQUENCY			
Eye disorders: **- Choroidal effusion** (buildup of liquid in your eyes): blind spots, eye pain, blurred vision **- Myopia:** sudden near sightedness or blurred vision **- Glaucoma:** increased pressure in your eye, eye pain		√	
Necrotizing vasculitis (inflammation of blood vessels under the skin or other tissues): chills, fever, skin discoloration		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15˚C to 30˚C).

Protect from light and moisture.

Do not take your tablets after the expiry date on the container.

Keep out of reach and sight of children.

If you want more information about AA-ATENIDONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.aapharma.ca/en/) or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc.

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