PRODUCT MONOGRAPH

Pr NTP-ATENOLOL/CHLORTHALIDONE

(atenolol/chlorthalidone tablets, USP)

50/25 mg and 100/25 mg

Antihypertensive Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablets 50/25 mg and 100/25 mg	none *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) is indicated for:

- the maintenance therapy of patients with hypertension who require atenolol and chlorthalidone in the dosage and ratios present in NTP-ATENOLOL/CHLORTHALIDONE.

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.

Geriatrics (> *65* years of age):
Clinical studies of atenolol/chlorthalidone 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.

Pediatrics:
The safety of use of atenolol in children has not been established; therefore, NTP-ATENOLOL/CHLORTHALIDONE is not recommended in the pediatric age group.

CONTRAINDICATIONS

NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) should not be used in the presence of:

- Hypersensitivity to NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) to sulfonamide-derived drugs or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- 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 AND PRECAUTIONS**)

WARNINGS AND PRECAUTIONS

General

Abrupt Cessation of Therapy with NTP-ATENOLOL/CHLORTHALIDONE

Patients with angina should be warned against abrupt discontinuation of NTP-ATENOLOL/CHLORTHALIDONE. 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 NTP-ATENOLOL/CHLORTHALIDONE 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, NTP-ATENOLOL/CHLORTHALIDONE 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 NTP-ATENOLOL/CHLORTHALIDONE 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.

Activities Requiring Mental Alertness

Use of NTP-ATENOLOL/CHLORTHALIDONE 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.

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 (eg, 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, NTP-ATENOLOL/CHLORTHALIDONE 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.

Cardiovascular

Cardiac Failure

Special caution should be exercised when administering NTP-ATENOLOL/CHLORTHALIDONE (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, NTP-ATENOLOL/CHLORTHALIDONE therapy should be withdrawn immediately and diuretic therapy maintained (see below).

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 AV conduction time, NTP-ATENOLOL/CHLORTHALIDONE should be used with caution in patients with first degree block.

Peripheral Arterial Circulatory Disorders
NTP-ATENOLOL/CHLORTHALIDONE may aggravate less severe peripheral arterial circulatory disorders (see **CONTRAINDICATIONS**).

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. NTP-ATENOLOL/CHLORTHALIDONE, therefore, should only be used in these patients with the utmost care.

Endocrine and Metabolism
Diabetes and Patients Subject to Hypoglycemia
NTP-ATENOLOL/CHLORTHALIDONE 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.

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.

Hepatic

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.

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 NTP-ATENOLOL/CHLORTHALIDONE with anaesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg iv).

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

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

Respiratory

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, the lowest possible dose of atenolol should be used. Despite these precautions, the respiratory status of some patients may worsen, and, in such cases, NTP-ATENOLOL/CHLORTHALIDONE should be withdrawn.

Sensitivity

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.

Skin

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 NTP-ATENOLOL/CHLORTHALIDONE in the event that they occur.

Special Populations

Pregnant Women: Use of NTP-ATENOLOL/CHLORTHALIDONE 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.

Nursing Women: NTP-ATENOLOL/CHLORTHALIDONE 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.

Pediatrics: The safety of use of atenolol in children has not been established; therefore, NTP-ATENOLOL/CHLORTHALIDONE is not recommended in the pediatric age group.

Geriatrics (> *65* years of age): Clinical studies of atenolol/chlorthalidone 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.

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse

events and for approximating rates.

Adverse Drug Reaction Overview
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%).

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Cardiovascular
Heart failure deterioration (see **WARNINGS AND PRECAUTIONS**)
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

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.

Respiratory:
Dyspnea,wheeziness
Cough
Bronchospasm

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-Market Adverse Drug Reactions
During postmarketing experience with atenolol, 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

DRUG INTERACTIONS

Drug-Drug Interactions

Alcohol, Barbituates or Narcotics:
Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates or narcotics.

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 atenolol/chlorthalidone, thus the anaesthetic used should be an agent with as little negative inotropic activity as possible (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Antiarrhythmic Agents:
Care should be taken when atenolol is used concomitantly with Class I antiarrhythmic agents since these drugs may potentiate the cardiac depressing activity of atenolol.

Antihypertensive Peripheral Vasodilator:
The combination of atenolol/chlorthalidone 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:
Combined use of beta-blockers and calcium channel blockers with negative inotropic effects can

lead to prolongation of SA and AV 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:
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:
Digitalis glycosides may potentiate the bradycardia of beta blockade.

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 NTP-ATENOLOL/CHLORTHALIDONE.

Non-Steroidal Anti-Inflammatory Agents:
The concomitant use of non-steroidal anti-inflammatory agents may blunt the antihypertensive effects of beta-blockers.

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:
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. NTP-ATENOLOL/CHLORTHALIDONE should not be combined with other drugs containing beta blockers.

Tubocurarine:
Thiazide diuretics may increase the responsiveness to tubocurarine.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
- 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 and chlorthalidone prescribing information.
- If dosage adjustment is necessary during maintenance therapy, it is advisable to use the individual drugs.

Recommended Dose and Dosage Adjustment
Dosage must be determined for individual patients by titration of each component separately. Where the fixed combination in NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) supplies the dosage so determined, the combination product may be used for maintenance therapy. One NTP-ATENOLOL/CHLORTHALIDONE 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.

Missed Dose
Patients should be advised to take the missed dose when remembered. However, two doses should not be taken at the same time.

OVERDOSAGE
No specific information is available with regard to overdosage of atenolol/chlorthalidone 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 1-2 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 1-10 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

NTP-ATENOLOL/CHLORTHALIDONE (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.

Pharmacodynamics

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

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. Peak plasma concentrations occur 2 - 4 hours after dosing and are subject to a 4-fold variability. The plasma levels are proportional to dose over the range 50-400 mg and 6 to 16% of atenolol is bound to plasma proteins. The plasma half-life is approximately 6-7 hours.

Chlorthalidone: 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

Special Populations and Conditions

Pediatrics: Pharmacokinetics of atenolol/chlorthalidone have not been studied in the pediatric population.

Geriatrics: Pharmacokinetics of atenolol/chlorthalidone have not been studied in the geriatric population.

Gender: Differences in pharmacokinetics based on gender have not been established.

Race: 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: Differences in pharmacokinetics based on hepatic function have not been established (See **WARNINGS AND PRECAUTIONS**).

Renal Insufficiency: Differences in pharmacokinetics based on renal function have not been established (See **WARNINGS AND PRECAUTIONS**).

Genetic Polymorphism: Differences in pharmacokinetics based on genetic polymorphism have not been established.

STORAGE AND STABILITY

Store at controlled room temperature between 15-30^{o}C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) 50/25 mg Tablets
White to off-white, round, biconvex, scored tablet, engraved with **N** on one side and **50** on the other side. **25**

NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) 100/25 mg Tablets
White to off-white, round, biconvex, scored tablet, engraved with **N** on one side and **100** on the other side. **25**

Composition

NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) 50/25 mg Tablets
Each tablet contains medicinal ingredients: atenolol 50 mg and chlorthalidone 25 mg and non-medicinal ingredients: magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycolate.

NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) 100/25 mg Tablets
Each tablet contains medicinal ingredients: atenolol 100 mg and chlorthalidone 25 mg and non-medicinal ingredients: magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycolate.

Packaging

NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) 50/25 mg Tablets
are packaged in bottles of 100 and unit dose blister packages of 30.

NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) 100/25 mg Tablets
are packaged in bottles of 100 and unit dose blister packages of 30.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

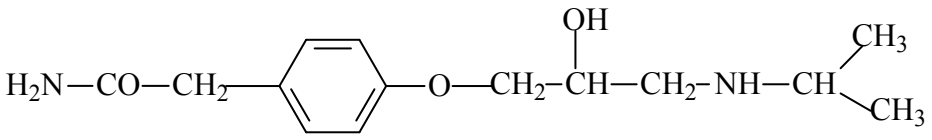
ATENOLOL

Common name: **atenolol**

Chemical name: 2-[4-[(2RS)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]-phenyl]acetamide

Molecular formula and molecular mass: $C_{14}H_{22}N_2O_3$ 266.34

Structural formula:



Physicochemical properties: A white or almost white powder, sparingly soluble in water, soluble in ethanol, slightly soluble in dichloromethane and practically insoluble in ether. Melting range: between 152-156.5°C.

PHARMACEUTICAL INFORMATION

Drug Substance

CHLORTHALIDONE

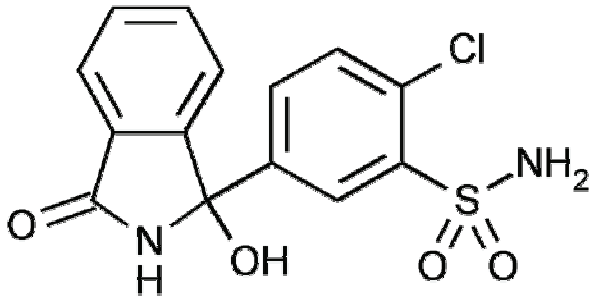
Common name: **chlorthalidone**

Chemical name: Benzenesulfonamide, 2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)

2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzenesulfonamide

Molecular formula and molecular mass: $C_{14}H_{11}ClN_2O_4S$ 338.77

Structural Formula:



Physicochemical properties: A white or yellowish-white powder, practically insoluble in water, soluble in acetone and in methanol, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of the alkali hydroxides. Chlorthalidone melts at about 220°C, with decomposition.

CLINICAL TRIALS

A blinded, single-dose, randomized, two-period, two-sequence, two treatment, crossover bioavailabilty study was performed on 35 healthy male subjects, 18 to 55 years of age to evaluate the comparative bioavailability of two formulations of atenolol/chlorthalidone 50/25 mg tablets under fasting conditions. The pharmacokinetic data calculated for the two atenolol/chlorthalidone formulations are tabulated below.

A Single-Dose, Comparative Bioavailability Study of Two Formulations of Atenolol/Chlorthalidone 50/25 mg Tablets Under Fasting Conditions

Atenolol (1 x 50/25 mg atenolol/chlorthalidone) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means#**	**90% Confidence Interval (%)#**
AUC_T (ng.h/mL)	2706.42 2865.73 (32)	2790.56 2946.59 (34)	96.98	88.73 - 106.01
AUC_I (ng.h/mL)	2755.33 2908.96 (31)	2864.71 3015.12 (33)	96.18	87.92 - 105.22
C_{max} (ng/mL)	288.19 310.34 (38)	290.45 319.59 (47)	99.22	89.27 - 110.29
T_{max}§ (h)	2.42 (39)	2.23 (45)		
$T_{½}$§ (h)	9.04 (34)	10.45 (51)		

* NTP-Atenolol/Chlorthalidone 50/25 mg Tablets (Teva Canada Limited, Canada)

† Tenoretic® 50/25 mg Tablets (AstraZeneca Canada Inc.), purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

Based on the least-squares mean estimates

Chlorthalidone (1 x 50/25 mg atenolol/chlorthalidone) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means#**	**90% Confidence Interval (%)#**
AUC_{72} (ng.h/mL)	2978.85 3047.17 (22)	2857.28 2931.00 (23)	104.25	100.68 - 107.95
AUC_I (ng.h/mL)	4170.07 4251.04 (20)	4087.73 4179.86 (21)	102.01	97.91 - 106.29
C_{max} (ng/mL)	200.33 210.31 (33)	177.66 187.42 (34)	112.76	104.42 - 121.77
T_{max}§ (h)	1.63 (55)	1.86 (45)		
$T_{½}$§ (h)	43.09 (17)	44.84 (20)		

* NTP-Atenolol/Chlorthalidone 50/25 mg Tablets (Teva Canada Limited, Canada)

† Tenoretic® 50/25 mg Tablets (AstraZeneca Canada Inc.), purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

Based on the least-squares mean estimates

A blinded, single-dose, randomized, two-period, two-sequence, two treatment, crossover bioavailabilty study was performed on 30 healthy male subjects, 18 to 55 years of age to evaluate the comparative bioavailability of two formulations of atenolol/chlorthalidone 100/25 mg tablets under fasting conditions. The pharmacokinetic data calculated for the two atenolol/chlorthalidone formulations are tabulated below.

A Single-Dose, Comparative Bioavailability Study of Two Formulations of Atenolol/Chlorthalidone 100/25 mg Tablets Under Fasting Conditions

Atenolol (1 x 100/25 mg) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90 % Confidence Interval (%)**
AUC_T (ng.h/mL)	5328.61 5528.77 (25)	5632.70 5829.40 (26)	94.60	89.28 - 100.24
AUC_I (ng.h/mL)	5444.64 5627.41 (24)	5749.04 5929.35 (25)	94.71	89.50 - 100.22
C_{max} (ng/mL)	507.89 541.07 (32)	554.03 592.03 (34)	91.67	84.32 - 99.66
T_{max}§ (h)	2.92 (42)	3.21 (31)		
$T_{½}$§ (h)	11.37 (50)	10.69 (56)		

* NTP-Atenolol/Chlorthalidone 100/25 mg tablets (Teva Canada Limited, Canada)

† Tenoretic® 100/25 mg tablets (AstraZeneca Canada Inc.), purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

Chlorthalidone (1 x 100/25 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval (%)**
AUC_{72} (ng.h/mL)	2980.43 3059.40 (25)	2815.48 2894.04 (25)	105.86	102.45 - 109.38
AUC_I (ng.h/mL)	4160.69 4262.90 (24)	3932.36 4025.42 (23)	105.81	102.06 - 109.69
C_{max} (ng/mL)	188.89 200.37 (39)	164.63 173.97 (35)	114.74	106.87 - 123.19
T_{max}§ (h)	1.62 (46)	2.07 (46)		
$T_{½}$§ (h)	43.19 (20)	42.83 (20)		

* NTP-Atenolol/Chlorthalidone 100/25 mg tablets (Teva Canada Limited, Canada)

† Tenoretic® 100/25 mg tablets (AstraZeneca Canada Inc.), purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

DETAILED 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 (5-20 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 8-9%.

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 12.5-100 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		>2500	>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.

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

		Sex		Dose		Duration	
Species	**Strain**	**M**	**F**	**Mg/kg/day**	**Route**	**(mo)**	**Effects**
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 6-15 of gestation in rats or at doses of up to 25 mg/kg/day, days 6-18 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.

REFERENCES

1. Amery A, et al.: Mechanism of hypotensive effect during beta-adrenergic blockade in hypertensive patients. Hemodynamic and renin response to a new cardioselective agent, TENORMIN or IC1 66,082. Am Heart J 91:634-642, 1976.

2. Azzolini A, et al.: A new beta-blocker (atenolol) and a diuretic (chlorthalidone) in combination with treatment of hypertension. Curr Therap Res 30:691-697, 1981

3. Barret AM. The pharmacology of atenolol. Postgrad Med J 53(Suppl 3):58-64, 1977.

4. Bateman DN, et al: Atenolol and chlorthalidone in combination for hypertension. Brit J Clin Pharmacol 7:357-363, 1979.

5. Bengtsson C, et al.: Effect of different doses of chlorthalidone on blood pressure, serum potassium and serum urate. Brit Med J 1:197-199, 1975.

6. Boike SC, et al.: Atenolol and chlorthalidone in combination for hypertension. Clin Pharmacol 1:449-453, 1982.

7. Deacon SP and Barnett D. Comparison of atenolol and propranolol during insulin-induced hypoglycaemia. Brit Med J 2:272-273, 1976.

8. Decelmer PBS, et al.: Beta blockers and asthma. Brit Heart J 40:184-189, 1978.

9. Foex P. Beta blockade in anaesthesia. J Clin Hosp Pharm 1983;8:183-190.

10. Harms HH and Spoelstra AJG. Cardiac and bronchial beta adrenoceptor antagonistic potencies of atenolol, metoprolol, acebutolol, practolol, propranolol and pindolol in the anaethestised dog. Clin Exp Pharmacol Physio 5:53-59, 1978,

11. Heel RC, et al.: Atenolol: A review of its pharmcological properties and therapeutic efficacy in angina pectoris and hypertension. Drugs 17:425-460, 1979.

12. Liedholm HI et al.: Accumulation of atenolol and metoprolol in human breast milk. Europ J Clin Pharmacol 20:229-231, 1981.

13. Lunell NO, et al: Circulatory and metabolic effects of acute beta-blockade in severe pre-eclampsia. Acta Obstet Gynecol Scand 58:443-445, 1979.

14. Melander A, et al: Tranplacental passage of atenolol in man. Europ J Clin Pharmacol 14:93-94, 1978.

15. Milocco I, Axison Lof B, William-Olsson GI Appelgren LK. Haemodynamic stability during anaesthesia induction and sternotomy in patients with ischaemic heart disease. A comparison of six anaesthetic techniques. Acta Anaesthesiol Scand 1985;29:465-473.

16. Mulley BA, et al: Placental transfer of chlorthalidone and its elimination in maternal milk. Europ J Clin Pharmacol 13:129-131, 1978.

17. Pritchard BNC, Battersby LA, Cruickshank JM. Overdosage with b-adrenergic blocking agents. Adv Drug React Ac Pois Rev 1984;3:91-111.

18. Reeves PR, et al: Metabolism of atenolol in man. Xenobiotica 8:313-320, 1978.

19. Roberts JG. Beta-adrenergic blockade and anaesthesia with reference to interactions with anaesthetic drugs and techniques. Anaesth Intensive Care 1980;8(3):318-335.

20. Russell JG, et al.: Chlorthalidone in mild hypertension - dose response relationship. Europ J Clin Pharmacol 20:407-411, 1981.

21. Seedat YK: Trial of atenolol and chlorthalidone for hypertension in black South Africans. Brit Med J 281:1241-1243, 1980.

22. Tabachnick IIA, et al: The hyperglycemic activity of benzothiadiazine and other diuretics. Life Sci 4:1931-1936, 1965.

23. Teeuw AH, et al: Atenolol and chlorthalidone on blood pressure, heart rate and plasma renin activity in hypertension. Clin Pharm Therap 25:294-302, 1979.

24. Thorley KT, McAinsh J and Cruickshank JM. Atenolol in the treatment of pregnancy induced hypertension. Brit J Clin Pharmacol 12:725-730, 1981.

25. Product Monograph Tenoretic®. AstraZeneca Canada Inc., Mississauga, Ontario. Date of Revision: July 27, 2005.

26. A Single-Dose, Comparative Bioavailability Study of Two Formulations of Atenolol/Chlorthalidone 50/25 mg Tablets Under Fasting Conditions. Data on file at Novopharm.

27. A Single-Dose, Comparative Bioavailability Study of Two Formulations of Atenolol/Chlorthalidone 100/25 mg Tablets Under Fasting Conditions. Data on file at Teva Canada Limited.

PART III: CONSUMER INFORMATION

PrNTP-ATENOLOL/CHLORTHALIDONE
(atenolol/chlorthalidone tablets)
USP

This leaflet is part III of a three-part "Product Monograph" published when NTP-ATENOLOL/CHLORTHALIDONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NTP-ATENOLOL/CHLORTHALIDONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
NTP-ATENOLOL/CHLORTHALIDONE (atenolol/chlorthalidone) is used to reduce high blood pressure.

What it does:
NTP-ATENOLOL/CHLORTHALIDONE Tablets contain two active ingredients. Atenolol is one of a group of drugs called beta-blockers. It has effects on the heart and circulation. Chlortalidone is one of a group of drugs called diuretics. It increases the amount of urine produced by the kidneys. Exactly how NTP-ATENOLOL/CHLORTHALIDONE Tablets reduce blood pressure is not known.

When it should not be used:
- You have ever had an allergic reaction to NOVO-ATENOLTHALIDONE, atenolol, or chlorthalidone, or to drugs known as sulfonamides, or to any of the other ingredients in this medicine (See "What the nonmedicinal ingredients are").
- You are pregnant, are trying to become pregnant or are breast-feeding.
- You have poor blood circulation, controlled heart failure or first-degree heart block.
- You have or have ever suffered from any heart conditions including heart failure which is not under control, second-or third-degree heart block.
- You have high blood pressure in the circulation to the lungs.
- You have ever suffered from very slow or very irregular heartbeats, very low blood pressure or very poor circulation.
- You have ever been told that you have phaeochromocytoma (high blood pressure caused by a tumour, usually near the kidney which is not being treated).
- You have been told you have metabolic acidosis (abnormal levels of acid in your blood).
- You are unable to produce urine.

What the medicinal ingredient is:
Atenolol and chlorthalidone.

What the nonmedicinal ingredients are:
Magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycolate.

What dosage forms it comes in:
NTP-ATENOLOL/CHLORTHALIDONE is available in tablets 50/25 mg and 100/25 mg strengths.

WARNINGS AND PRECAUTIONS

BEFORE you use NTP-ATENOLOL/CHLORTHALIDONE talk to your doctor or pharmacist if:

- you are taking any other medicines, including any you have bought from the pharmacy.
- you have problems with your kidneys.
- you have asthma, wheezing or any other similar breathing problems, or you get allergic reactions, for example to insect stings. If you have ever had asthma or wheezing, you should not take these tablets unless you have discussed these symptoms with the doctor who first gave you the tablets.
- you have a type of chest pain (angina) called Prinzmetal's angina.
- you have diabetes. NTP-ATENOLOL/CHLORTHALIDONE may modify your normal response to low blood sugar, which usually involves an increase in heart rate.
- you have thyrotoxicosis (a condition caused by an overactive thyroid gland). NTP-ATENOLOL/CHLORTHALIDONE may hide the symptoms of thyrotoxicosis.
- you go into hospital to have an operation, tell the anaesthetist and/or the medical staff that you are taking NTP-ATENOLOL/CHLORTHALIDONE.

NTP-ATENOLOL/CHLORTHALIDONE must not be given to children.

You may notice that your pulse rate becomes slower while you are taking the tablets. This is normal, but if you are concerned, please tell your doctor about it.

Driving and using machines
- Your medicine is unlikely to affect your ability to drive or to operate machinery. However, some people may occasionally feel dizzy or tired when taking NTP-ATENOLOL/CHLORTHALIDONE. If this happens to you, ask your doctor for advice.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with NTP-ATENOLOL/CHLORTHALIDONE include:

- Clonidine (for hypertension or migraine). If you are taking clonidine and NTP-ATENOLOL/CHLORTHALIDONE together, you must not stop taking clonidine unless your doctor tells you to do so. If you have to stop taking clonidine, your doctor will give you careful instructions how to do it.

- Verapamil, diltiazem and nifedipine (which are used to treat hypertension or angina).
- Disopyramide (for irregular heartbeats).
- Digoxin (for heart failure).
- Norepinephrine (a heart stimulant).
- Ibuprofen and indomethacin (for pain and inflammation).
- Lithium (for certain psychiatric disturbances).
- Reserpine or guanethidine.
- Nasal decongestants or other cold remedies (including the ones you can buy in the pharmacy).

If you are taking any other medicines, including any you have bought from the pharmacy, you should tell your doctor.

PROPER USE OF THIS MEDICATION

Usual dose:
Your doctor will tell you how many NTP-ATENOLOL/CHLORTHALIDONE tablets to take each day and when to take them, depending on your condition. Also, read the label on the container. Your pharmacist can help you if you are not sure.

Swallow NTP-ATENOLOL/CHLORTHALIDONE tablets with a drink of water.

Do not stop taking your medicine without talking to your doctor first. In some cases, it may be necessary to stop taking the medicine gradually.

Overdose:
If you accidentally take an overdose NTP-ATENOLOL/CHLORTHALIDONE tablets, either call your doctor straight away, or go to your nearest hospital emergency department. Always take any remaining tablets, the container and the label with you, so that the medicine can be identified.

Missed Dose:
If you forget to take your NTP-ATENOLOL/CHLORTHALIDONE tablets at the right time, take your dose when you remember and then take your next dose at the usual time. Don't take two doses at the same time. If you are worried, ask your doctor or pharmacist for advice.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, there may be some possible side effects while you are taking NTP-ATENOLOL/CHLORTHALIDONE.

Occasionally, a few people may suffer from the following:

Cold hands and feet, tiredness, slow heartbeat, headache, dry mouth, nausea (feeling like vomiting), diarrhea, disturbed sleep, thinning of the hair, mood changes, confusion, delirium or hallucinations, tingling of the hands, dry eyes, disturbances of vision, skin rashes, worsening of psoriasis, dizziness (particularly when standing up), impotence.

Some people may also suffer from numbness and spasm in the fingers (Raynaud's phenomenon).

Other possible side effects are a reduction in the amount of sodium in the blood, which may cause weakness, vomiting and cramps, a reduction in the amount of potassium in the blood, an increase in the amount of uric acid in the blood or a reduction in the number of white blood cells. Your doctor may take blood samples every so often to check on these levels.

Do not stop or restart NTP-ATENOLOL/ CHLORTHALIDONE on your own.

Do not be alarmed by this list of possible side effects. You may not have any of them.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Slow heartbeat and heart block (which can cause dizziness or fainting).		✓	
	Bronchospams, breathlessness, asthma attack			✓
	Swollen ankles, if you have heart failure		✓	
	Decrease in sodium or Potassium		✓	
Uncommon	Pancreatitis (inflammation of a large gland behind the stomach)		✓	
	Jaundice (yellowing of the skin or the whites of your eyes).		✓	

This is not a complete list of side effects. For any unexpected effects while taking NTP-ATENOLOL/CHLORTHALIDONE*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store at room temperature between 15-30°C.
Keep Out of the Reach of Children.

The tablets are only for you and must never be given to anyone else.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited
at: 1-800-268-4127 ext. 5005
or druginfo@novopharm.com

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