

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18240/S26

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 18-240/S-026
NDA 18-760/S-023
NDA 19-058/S-013

JUL 21 1999

Zeneca Pharmaceuticals
Attention: W. J. Kennedy, Ph.D.
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kennedy:

Please refer to your supplemental new drug applications dated June 2, 1999, received June 3, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tenormin (atenolol) 25, 50 and 100 mg Tablets (18-240/S-026), Tenoretic (atenolol and chlorthalidone) 50/25 and 100/25 mg Tablets (18-760/S-023), and Tenormin (atenolol) 5mg/10mL I.V. Injection Ampules (19-058/S-013).

We note that these supplements were submitted as 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

These supplemental new drug applications provide for final printed labeling revised as follows:

NDA 18-240
18-760
19-058

The phrase, "dry mouth" has been added to the **ADVERSE REACTIONS** section.

The address information has been changed to reflect a new logo.

NDA 18-240
18-760

Under the **HOW SUPPLIED** section, the following sentence has been changed from:

to:

Store at controlled room temperature, 20⁰-25⁰ C (68⁰-77⁰F) [see USP].

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NDA 18-760/S-023
NDA 19-058/S-013
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NDA 19-058

Under the **HOW SUPPLIED** section, the following sentence has been changed from:

to:

Store at controlled room temperature, 20⁰-25⁰ C (68⁰-77⁰F) [see USP].

Your submission stated that these changes will be implemented during the first week of July 1999.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling included in your June 2, 1999 submission. Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5300

Sincerely,

JS 7/21/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18240/26

FINAL PRINTED LABELING



PROFESSIONAL INFORMATION BROCHURE

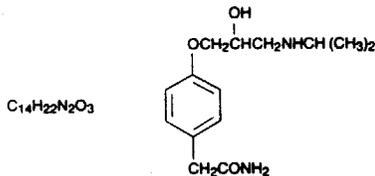
Tenoretic®

(atenolol and chlorthalidone)

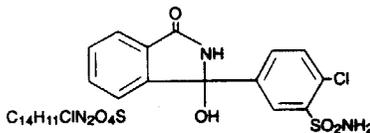
APPROVED
JUL 21 1999

DESCRIPTION

TENORETIC® (atenolol and chlorthalidone) is for the treatment of hypertension. It combines the antihypertensive activity of two agents: a beta₁-selective (cardioselective) hydrophilic blocking agent (atenolol, TENORMIN®) and a monosulfonamide diuretic (chlorthalidone). Atenolol is Benzeneacetamide, 4-[(2-hydroxy-3'-(1-methylethyl) amino) propyl]-.



Atenolol (free base) is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37° C. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C). Chlorthalidone is 2-Chloro-5-[(1-hydroxy-3-oxo-1-isoindolinyl) benzene sulfonamide].



Chlorthalidone has a water solubility of 12 mg/100 mL at 20°C.

Each TENORETIC 100 Tablet contains:	
Atenolol (TENORMIN®)	100 mg
Chlorthalidone	25 mg
Each TENORETIC 50 Tablet contains:	
Atenolol (TENORMIN®)	50 mg
Chlorthalidone	25 mg

Inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

CLINICAL PHARMACOLOGY**TENORETIC**

Atenolol and chlorthalidone have been used singly and concomitantly for the treatment of hypertension. The antihypertensive effects of these agents are additive, and studies have shown that there is no interference with bioavailability when these agents are given together in the single combination tablet. Therefore, this combination provides a convenient formulation for the concomitant administration of these two entities. In patients with more severe hypertension, TENORETIC may be administered with other antihypertensives such as vasodilators.

Atenolol

Atenolol is a beta₁-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits beta₂-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Pharmacodynamics: In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by: (1) reduction in resting and exercise heart rates and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours and persists for at least 24 hours. The effect at 24 hours is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. However, as has been shown for all beta blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the beta₁-selectivity of atenolol has been shown by its reduced ability to reverse the beta₂-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of atenolol producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equivalent oral doses of several beta blockers, atenolol produced a significantly smaller decrease of FEV₁ than nonselective beta blockers, such as propranolol and unlike those agents did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, atenolol increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. Atenolol is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and exercise.

In controlled clinical trials, atenolol given as a single daily dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. Atenolol has been studied in combination with thiazide-type diuretics and the blood pressure effects of the combination are approximately additive. Atenolol is also compatible with methylglucoside, hydralazine and prazosin, the combination resulting in a larger fall in blood pressure than with the single agents. The dose range of atenolol is narrow, and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of atenolol with prolonged use.

Pharmacokinetics and Metabolism: In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between 2 and 4 hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, hydrophilic atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Atenolol also differs from propranolol in that only a small amount (6-16%) is bound to proteins in the plasma. This kinetic profile results in a relatively consistent plasma drug levels with about a fourfold interpatient variation. There is no information as to the pharmacokinetic effect of atenolol on chlorthalidone.

The elimination half-life of atenolol is approximately 6 to 7 hours and there is no alteration of the kinetic profile of the drug by chronic administration. Following doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; but significant accumulation does not occur until the creatinine clearance falls below 35 mL/min/1.73m² (see circular for atenolol [TENORMIN®]).

Chlorthalidone

Chlorthalidone is a monosulfonamide diuretic which differs chemically from thiazide diuretics in that a double ring system is incorporated in its structure. It is an oral diuretic with prolonged action and low toxicity. The diuretic effect of the drug occurs within 2 hours of an oral dose. It produces diuresis with greatly increased excretion of sodium and chloride. At maximal therapeutic dosage, chlorthalidone is approximately equal in its diuretic effect to comparable maximal therapeutic doses of benzothiazide diuretics. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron.

INDICATIONS AND USAGE

TENORETIC is indicated in the treatment of hypertension. This fixed dose combination drug is not indicated for initial therapy of hypertension. If the fixed dose combination represents the dose appropriate to the individual patient's needs, it may be more convenient than the separate components.

CONTRAINDICATIONS

TENORETIC is contraindicated in patients with: sinus bradycardia; heart block greater than first degree; cardiogenic shock; overt cardiac failure (see WARNINGS); anuria; hypersensitivity to this product or to sulfonamide-derived drugs.

WARNINGS

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORETIC should be administered cautiously. Both digitalis and atenolol slow AV conduction.

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. At the first sign or symptom of impending cardiac failure, patients receiving TENORETIC should be digitalized and/or be given additional diuretic therapy. Observe the patient closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, TENORETIC therapy should be withdrawn.

Renal and Hepatic Disease and Electrolyte Disturbances: Since atenolol is excreted via the kidneys, TENORETIC should be used with caution in patients with impaired renal function.

In patients with renal disease, thiazides may precipitate azotemia. Since cumulative effects may develop in the presence of impaired renal function, if progressive renal impairment becomes evident, TENORETIC should be discontinued.

In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma. TENORETIC should be used with caution in these patients.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORETIC is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORETIC should be reinstated if withdrawal symptoms occur. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORETIC therapy abruptly even in patients treated only for hypertension.

Concomitant Use of Calcium Channel Blockers: Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible. (See PRECAUTIONS.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁-selectivity, however, TENORETIC may be used with caution in patients with bronchospastic disease who do not respond to or cannot tolerate, other antihypertensive treatment. Since beta₁-selectivity is not absolute, the lowest possible dose of TENORETIC should be used and a beta₂-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Beta blockers are competitive inhibitors of beta-receptor agonists and their effects on the heart can be reversed by administration of such agents; eg, dobutamine or isoproterenol with caution (see section on Overdosage).

Metabolic and Endocrine Effects: TENORETIC may be used with caution in diabetic patients. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Insulin requirements in diabetic patients may be increased, decreased or unchanged; latent diabetes mellitus may become manifest during chlorthalidone administration.

Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORETIC therapy is to be withdrawn should be monitored closely.

Because calcium excretion is decreased by thiazides, TENORETIC 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.

Hyperuricemia may occur, or acute gout may be precipitated in certain patients receiving thiazide therapy.

Pregnancy and Fetal Injury: Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

TENORETIC was studied for teratogenic potential in the rat and rabbit. Doses of atenolol/chlorthalidone of 8/2, 80/20, and 240/60 mg/kg/day were administered orally to pregnant rats with no evidence of embryofetotoxicity observed. Two studies were conducted in rabbits. In the first study, pregnant rabbits were dosed with 8/2, 80/20, and 160/40 mg/kg/day of atenolol/chlorthalidone. No teratogenic effects were noted, but embryonic resorptions were observed at all dose levels (ranging from approximately 5 times to 100 times the maximum recommended human dose). In the second rabbit study, doses of atenolol/chlorthalidone were 4/1, 8/2, and 20/5 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated.

Atenolol — Atenolol has been shown to produce a dose-related increase in embryofetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.*

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Chlorthalidone — Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS

General: TENORETIC may aggravate peripheral arterial circulatory disorders.

Electrolyte and Fluid Balance Status: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance, ie, hyponatremia, hypochloremic alkalosis, and hypokalemia. 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,

(CONTINUED ON REVERSE SIDE)

adverse effects have been mild and transient. The adverse effects observed for TENORETIC are essentially the same as those seen with the individual components.

Assess: The frequency estimates in the following table were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for atenolol and placebo is similar, causal relationship to atenolol is uncertain.

TENORETIC® (atenolol and chlorthalidone) Tablets

origins, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Measurement of potassium levels is appropriate especially in elderly patients, those receiving digitalis preparations for cardiac failure, patients whose dietary intake of potassium is abnormally low, or those suffering from gastrointestinal complaints.

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 or foods with a high potassium content.

Any chloride deficit during thiazide 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.

Drug Interactions: TENORETIC may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with TENORETIC plus a catecholamine depletor (eg, reserpine) should be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.

Calcium channel blockers may also have an additive effect when given with TENORETIC. (See WARNINGS.)

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read cautions for lithium preparations before use of such preparations with TENORETIC.

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Other Precautions: In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose, did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Six month oral administration studies were conducted in rats and dogs using TENORETIC doses up to 12.5 mg/kg/day (atenolol/chlorthalidone 10/2.5 mg/kg/day — approximately five times the maximum recommended human antihypertensive dose). There were no functional or morphological abnormalities resulting from dosing either compound alone or together other than minor changes in heart rate, blood pressure and urine chemistry which were attributed to the known pharmacologic properties of atenolol and/or chlorthalidone.

Chronic studies of atenolol 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 (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose) and 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 antihypertensive dose), respectively.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Use in Pregnancy: Pregnancy Category D: See WARNINGS - Pregnancy and Fetal Injury.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

	Total-Volunteered and Elicited (US Studies)		Total-Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164)	Placebo (n = 205)	Atenolol (n = 399)	Placebo (n = 407)
	%	%	%	%

	Total-Volunteered and Elicited (US Studies)		Total-Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164)	Placebo (n = 205)	Atenolol (n = 399)	Placebo (n = 407)
	%	%	%	%
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Lag Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-Headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see Warnings)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

During postmarketing experience, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasisiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, and dry mouth. TENORETIC, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

Chlorthalidone: Cardiovascular: orthostatic hypotension; Gastrointestinal: anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; CNS: vertigo, paresthesia, xanthopsia; Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis); Miscellaneous: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Clinical trials of TENORETIC conducted in the United States (89 patients treated with TENORETIC) revealed no new or unexpected adverse effects.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects not observed in clinical trials with atenolol but reported with other beta-adrenergic blocking agents should be considered potential adverse effects of atenolol. Nervous System: Reversible mental depression progressing to cataplexy; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on neuro-psychometric tests; Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS); Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis; Hematologic: Agranulocytosis; Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. Other: Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (See DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with atenolol (TENORMIN). Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol (TENORMIN) therapy with subsequent resolution or quiescence of the reaction.

Clinical Laboratory Test Findings: Clinically important changes in standard laboratory parameters were rarely associated with the administration of TENORETIC. The changes in laboratory parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in uric acid and decreases in serum potassium.

OVERDOSAGE

No specific information is available with regard to overdosage and TENORETIC in humans. 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.

Assess: 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 overdose 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. 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.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or 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 (levateranol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta₂-stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

ELECTROLYTE DISTURBANCE: Monitor electrolyte levels and renal function. Institute measures to maintain hydration and electrolytes.

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

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

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED (See INDICATIONS AND USAGE)

Chlorthalidone is usually given at a dose of 25 mg daily; the usual initial dose of atenolol is 50 mg daily. Therefore, the initial dose should be one TENORETIC 50 tablet given once a day. If an optimal response is not achieved, the dosage should be increased to one TENORETIC 100 tablet given once a day.

When necessary, another antihypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs until creatinine clearance falls below 35 mL/min/1.73m² (normal range is 100-150 mL/min/1.73m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (mL/min/1.73m ²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

HOW SUPPLIED

TENORETIC 50 Tablets (atenolol 50 mg and chlorthalidone 25 mg), NDC 0310-0115, (white, round, biconvex, uncoated tablets with TENORETIC on one side and 115 on the other side, bisected) are supplied in bottles of 100 tablets.

TENORETIC 100 Tablets (atenolol 100 mg and chlorthalidone 25 mg), NDC 0310-0117, (white, round, biconvex, uncoated tablets with TENORETIC on one side and 117 on the other side) are supplied in bottles of 100 tablets.

Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Dispense in well-closed, light-resistant containers.

ZENECA

Manufactured for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
By: IPR Pharmaceuticals, Inc.
Carolina, Puerto Rico 00984-1967

64112-01

Rev D 01/99



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 18240/S26

CHEMISTRY REVIEW(S)

AUG 26 1999

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 18-760
3. Name and Address of Applicant (City & State) Zeneca Pharmaceuticals Group 1800 Concord Pike Wilmington, DE 19850-5437		4. Supplement(s) Number(s) Date(s) S-023 6-2-99	
5. Drug Name Tenoretic	6. Nonproprietary Name 1.) atenolol 2.) chlorothalidone		8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Special Supplement Changes being Effected, final printed labeling.			
9. Pharmacological Category Antihypertensive	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablet	13. Potency(ies) (1.) (2.) a. 100 and 25mg/tab b. 50 and 25mg/tab		
14. Chemical Name and Structure		15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No	
<p>16. Comments:</p> <p>Labeling supplement S-19 submitted march 8, 1996, was withdrawn 8-18-97. On 4-9-99 Zeneca submitted supplement 022, which contained some of the changes addressed in S-19. The firm received an approvable letter from FDA on 5-11-99 with a request for final printed labeling.</p> <p>This supplement does not contain the labeling revisions which were the subject of S-22. It does contain a change to the ADVERSE REACTIONS section which was proposed in the S-19 submission. The necessary supporting documentation is provided. In addition the address information is updated to reflect the new logo.</p> <p>This new labeling will be put into production the first week in July 1999.</p> <p>Chemistry portion of labeling is unchanged.</p>			
<p>17. Conclusions and Recommendations:</p> <p>Chemistry portion of labeling is satisfactory.</p>			
18. REVIEWER			
Name Charlotte Brunner	Signature <i>/S/</i>		Date Completed June 25, 1999
<p>Distribution: <input type="checkbox"/> Original Jacket <input type="checkbox"/> Review <input type="checkbox"/> Division File <input type="checkbox"/> CSO</p>			

/S/ x-18-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18240/S26

ADMINISTRATIVE DOCUMENTS

RHPM Review of Final Printed Labeling
NDAs
18-240/S-026; 18-760/S-023; 19-058/S-013

JUL 21 1999

Date of Submissions: June 2, 1999
Date of Review: June 30, 1999
Applicant Name: Zeneca Pharmaceuticals
Product Names: Tenormin (atenolol) 25, 50 and 100 mg Tablets (18-240/S-026)
Tenoretic (atenolol and chlorthalidone) 50/25 and 100/25 mg Tablets (18-760/S-023)
Tenormin (atenolol) 5mg/10mL I.V. Injection Ampules (19-058/S-013)

Evaluation:

These submissions provides for "Special Supplements: Changes Being Effectuated" with final printed labeling revised as follows:

NDAs 18-240
18-760
19-058

1. The phrase, "dry mouth" has been added to the Adverse Reactions section.
2. The address information has been changed to reflect a new logo

NDAs: 18-240
18-760

Under the How Supplied section, the following sentence has been changed from:

to:

Store at controlled room temperature, 20°-25° C (68°-77°) [see USP].

NDA: 19-058

Under the How Supplied section, the following sentence has been changed from:

to:

Store at controlled room temperature, 20°-25° C (68°-77°) [see USP].

There are no other changes from the last approved package inserts.

Recommendation:

An approval letter should issue for these supplements as set forth under 21 CFR 314.70 (c) (i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

cc: orig. NDAs
HFD-110
HFD-110/McDonald
HFD-110/Benton
HF-2

/S/
Zelda McDonald, RHPM