

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18240/S025

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 4 2000

NDA 18-240/S-025
NDA 18-760/S-022
NDA 19-058/S-012

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 April 5, 1999 (NDA 19-058), April 6, 1999 (NDA 18-760) and April 9, 1999 (NDA 18-240) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tenormin (atenolol) 25, 50 and 100 mg Tablets (NDA 18-240), Tenoretic (atenolol and chlorthalidone) 50/25 and 100/25 mg Tablets (NDA 18-760), Tenormin (atenolol) 5mg/10ml Injection (NDA 19-058).

We acknowledge receipt of your submissions dated October 8, 1999. Your submissions of October 8, 1999 constituted a complete response to our May 11, 1999 action letter.

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

NDA 18-240, 18-760 and 19-058

1. The following has been added to the PRECAUTIONS/Drug Interactions subsection:
/ Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.
2. Under the POTENTIAL ADVERSE EFFECTS/Other subsection, "Raynaud's phenomenon" has been moved to the ADVERSE REACTIONS section.

NDA 18-240 & 19-058

Under the CONTRAINDICATIONS section the sentence, "TENORMIN" is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components." has been added.

NDA 18-240

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

to:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORMIN should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

During postmarketing experience with TENORMIN, 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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome, and dry mouth. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

NDA 18-760

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

to:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORETIC should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORETIC should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome and dry mouth. TENORETIC, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

NDA 19-058

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

to:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN I.V. should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORMIN I.V. should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

During postmarketing experience with TENORMIN, 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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome and dry mouth. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

We have completed the review of these supplemental applications, as amended, 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 submitted final printed labeling (package inserts included with your October 8, 1999 submission). Accordingly, these supplemental applications are approved effective on the date of this letter.

NDA 18-240/S-025
NDA 18-760/S-002
NDA 19-058/S-012
Page 5

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 call:

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

Sincerely,

JS *4/4/00*
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/S025

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 18-240/S-025
NDA 18-760/S-022
NDA 19-058/S-012

MAY 11 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 April 5, 1999 (NDA 19-058), April 6, 1999 (NDA 18-760), and April 9, 1999 (NDA 18-240) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tenormin (atenolol) 25, 50 and 100 mg Tablets (NDA 18-240), Tenoretic (atenolol and chlorthalidone) 50/25 and 100/25 mg Tablets (NDA 18-760), Tenormin (atenolol) 5 mg/10 mL I.V. Injection (NDA 19-058).

These supplemental applications provide for draft labeling revised as follows:

NDA 18-240, 18-760 and 19-058

1. The following has been added to the **PRECAUTIONS/Drug Interactions** subsection:

Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.
2. Under the **POTENTIAL ADVERSE EFFECTS/Other** subsection, "Raynaud's phenomenon" has been moved to the **ADVERSE REACTIONS** section.

NDA 18-240 & 19-058

Under the **CONTRAINDICATIONS** section the sentence, "TENORMIN" is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components." has been added.

NDA 18-240

1. Under the **WARNINGS/In Patients Without a History of Cardiac Failure** subsection, the last two sentences have been changed from:

to:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the **WARNINGS** section:

Untreated Pheochromocytoma: TENORMIN should not be given to patients with untreated pheochromocytoma.
3. Under the **ADVERSE REACTIONS**, the last paragraph has been revised from:

to:

During postmarketing experience with TENORMIN, 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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances and sick sinus syndrome. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

NDA 18-760

1. Under the **WARNINGS/In Patients Without a History of Cardiac Failure** subsection, the last two sentences have been changed from:

to:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORETIC should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the **WARNINGS** section:

Untreated Pheochromocytoma: TENORETIC should not be given to patients with untreated pheochromocytoma.

3. Under the **ADVERSE REACTIONS**, the last paragraph has been revised from:

to:

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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances and sick sinus syndrome. TENORETIC, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

NDA 19-058

1. Under the **WARNINGS/In Patients Without a History of Cardiac Failure** subsection, the last two sentences have been changed from:

to:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN I.V. should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the **WARNINGS** section:

Untreated Pheochromocytoma: TENORMIN I.V. should not be given to patients with untreated pheochromocytoma.

3. Under the **ADVERSE REACTIONS**, the last paragraph has been revised from:

to:

During postmarketing experience with TENORMIN, 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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances and sick sinus syndrome. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

We have completed the review of these applications and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the draft labeling submitted on April 5, 1999 (NDA 19-058), April 6, 1999 (NDA 18-760) and April 9, 1999 (NDA 18-240).

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

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Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Sincerely yours,

JS/ 5/11/99

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

cc:

Archival NDAs 18-240, 18-760, 19-058

HFD-110/Div. Files

HFD-95/DDMS

DISTRICT OFFICE

HFD-110/Z.McDonald

sb/5/3/99;5/7/99

Initialed by: K Srinivasachar/5/3/99

C Resnick/5/4/99

M Gordon/5/4/99

C Ganley/5/4/99

Z McDonald for N Morgenstern

filename: 18240s025ae2.doc

approval dates: August 19, 1981 (NDA 18-240)

June 8, 1984 (NDA 18-760)

September 13, 1989 (NDA 19-058)

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18240/S025

FINAL PRINTED LABELING

64108-02



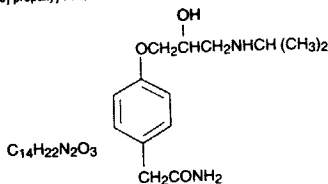
Rev M 07/99

PROFESSIONAL INFORMATION BROCHURE

ONE TABLET A DAY
TENORMIN[®]
 (atenolol)

APPROVED
 APR 1999

DESCRIPTION: TENORMIN[®] (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-(1'-methylethyl) amino] propyl-. The molecular and structural formulas are:



Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 25, 50 and 100 mg tablets for oral administration.

Inactive Ingredients: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

CLINICAL PHARMACOLOGY: TENORMIN 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, TENORMIN inhibits beta₂-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

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 two (2) and four (4) hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, TENORMIN undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. TENORMIN also differs from propranolol in that only a small amount (6%-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation.

The elimination half-life of oral TENORMIN is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral 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 TENORMIN is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73m². (See DOSAGE AND ADMINISTRATION.)

Pharmacodynamics: In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of TENORMIN has been demonstrated by: (1) reduction in resting and exercise heart rate 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 TENORMIN, 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. Maximum reduction in exercise tachycardia occurs within 5 minutes of an intravenous dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma TENORMIN concentration. The effect on exercise tachycardia of a single 10 mg intravenous dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration. 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 TENORMIN 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 TENORMIN 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 equipotent oral doses of several beta blockers, TENORMIN 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, TENORMIN increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. TENORMIN 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 during exercise.

In controlled clinical trials, TENORMIN, given as a single daily oral dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. TENORMIN has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. TENORMIN is also compatible with methyldopa, hydrochlorazine, and prazosin, each combination resulting in a larger fall in blood pressure than with the single agents. The dose range of TENORMIN 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 possible 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 TENORMIN with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

In a multicenter clinical trial (ISIS-1) conducted in 16,027 patients with suspected myocardial infarction, patients presenting within 12 hours (mean = 5 hours) after the onset of pain were randomized to either conventional therapy plus TENORMIN (n = 8,037), or conventional therapy alone (n = 7,990). Patients with a heart rate of < 50 bpm or systolic blood pressure < 100 mm Hg, or with other contraindications to beta blockade were excluded. Thirty-eight percent of each group were treated within 4 hours of onset of pain. The mean time from onset of pain to entry was 5.0 ± 2.7 hours in both groups. Patients in the TENORMIN group were to receive TENORMIN I.V. injection 5-10 mg given over 5 minutes plus TENORMIN Tablets 50 mg every 12 hours orally on the first study day (the first oral dose administered about 15 minutes after the IV dose) followed by either TENORMIN Tablets 100 mg once daily or TENORMIN Tablets 50 mg twice daily on days 2-7. The groups were similar in demographic and medical history characteristics and in electrocardiographic evidence of myocardial infarction, bundle branch block, and first degree atrioventricular block at entry.

During the treatment period (days 0-7), the vascular mortality rates were 3.89% in the TENORMIN group (313 deaths) and 4.57% in the control group (365 deaths). This absolute difference in rates, 0.68%, is statistically significant at the P < 0.05 level. The absolute difference translates into a proportional reduction of 15% (3.89-4.57/4.57 = -0.15). The 95% confidence limits are 1%-27%. Most of the difference was attributed to mortality in days 0-1 (TENORMIN - 121 deaths; control - 171 deaths).

Despite the large size of the ISIS-1 trial, it is not possible to identify clearly subgroups of patients most likely or least likely to benefit from early treatment with atenolol. Good clinical judgment suggests, however, that patients who are dependent on sympathetic stimulation for maintenance of adequate cardiac output and blood pressure are not good candidates for beta blockade. Indeed, the trial protocol reflected that judgment by excluding patients with blood pressure consistently below 100 mm Hg systolic. The overall results of the study are compatible with the possibility that patients with borderline blood pressure (less than 120 mm Hg systolic), especially if over 60 years of age, are less likely to benefit.

The mechanism through which atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other beta blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

TENORMIN is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components.

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, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

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 of symptoms of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinitiated, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

Concomitant Use of Calcium Channel Blockers: Bradycardia and heart block can occur and the left ventricular and 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.)

Labeling: ORIGINAL
 NDA No: 16-244D Rev'd. 10-12-99
 Reviewed by: J. McArnold
3/20/00

APPROVED
 APR 7 2000

Bronchospastic Disease: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN 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 TENORMIN should be used with therapy initiated at 50 mg 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-adrenergic 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).

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents; eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: 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 TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

Untreated Pheochromocytoma: TENORMIN should not be given to patients with untreated pheochromocytoma.

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.

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 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.

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. TENORMIN may aggravate peripheral arterial circulatory disorders.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore 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 TENORMIN (See WARNINGS).

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.

Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

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.

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

(CONTINUED ON REVERSE SIDE)

TENORMIN® (atenolol) Tablets

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 cytogenetic 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: Chronic studies employing oral 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 of atenolol (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.

Usage 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 5.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN 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

Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients 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 TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

	Volunteered (US Studies)		Total - Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	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
Leg 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

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

	Conventional Therapy Plus Atenolol (n=244)	Conventional Therapy Alone (n=233)
Bradycardia	43 (18%)	24 (10%)
Hypotension	60 (25%)	34 (15%)
Bronchospasm	3 (1.2%)	2 (0.9%)
Heart Failure	46 (19%)	56 (24%)
Heart Block	11 (4.5%)	10 (4.3%)
BBB + Major		
Axis Deviation	16 (6.6%)	28 (12%)
Supraventricular Tachycardia	28 (11.5%)	45 (19%)
Atrial Fibrillation	12 (5%)	29 (11%)
Atrial Flutter	4 (1.6%)	7 (3%)
Ventricular Tachycardia	39 (16%)	52 (22%)
Cardiac Reinfarction	0 (0%)	6 (2.6%)
Total Cardiac Arrests	4 (1.6%)	16 (6.9%)
Nonfatal Cardiac Arrests	4 (1.6%)	12 (5.1%)
Deaths	7 (2.9%)	16 (6.9%)
Cardiogenic Shock	1 (0.4%)	4 (1.7%)
Development of Ventricular Septal Defect	0 (0%)	2 (0.9%)
Development of Mitral Regurgitation	0 (0%)	2 (0.9%)
Renal Failure	1 (0.4%)	0 (0%)
Pulmonary Emboli	3 (1.2%)	0 (0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

	IV Atenolol Reduced Dose ($< 5\text{mg}$)*	Oral Partial Dose
Hypotension/Bradycardia	105 (1.3%)	1168 (14.5%)
Cardiogenic Shock	4 (0.4%)	35 (4.4%)
Reinfarction	0 (0%)	5 (0.6%)
Cardiac Arrest	5 (0.6%)	28 (3.4%)
Heart Block (> first degree)	5 (0.6%)	143 (1.7%)
Cardiac Failure	1 (0.1%)	233 (2.9%)
Arrhythmias	3 (0.4%)	22 (2.7%)
Bronchospasm	1 (0.1%)	50 (6.2%)

*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with TENORMIN, 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, sick sinus syndrome, and dry mouth. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Cerebrovascular: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash.

Idiosyncrasies: 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 TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: Overdosage with TENORMIN 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 TENORMIN overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in TENORMIN overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENORMIN can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levaterenol). Monitor blood pressure continuously.

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

HYPOGLYCEMIA: Intravenous glucose.

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

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued. (See full prescribing information prior to initiating therapy with TENORMIN Tablets.)

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Elderly Patients or Patients with Renal Impairment: TENORMIN is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased-renal function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m². Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

The following maximum oral dosages are recommended for elderly, renally-impaired patients and for patients with renal impairment due to other causes:

Creatinine Clearance (mL/min/1.73m ²)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	25 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of TENORMIN: 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

HOW SUPPLIED: TENORMIN Tablets: Tablets of 25 mg atenolol, NDC 0310-0107, (round, flat, uncoated white tablets identified with "T" debossed on one side and 107 debossed on the other side) are supplied in bottles of 100 tablets.

Tablets of 50 mg atenolol, NDC 0310-0105, (round, flat, uncoated white tablets identified with "TENORMIN" debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets.

Tablets of 100 mg atenolol, NDC 0310-0101, (round, flat, uncoated white tablets identified with "TENORMIN" debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets, and unit dose packages 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

64108-02

Rev M 07/99



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18240/S025

CHEMISTRY REVIEW(S)

OCT 27 1999

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 18-240
3. Name and Address of Applicant (City & State) Zeneca Pharmaceuticals 1800 Concord Pike Wilmington, Delaware 19850-5437		4. Supplement(s) Number(s) Date(s) S-025 4/9/99	
5. Drug Name Tenormin	6. Nonproprietary Name Atenolol		8. Amendments & Other (reports, etc) - Dates 10-8-99 amendment
7. Supplement Provides For: 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) Oral tablets	13. Potency(ies) 25, 50 & 100 mg tablets		
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
16. Comments: Final printed labeling is being submitted for S-25 which was requested in the FDA's approvable letter of May 11, 1999 and approval letter 7-21-99 for S-26 submitted on June 2, 1999. The changes are being made in the Contraindications, Precautions, Adverse Reactions, and Potential Adverse Effects sections of the package insert. Chemistry portion of labeling is unchanged.			
17. Conclusions and Recommendations: Chemist portion of labeling is satisfactory.			
18. REVIEWER			
Name Charlotte Brunner	Signature: <i>[Signature]</i>		Date Completed 10-15-99
Distribution: <input type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO			

[Signature]
10-25-99

MAY 27 1999

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 18-240-
3. Name and Address of Applicant (City & State) Zeneca Pharmaceuticals 1800 Concord Pike Wilmington, Delaware 19850-5437		4. Supplement(s) Number(s) Date(s) S-025 4/9/99	
5. Drug Name Tenormin	6. Nonproprietary Name Atenolol		8. Amendments-& Other (reports, etc) - Dates
7. Supplement Provides For: proposed labeling information.			
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) Oral tablets	13. Potency(ies) 25, 50 & 100 mg tablets		
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	
16. Comments: Labeling supplement was withdrawn The firm is now resubmitting the changes from the march 8, 1996 supplement which can be supported with primary references, case reports or additional supportive clinical information. The changes are being made in the Contraindications, Precautions, Adverse Reactions, and Potential Adverse Effects sections of the package insert. If proposed text is approved, firm will institute it at the next printing. Chemistry portion of labeling is unchanged.			
17. Conclusions and Recommendations: Chemist portion of labeling is satisfactory.			
18. REVIEWER			
Name Charlotte Brunner	Signature <i>JSF</i>		Date Completed 4-23-99
Distribution: <input type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO			

JSF 24 99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18240/S025

ADMINISTRATIVE DOCUMENTS

RHPM Review of Final Printed Labeling
NDA 18-240/S-025
18-760/S-022
19-058/S-012

Dates of Submissions October 8, 1999
Date of Review: March 20, 2000
Applicant Name: Zeneca Pharmaceuticals
Product Names: Tenormin (atenolol) Tablets (NDA 18-240), Tenoretic (atenolol and chlorthalidone) Tablets (18-760), Tenormin (atenolol) IV Injection (19-058)

Evaluation:

These submissions provide for final printed labeling in accordance with the May 11, 1999 approvable letters as follows:

NDA 18-240, 18-760 and 19-058

1. The following has been added to the PRECAUTIONS/Drug Interactions subsection:

Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.
2. Under the POTENTIAL ADVERSE EFFECTS/Other subsection, "Raynaud's phenomenon" has been moved to the ADVERSE REACTIONS section.

NDA 18-240 & 19-058

Under the CONTRAINDICATIONS section the sentence, "TENORMIN" is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components." has been added.

NDA 18-240

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

To:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORMIN should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

During postmarketing experience with TENORMIN, 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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome, and dry mouth. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

NDA 18-760

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

To:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORETIC should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORETIC should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome and dry mouth. TENORETIC, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

NDA 19-058

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

To:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN I.V. should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORMIN I.V. should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

During postmarketing experience with TENORMIN, 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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome and dry mouth. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

There were no other changes from the approvable letter and the last approved package insert.

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].

Zelda McDonald, RHPM

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

MAY 11 1999

RHPM Review of Draft Labeling
NDA 18-240/S-025
18-760/S-022
19-058/S-012

Dates of Submissions April 5, 1999 (19-058), April 6, 1999 (18-760), April 9, 1999 (18-240)
Date of Review: April 22, 1999
Applicant Name: Zeneca Pharmaceuticals
Product Names: Tenormin (atenolol) Tablets (NDA 18-240), Tenoretic (atenolol and chlorthalidone) Tablets (18-760), Tenormin (atenolol) IV Injection (19-058)

Evaluation:

These submissions provide for draft labeling as follows:

NDA 18-240, 18-760 and 19-058

1. The following has been added to the PRECAUTIONS/Drug Interactions subsection:

Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.

2. Under the POTENTIAL ADVERSE EFFECTS/Other subsection, "Raynaud's phenomenon" has been moved to the ADVERSE REACTIONS section.

NDA 18-240 & 19-058

Under the CONTRAINDICATIONS section the sentence, "TENORMIN" is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components." has been added.

NDA 18-240

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

To:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORMIN should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

During postmarketing experience with TENORMIN, 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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances and sick sinus syndrome. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

NDA 18-760

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

To:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORETIC should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORETIC should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances and sick sinus syndrome. TENORETIC, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

NDA 19-058

1. Under the WARNINGS/In Patients Without a History of Cardiac Failure subsection, the last two sentences have been changed from:

To:

At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN I.V. should be withdrawn. (see DOSAGE AND ADMINISTRATION)

2. The following subsection has been added to the WARNINGS section:

Untreated Pheochromocytoma: TENORMIN I.V. should not be given to patients with untreated pheochromocytoma.

3. Under the ADVERSE REACTIONS, the last paragraph has been revised from:

to:

During postmarketing experience with TENORMIN, 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, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances and sick sinus syndrome. TENORMIN, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

Dr. Gordon has reviewed these supplements and agrees that the requested changes should be made.

There were no other changes from the last approved package insert.

Recommendation:

An approvable 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].

/s/
Zelda McDonald, RHPM

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