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

APR 4 2000

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:

NDAs 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.

NDAs 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:

At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn.
(See DOSAGE AND ADMINISTRATION.)

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 If cardiac failure continues despite adequate treatment, TENORMIIN should be withdrawn.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:

During postmarketing experience with TENORIVUN, 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, and visual disturbances. TENORMIN, like other beta —blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

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 changed from:

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 diuresis, TENORETIC therapy should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

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:

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 and visual disturbances. TENORETIC, like other beta —blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

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:

At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN therapy should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

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: TENORIVIIN I.V. should not be given to patients with untreated pheochromocytoma.

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

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 and visual disturbances. TENORMIN, like other beta —blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

to:

During postmarketing experience with TENORMTN, 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.

We remind you that you must comply with the requirements for an approved NIDA set forth under 21 CFR314.80 and 314.81.

If you have any questions, please call:

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

Sincerely,

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