**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 20-186/S-015 and 19-982/S-010

Wyeth Pharmaceuticals
Attention: Ms. Patricia Kuker Staub
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Staub:

Please refer to your supplemental new drug applications dated December 3, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ziac (bisoprolol fumarate and hydrochlorothiazide) 2.5/6.25 mg, 5/6.25 mg, and 10/6.25 mg Tablets (20-186/S-015) and Zebeta (bisoprolol fumarate) 5 and 10 mg Tablets (19-982/S-010).

We acknowledge receipt of your submission dated January 13, 2003.

These "Changes Being Effected" supplemental new drug applications provide for harmonizing the adverse reactions pertaining to bisoprolol fumarate in the ADVERSE REACTIONS section of the Ziac and Zebeta labeling. In addition, numerous editorial changes were made to both labels.

These supplements propose the following changes:

NDA 20-186

1. Under the DESCRIPTION section, the second sentence of the fourth paragraph, the word "sparingly" has been added to the description of solubility in methanol.

2. Under the PRECAUTIONS/Bisoprolol Fumarate subsection, the heading "Risk of Anaphylactic Reaction:" has been put in bold type.

3. Under the INFORMATION FOR PATIENTS/Mutagenesis subsection, in all cases where the words in vitro or in vivo appeared in the text in Italics, they are now in regular type.

4. Under the ADVERSE REACTIONS/Bisoprolol Fumarate subsection, the first sentence has been changed from:

   In clinical trials worldwide, a variety of other AEs, in addition to those listed above, have been reported.

   To:

   In clinical trials worldwide, or in postmarketing experience, a variety of other AEs, in addition to those listed above, have been reported.

5. Under the ADVERSE REACTIONS/Bisoprolol Fumarate subsection, the following changes have been made:

   a. Central Nervous System: Unsteadiness, vertigo, syncope, paresthesia, hyperesthesia, sleep disturbance/vivid dreams, depression, anxiety/restlessness, decreased concentration/memory.

      To:

      Central Nervous System: Unsteadiness, dizziness, vertigo, headache, syncope, paresthesia, hypoesthesia, hyperesthesia, sleep disturbance/vivid dreams, insomnia, somnolence, depression, anxiety/restlessness, decreased concentration/memory.

b. Cardiovascular: Palpitations and other rhythm disturbances, cold extremities, claudication, hypotension, orthostatic hypotension, chest pain, congestive heart failure.

To:

Cardiovascular: Bradycardia, palpitations and other rhythm disturbances, cold extremities, claudication, hypotension, orthostatic hypotension, chest pain, congestive heart failure, dyspnea on exertion.

c. Gastrointestinal: Gastric/epigastric/abdominal pain, peptic ulcer, gastritis, vomiting, constipation, dry mouth.

To:

Gastrointestinal: Gastric/epigastric/abdominal pain, peptic ulcer, gastritis, dyspepsia, nausea, vomiting, diarrhea, constipation, dry mouth.

d. Musculoskeletal: Arthralgia, muscle/joint pain, back/neck pain, twitching/tremor.

To:

Musculoskeletal: Arthralgia, muscle/joint pain, back/neck pain, muscle cramps, twitching/tremor.

e. Respiratory: Asthma, bronchitis, dyspnea, pharyngitis, sinusitis.

To:

Respiratory: Asthma, bronchospasm, bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis, URI (upper respiratory infection).

f. Genito-urinary: Peyronie's disease (very rarely), cystitis, renal colic, polyuria.

To:

Genito-urinary: Decreased libido/impotence, Peyronie's disease (very rarely), cystitis, renal colic, polyuria.

g. General: Malaise, edema, weight gain, angioedema.

To:

General: Fatigue, asthenia, chest pain, malaise, edema, weight gain, angioedema.

NDA 19-982

1. Under the ADVERSE REACTIONS section the following changes have been made:

a. Central Nervous System: Dizziness, vertigo, headache, paresthesia, hypoaesthesia, somnolence, anxiety/restlessness, decreased concentration/memory.

To:

Central Nervous System: Dizziness, *unsteadiness*, vertigo, *syncope*, headache, paresthesia, hypoesthesia, hyperesthesia, somnolence, *sleep disturbances*, anxiety/restlessness, decreased concentration/memory.

b. Gastrointestinal: Gastric/epigastric/abdominal pain, gastritis, dyspepsia, nausea, vomiting, diarrhea, constipation.

To:

Gastrointestinal: Gastric/epigastric/abdominal pain, gastritis, dyspepsia, nausea, vomiting, diarrhea, constipation, peptic ulcer.

c. Musculoskeletal: Muscle/joint pain, back/neck pain, muscle cramps, twitching/tremor.

   To:

   Musculoskeletal: Muscle/joint pain, *arthralgia*, back/neck pain, muscle cramps, twitching/tremor.

d. Skin: Rash, acne, eczema, skin irritation, pruritus, flushing, sweating, alopecia, *angioedema, exfoliative dermatitis,* cutaneous vasculitis.

   To:

   Skin: Rash, acne, eczema, *psoriasis*, skin irritation, pruritus, flushing, sweating, alopecia, *dermatitis*, *angioedema, exfoliative dermatitis,* cutaneous vasculitis.

e. Special Senses: Visual disturbances, ocular pain/pressure, abnormal lacrimation, tinnitus, earache, taste abnormalities.

   To:

   Special Senses: Visual disturbances, ocular pain/pressure, abnormal lacrimation, tinnitus, *decreased hearing*, earache, taste abnormalities.

f. Genitourinary: Decreased libido/impotence, *Peyronie's disease,* cystitis, renal colic.

   To:

   Genitourinary: Decreased libido/impotence, *Peyronie's disease,* cystitis, renal colic, polyuria.

g. General: Fatigue, asthenia, chest pain, malaise, edema, weight gain.

   To:

   General: Fatigue, asthenia, chest pain, malaise, edema, weight gain, angioedema.

In addition, the following change was also noted in both supplements:

1. In the DESCRIPTION section of the labeling, under the Inactive Ingredients listing, "Hydroxypropyl Methylcellulose" has been changed to "Hypromellose".

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling submitted electronically on December 3, 2002.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Doug Throckmorton

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