CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-017/S-036

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-017/S-036

Merck & Co., Inc.
Attention: Mr. Kenneth A. Kramer
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Mr. Kramer:

Please refer to your supplemental new drug application dated August 10, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Blocadren (timolol maleate) 5mg, 10mg & 20mg tablets.

Your submission of August 8, 2002 constituted a complete response to our March 26, 2002 action letter.

This supplemental new drug application provides for electronic final printed labeling (FPL) revised as follows:

1. The addition of a Geriatric Use subsection to the PRECAUTIONS section of the labeling as follows:

   Geriatric Use

   Clinical studies of BLOCADREN for the treatment of hypertension or migraine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

   In a clinical study of BLOCADREN in patients who had survived the acute phase of a myocardial infarction, approximately 350 patients (37%) were 65-75 years of age. Safety and efficacy were not different between these patients and younger patients (see CLINICAL PHARMOCOLOGY, *Pharmacodynamics*).

   Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

   This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See PRECAUTIONS, *Impaired Hepatic or Renal Function and Dosing in the Presence of Marked Renal Failure*).

2. Under CLINICAL PHARMACOLGY/Pharmacodynamics, the first sentence of the eighth paragraph has been changed from:

   A Norwegian multi-center, double-blind study compared the effects of timolol maleate with placebo in 1,884 patients who had survived the acute phase of myocardial infarction.

   To:

   A Norwegian multi-center, double-blind study, which included patients 20-75 years of age, compared the effects of timolol maleate with placebo in 1,884 patients who had survived the acute phase of myocardial infarction.

3. Under the ADVERSE REACTIONS section, in the third paragraph, the word "anaphylaxis" was added as one of the additional adverse effects that have been reported in clinical experience with the drug in the *Body as a Whole* subsection.

4. The following have been deleted from the HOW SUPPLIED section:

(6506-01-132-0651, 10mg 100's)

(6505-01-132-0652, 20mg 100's).

We have 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 on August 8, 2002.

At the time of the next printing, please make the following change:

1. Under the Geriatric Use subsection of the PRECAUTIONS section, please add the following:

   The results from 5 single and/or multiple dose PK studies comparing the impact of age on the PK of hydrochlorothiazide, when given in combination with other antihypertensive drugs, were consistent. They indicated a median increase in Cmax and AUC of 38% and 99%, respectively, in elderly relative to younger subjects.

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 the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

/S/

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doug Throckmorton
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Food and Drug Administration
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NDA 18-017/S-036

Merck & Co., Inc.
Attention: Mr. Kenneth A. Kramer
Sumney Town Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear : Mr. Kramer:

Please refer to your supplemental new drug application dated August 10, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Blocadren (timolol maleate) 5, 10 and 20 mg Tablets.

This supplement proposes addition of the following subsection to the PRECAUTIONS section of the labeling:

> *Geriatric Use*
>
> Clinical studies of BLOCADREN for the treatment of hypertension or migraine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.
>
> In a clinical study of BLOCADREN in patients who had survived the acute phase of a myocardial infarction, approximately 350 patients (37%) were 65-75 years of age. Safety and efficacy were not different between these patients and younger patients (see CLINICAL PHARMACOLOGY, *Pharmacodynamics*).
>
> Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.
>
> This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See PRECAUTIONS, *Impaired Hepatic or Renal Function and Dosing in the Presence of Marked Renal Failure*).

In addition, under CLINICAL PHARMACOLOGY/Pharmacodynamics, the first sentence of the eighth paragraph has been changed from:

> A Norwegian multi-center, double-blind study compared the effects of timolol maleate with placebo in 1,884 patients who had survived the acute phase of myocardial infarction.

To:

A Norwegian multi-center, double-blind study, which included patients 20-75 years of age, compared the effects of timolol maleate with placebo in 1,884 patients who had survived the acute phase of myocardial infarction.

We have completed the review of this application, as amended, and it is approvable. Before this application 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 included in your August 10, 2001 submission.

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 the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, 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 application. 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.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please call Ms. Zelda McDonald, Regulatory Health Project Manager, at (301) 594-5333.

Sincerely,

{See appended electronic signature page}

/S/

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doug Throckmorton
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