



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 PHARMACOLOGY, *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}

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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