DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-061/S-029

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 Timolide (timolol maleate-hydrochlorothiazide) 10/25 mg Tablets.

We acknowledge receipt of your submissions dated June 12, 2002 and August 8, 2002. Your submission of August 8, 2002 constituted a complete response to our May 31, 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 TIMOLIDE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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 more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See WARNINGS, *Renal and Hepatic Disease and Electrolyte Disturbances.*)

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 changes:

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

   Published data from single and/or multiple dose pharmacokinetic (PK) studies comparing the impact of age on the PK of hydrochlorothiazide, when given in combination with other antihypertensive drugs, were consistent. The results indicated a median increase in the Cmax and AUC for hydrochlorothiazide of approximately 40% and 100%, respectively, in elderly compared with younger subjects."

2. Under the Geriatric Use subsection of the PRECAUTIONS section, please change the first sentence of the first paragraph from:

   (b)(4)----------

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   To:

   Both timolol and hydrochlorothiazide are known to be excreted substantially by the kidney, and the risk of toxic reactions to these drugs may be greater in patients with impaired renal function.

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 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

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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