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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-017/S-036

Administrative Documents

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

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Transmitted to FAX Number: 484-344-2516

Attention: Ken Kramer

Company Name: Merck

Phone: 484-344-3000

Subject: References; NDAs 18-061/S-029 & 18-017/S-036

Date: 5/28/03

Pages including this sheet: 2

From: Melissa Robb

Phone: 301-594-5313

Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU.

REFERENCES

1. Williams RL, Thornhill MD, Upton RA, Blume C, Clark TS, Lin E, Benet LZ. Absorption and disposition of two combination formulations of hydrochlorothiazide and triamterene: Influence of age and renal function. *Clin Pharmacol Ther* (1986);40 :226-232
2. Laher MSM, Mulkerrins E, Hosie J, Connell PA, Smith RP, Swaisland AJ. The effects of age and renal impairment on the pharmacokinetics of co-administered lisinopril and hydrochlorothiazide. *J Human Hypertension* (1991);5 (Suppl):77-84
3. Fliser D, Bischoff I, Hanses A, Block S, Joest M, Ritz E, Mutschler E. Renal handling of drugs in the healthy elderly, creatinine clearance underestimates renal function and pharmacokinetics remain virtually unchanged. *Eur J Clin Pharmacol* (1999);55:205-211
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5. Much DR, Uderman HD, Ameer B, Brennan J, Stouffer BC, Whigan D, DeVault A, VanHarken D. Pharmacokinetics of fosinopril and hydrochlorothiazide in healthy elderly and young men. *Clin Drug Invest* (1999);17:225-321
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8. Currie WJC, Vandenburg MJ, Cooper WD. Do elderly patients respond differently to treatment with Moducren? *Brit J Clin Pract* (March 1984):102-107

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/s/

Melissa Robb

5/28/03 10:41:44 AM

CSO

Faxed to sponsor on 5/28/03 per request on 5/23/03

RHPM Review Addendum of FPL
NDAs 18-061/S-029 & 18-017/S-036

Sponsor: Merck & Co., Inc.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

NDA 18-061/S-029 was approved on March 4, 2003. In the AP letter, the sponsor was instructed to make the following changes at the time of the next printing:

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:

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.

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.

NDA 18-017/S-036 was approved on February 25, 2003. In the AP letter, the sponsor was instructed to make the following change at the time of the next printing:

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.

On May 23, 2003, Mr. Ken Kramer called and left a message for Regulatory Health Project Manager, Melissa Robb, inquiring about the different values in median increase in Cmax and AUC in the two letters. This issue was discussed with Dr. Marroum and he agreed that the values should be consistent in both labels. Dr. Marroum stated that the sponsor should be advised that both labels should use the values 40 % and 100%. On May 28, 2003 this information was conveyed to Mr. Kramer via telephone. Mr. Kramer also requested the references. The list of references was faxed to Mr. Kramer on May 28, 2003.

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/s/

Melissa Robb
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RHPM Review of Final Printed Labeling
NDA 18-017/S-036

Date of Submission: August 9, 2002
Date of Review: November 13, 2002
Applicant Name: Merck & Co., Inc.
Product Name: Blocadren (timolol maleate) 5mg, 10mg, & 20mg tablets

Evaluation:

This submission provides for final printed labeling submitted in accordance with the August 27, 1997 Federal Register Notice that provides for adding a "Geriatric Use" subsection to the Precautions section of the labeling. The following changes were found between submitted final printed labeling and approvable draft labeling dated August 10, 2001.:

1. 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.
2. The following changes have been made to the HOW SUPPLIED section:

No.3343- Tablets BLOCADREN, 5 mg, are light blue, round, compressed tablets, with code MSD 59 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0059-68 bottles of 100.

No.3344- Tablets BLOCADREN, 10 mg, are light blue, round, scored, compressed tablets, with code MSD 136 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0136-68 bottles of 100

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

No.3371- Tablets BLOCADREN, 20 mg, are light blue, capsule shaped, scored, compressed tablets, with code MSD 437 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0437-68 bottles of 100

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

To:

No.3343- Tablets BLOCADREN, 5 mg, are light blue, round, compressed tablets, with code MSD 59 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0059-68 bottles of 100.

No.3344- Tablets BLOCADREN, 10 mg, are light blue, round, scored, compressed tablets, with code MSD 136 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0136-68 bottles of 100

No.3371- Tablets BLOCADREN, 20 mg, are light blue, capsule shaped, scored, compressed tablets, with code MSD 437 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0437-68 bottles of 100

A supplement was submitted to the Agency dated September 19, 2001 and received on September 20, 2001 that provided for both of these changes. This Special Supplement stated this new labeling would be used on or before October 1, 2001 in all packages sold or distributed from the Company's manufacturing facilities. This information can be referenced in NDA18-017/SLR-037.

Per a biopharmaceutics review dated January 2, 2003 and agreement with Dr. Throckmorton, the following paragraph should be added to the Geriatric Use section at the next printing:

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 C_{max} and AUC of 38% and 99%, respectively, in elderly relative to younger subjects.

There are no other changes from the last approved package insert.

Recommendation:

An approval letter should issue for these supplements as set forth under 21 CFR 314.70 (b) (3) [Any change in labeling].

/S/

Melissa Robb, RHPM

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/s/

Melissa Robb
2/26/03 09:41:41 AM
CSO

RHPM Review of Draft Labeling
NDA 18-017/S-036

Date of Submission: August 10, 2001
Date of Review: March 20, 2002
Applicant Name: Merck
Product Name: Blocadren (timolol maleate) 5, 10 and 20 mg Tablets

Evaluation:

This submission provides for draft labeling submitted in accordance with the August 27, 1997 Federal Register Notice that provides for adding 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 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.

In her review dated February 25, 2002, Dr. Targum agreed with the sponsor's suggested changes.

There were no other changes from the last approved package insert.

Recommendation:

An approvable letter should issue for this supplement as set forth under 21 CFR 314.70 (c) (i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

Zelda McDonald
Regulatory Health Project Manager

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/s/

Zelda McDonald
3/26/02 03:17:16 PM
CSO



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:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Blocadren (timolol maleate) Tablets

NDA Number: 18-017

Supplement number: S-036

Date of supplement: August 10, 2001

Date of receipt: August 13, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 12, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Ms. Zelda McDonald
Regulatory Project Manager
(301) 594-5333

Sincerely yours,

A handwritten signature in black ink, appearing to be 'N.A.M.', written in a stylized, cursive-like font.

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
8/24/01 10:32:12 AM
For Natalia Morgenstern