19-915-S-032

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-915/S-032

Bristol-Myers Squibb Company
Attention: Ms. Grace D. Heckman
Box 5400
Princeton, NJ 08543-4000

Dear Ms. Heckman:

Please refer to your supplemental new drug application dated August 25, 1999 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Monopril (fosinopril soidum) 10, 20, and 40 mg Tablets.

We acknowledge receipt of your submissions dated July 21, 2000 and April 16, 2002 that constituted a complete response to our July 11, 2001 action letter.

This supplemental new drug application provides for final printed labeling revised as follows:

1. The following section has been added to the **PRECAUTIONS** section:

   Geriatric Use
   Clinical studies of MONOPRIL 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 responses between 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.

2. The following revision is noted in the **STORAGE** section:

   Change from:
   " Store between 15° C (59° F) and 30° C (86° F). Avoid prolonged exposure to temperature above 30° C (86° F). Keep bottles tightly closed (protect from moisture)."

   Revised to:
   " Store at 25° C (77° F); excursions permitted to 15° C - 30° C (59° F - 86° F) [see USP Controlled Room temperature]. Protect from moisture by keeping bottle tightly closed."

We completed our review of this supplemental new drug application, as amended and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your April 16, 2002 submission. Accordingly, this supplemental application is approved effective on the date of this letter.

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:

Alisea Sermon, Pharm.D.
Regulatory Health Project Manager
(301) 594-5334

Sincerely,

/S/

{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/

Doug Throckmorton
8/29/02 09:53:14 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-915/S-032

Bristol-Myers Squibb Company
Attention: Ms. Grace D. Heckman
Box 5400
Princeton, NJ 08543-5400

Dear Ms. Heckman:

Please refer to your supplemental new drug application dated July 21, 2000, received July 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Monopril (fosinopril sodium).

We acknowledge receipt of your submission dated July 21, 2000. Your submission of July 21, 2000 constituted a complete response to our November 3, 1999 action letter.

This supplement proposes the following changes:

We also note your editorial changes for consistency in the labeling and to reflect the name change of the sponsor.

We have completed the review of this application, as amended. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

> Clinical studies of MONOPRIL 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 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.

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 to be 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 contact:

Ms. Sandra Birdsong
Regulatory Health Project Manager
(301) 594-5334

Sincerely,

{See appended electronic signature page}

/S/

Raymond J. Lipicky, 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/

Raymond Lipicky
7/11/01 03:12:32 PM

NDA 19-915/S-032

Bristol-Myers Squibb Company
Attention: Douglas B. Hay, Ph.D.
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Dr. Hay:

Please refer to your supplemental new drug application dated August 25, 1999, received August 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Monopril (fosinopril sodium) Tablets.

This supplement provides for draft labeling revised under the **Geriatric Use/PRECAUTIONS** subsection to include information on the percentage of patients who received fosinopril in the heart failure studies who were geriatric. The number of patients who received fosinopril in the hypertension studies has been added to this section, as well. The first paragraph in this subsection has been changed from the following:

to the following:

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

The paragraph proposed to replace the first paragraph in the **Geriatric Use/PRECAUTIONS** subsection should be replaced with the following:

Clinical studies of MONOPRIL 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 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.

Additionally, we note your commitment, as agreed to by Dr. Douglas Hay, Director, U.S. Regulatory Liaison, Bristol-Myers Squibb in an October 1, 1999 telephone conversation with Ms. Colleen LoCicero, Regulatory Health Project Coordinator, Division of Cardio-Renal Drug Products, to include in the final printed labeling the two "≥" symbols that were inadvertently omitted from the **CLINICAL PHARMACOLOGY/Pharmacodynamics and Clinical Effects and ADVERSE REACTIONS/Hypertension** subsections.

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 20 copies of the final printed labeling ten of which are 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 to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, please contact:

Ms. Colleen LoCicero
Regulatory Health Project Coordinator
(301) 594-5334

Sincerely yours,

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 19-915
HFD-110/Div. Files
HFD-110/ZMcDonald
HFD-110/C.LoCicero
HFD-110/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: cll/October 14, 1999
Initialed by: D Cunningham/10/20/99
K Srinivasachar/10/20/99
C Resnick/10/20/99
J Pelayo/10/21/99
S Chen/10/21/99
N Morgenstern/10/21/99
final: asb/10/21/99
filename: 19-915s032(ae).doc

APPROVABLE (AE)

RHPM Review of Final Printed Labeling
NDA 19-915/S-032

Date of Submission: August 25, 1999
FPL Submitted: April 16, 2002
Date of Review: August 15, 2002
Sponsor Name: Bristol-Myers Squibb Company
Product Name: Monopril® (fosinopril sodium)

Evaluation:

This supplemental new drug application provides for FPL revised under the **Geriatric Use** subsection to the **PRECAUTIONS** and **STORAGE** sections of the labeling. The FPL for the Geriatric Use subsection is identical to the labeling described in the approvable letter dated July 11, 2001.

In addition, the following revision is noted in the **STORAGE** section
Change from:

"Store between 15° C (59° F) and 30° C (86° F). Avoid prolonged exposure to temperature above 30° C (86° F). Keep bottles tightly closed (protect from moisture."

Revised to:

"Store at 25° C (77° F); excursions permitted to 15° C - 30° C (59° F - 86° F) [see USP Controlled Room temperature]. Protect from moisture by keeping bottle tightly closed."

Recommendation:

Editorial revision in the storage section is permitted based on previous discussion between the chemist and the sponsor.
An approval letter should be issued for this supplemental new drug application.

/S/
Alisea Sermon, RHPM

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

/s/

Alisea Sermon
8/29/02 11:09:29 AM
CSO

RHPC Review of Draft Labeling
NDA 19-915/SLR-032

Date of supplement:	August 25, 1999
Date of review:	September 30, 1999
Applicant Name:	Bristol-Myers Squibb Company
Product:	Monopril (fosinopril sodium) Tablets, 10, 20, and 40 mg.

Evaluation:

This supplement provides for draft labeling revised under the **Geriatric Use/PRECAUTIONS** subsection. Language has been added to the first paragraph of this subsection, which is based on the template under 21 CFR 201.57(f)(10)(ii)(B), to include information on the percentage of patients who received fosinopril in the heart failure studies who were geriatric. The number of patients that received fosinopril in the hypertension studies has been added to the section, as well. The first paragraph in this subsection has been changed from the following:

to the following:

In addition to the change to the **Geriatric Use/PRECAUTIONS** subsection, the following changes from the last approved labeling supplement (SLR-021, approved January 8, 1997) were noted:

1. The sponsor name and logo at the front of the package insert and name and address at the back of the package insert were changed from to Bristol-Myers Squibb, the current sponsor of the application. These changes were submitted in accordance with 21 CFR 314.70(d)(2) in the January 15, 1997 annual report for this application and were reviewed and determined to be acceptable at that

time by Dr. Cunningham (see her August 27, 1997 review of the annual report).

2. In the **ADVERSE REACTIONS/Heart Failure** subsection, the generic name, (fosinopril sodium tablets), immediately following the brand name has been added to one part and removed from another part of the text.

3. The tablet descriptions in the **HOW SUPPLIED** section were changed as a result of the change in sponsor. The text now describes each tablet as having an imprint of BMS on one side and MONOPRIL with the strength of the tablet (i.e., 10, 20, or 40) on the other side. These labeling changes, along with the manufacturing and control data for the changes in tablet imprinting, were submitted in accordance with 21 CFR 314.70(d)(9) in the July 15, 1997 annual report for this application. They were reviewed and determined to be acceptable at that time by Dr. Cunningham (see her August 27, 1997 review of the annual report).

Additionally, I noted two areas of the text with the same typographical error. In the first sentence of the first paragraph of the **CLINICAL PHARMACOLOGY/Pharmacodynamics and Clinical Effects** subsection, the symbol "≥" was omitted prior to the number 90. Furthermore, in the second paragraph of the **ADVERSE REACTIONS/Hypertension** subsection, the symbol "≥" was omitted prior to the number 65. In an October 1, 1999 telephone conversation, Dr. Douglas Hay of Bristol-Myers Squibb confirmed that the omission of the "≥" symbols was inadvertent and that the final printed labeling would include the omitted symbols.

Medical Review

Dr. Lipicky reviewed the proposed change to the **Geriatric Use/PRECAUTIONS** subsection on October 12, 1999, and determined that the proposed paragraph should be replaced with the boilerplate paragraph of 21 CFR 201.57(f)(10)(ii)(A).

Conclusion:

I will prepare an approvable letter for this supplement. The letter will request the sponsor to submit final printed labeling revised so that the paragraph proposed to replace the first paragraph in the **Geriatric Use/PRECAUTIONS** subsection is changed to the boiler plate paragraph of 21 CFR 201.57(f)(10)(ii)(A).

/S/

Colleen LoCicero, RHPC

cc: orig NDA 19-915
HFD-110
HFD-110/Blount
HFD-110/ZMcDonald
HFD-110/LoCicero