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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-221/S-026
18-998/S-058

Administrative Documents

RHPM Review of Final Printed Labeling

Applications:	NDA 18-998/S057 Vasotec (enalapril maleate)
	NDA 19-221/S-026 Vaseretic (enalapril maleate/hydrochlorothiazide)
Applicant:	Merck and Company, Inc.
Document Date:	January 11, 2001
Receipt Date:	January 16, 2001

Background

These supplemental applications provide for Final Printed Labeling with revisions that standardize labeling and comply with class labeling regarding non-steroidal anti-inflammatory drugs. An approvable letter on draft labeling issued on January 2, 2001.

Review

The labeling was reviewed and found to be identical to the changes requested by the Division in the January 2, 2001 approvable letter.

Recommendation

An approval letter will be drafted for Dr. Lipicky's signature.

/S/

Sandra Birdsong
Regulatory Health Project Manager

slb/30 Jan 01

/s/

Sandra Birdsong
2/15/01 10:04:19 AM
CSO

RHPM Review of Draft Labeling

Applications:	NDA 18-998/S-058 Vasotec (enalapril maleate) NDA 19-221/S-026 Vaseretic (enalapril maleate/hydrochlorothiazide)
Applicant:	Merck and Company, Inc.
Document Date:	July 20, 1999
Receipt Date:	July 21, 1999

Background

These supplemental applications were submitted in response to a letter from the Agency (Division of Anti-Inflammatory, Analgesic, and Opthalmic Drug Products) dated December 20, 1996. The letter requested labeling revisions that would standardize labeling and comply with class labeling regarding non-steroidal anti-inflammatory drugs.

Dr. Maryann Gordon was the medical reviewer assigned to NDA 18-998 and Dr. Steven Rodin was the medical reviewer for NDA 19-221 at the time of submission. Amendments to both applications were submitted on September 1, 1999 in response to a telephone request by Dr. Gordon for additional information regarding the rationale for the wording of the labeling text. Subsequently, both NDAs were assigned to Dr. Rodin.

Prior to this RHPM review, Drs. Gordon and Lipicky reviewed and approved the labeling revisions as submitted.

Evaluation

I reviewed the revised draft labeling of both NDAs, submitted July 20, 1999. The labeling for NDA 18-998 is identical to the most recently approved labeling dated February 17, 1999, with the exception of the revisions noted below. The labeling for NDA 19-221 is identical to the most recently approved labeling dated February 17, 1999, with the exception of the revisions noted below.

Revisions to the draft labeling of both supplements are as follows:

NDA 19-221/S-026

Under the **CLINICAL PHARMACOLOGY**/*Pharmacodynamics/Enalapril Maleate* section, the following statement has been added at the end of the last paragraph:

> (See PRECAUTIONS, *Drug Interactions, Enalapril Maleate*)

Under **PRECAUTIONS**/*Drug Interactions/Enalapril Maleate/Non-steroidal Anti-inflammatory Agents,* a second paragraph has been added:

> In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate. However, reports suggest that NSAIDs may

diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

NDA 18-998/S-058

Under the **CLINICAL PHARMACOLOGY**/*Pharmacodynamics and Clinical Effects* section, the following statement has been added at the end of the last paragraph:

(See PRECAUTIONS, *Drug Interactions*)

Under **PRECAUTIONS**/*Drug Interactions/Non-steroidal Anti-inflammatory Agents,* a second paragraph has been added:

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving VASOTEC. In this study there was no evidence of a blunting of the antihypertensive action of VASOTEC. However, reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Recommendation

I recommend that the Division issue an approvable letter for these supplements in accordance with 21 CFR 314.70(b)(3)(i). The letter should request final printed labeling that incorporates the revisions proposed in these submissions.

/S/

Sandra Birdsong, RHPM

cc. orig NDA 18-998
orig NDA 19-221
HFD-110
HFD-110/Blount
HFD-110/Birdsong

/s/

Sandra Birdsong
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CSO