CMC

DIVISION OF CARDIOPULMONARY AND RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #2

Date Completed: April 3, 1985

1. ~~IND~~ NDA: 18-998

Applicant: Merck Sharp & Dohme Research Labs

Address: Division of Merck and Co., Inc.

AF#: 12-611

2. Product Names (2):

Proprietary: Vasotec

Nonproprietary: Enalapril Maleate, MSD

USAN: As above

Compendium: None

Code Name and/or number: (MK-421) L-154,739

3. Dosage Form and Route of Administration:
Oral Tablets, 5, 10, 20, and 40 mg.

4. Pharmacological Category and/or Principal Indication:
An angiotensin converting enzyze inhibitor.

5. Structural Formula and Chemical Name: See Chemist's Review, #1

B. 1. Initial Submission: 9-15-83

2. Amendments

Certain documents are accounted for in certain specific sort modes. Not all searches give the same results. In an effort to provide more complete assurance that all relevant documemts have been adequately accounted for, I have sorted each search in terms of another. Keys to foot notes are provided for interpretation. According to the document and record card on 2-11-85, I am charged for the following assignments:

4-15-83 (1)
6-01-83 (confirms meeting time)
7-19-83 (1)
8-03-83 (1)
9-23-83 (deals with page substitution)
12-28-83 (2)
3-27-84 (2)
4-11-84 (pharmacology only)
5-21-84 (background for advisory committee)
6-11-84 (1) 7-26-84
9-11-84 (1)
10-30-84 SBA (Clinical only)
2-06-85 Not received yet but not considered related to controls.
2-19-85 Copies of Vasotec carton labels

Key for above footnotes in listing:

Key to above listing:

C. Remarks

Several issues were covered in the "Record of Meeting" on 5-9-83 between Mr. Hitchings of Merck and Dr. Zimmerman of this agency.

A record of telephone conversation dated 8-7-84 between Dr. O'Brien of merck and Stuart Zimmerman of this agency deals with interpretation of our laboratory results.

Anumber of adificiency concerns were addressed to the applicant via the meeting on March 15, 1984 (refer to the "Record of Conversation/Meeting").

In the record of telephone conversation dated 7-27-84 between Mr. Lantorow of Merch and Dr. Struart Zimmerman of this agency a number of deficiency issues were mentioned concerning the validation of samples.

D. Conclusions and Results:

This application is now considered to be approvable from the standpoint of chemistry and manufacturing controls for this drug. The "Chemist's Part of the Summary Basis for Approval" is provided to confirm this contention.

Stuart Zimmerman 4-9-85
Stuart Zimmerman Ph.D.

cc:
Orig:
HFN-110
HFN-110/CSO
HFN-110/SZimmerman/4/8/85
cb/4/8/85/0259v

Review Notes:

8. Manufacturing and Processing:

Satisfactory

Appropriate information is now provided in the update amendments.

11. Laboratory Controls on Finished Dosage Form: Satisfactory

The outstanding questions have been resolved (refer to appropriate updated amendments that deal with these matters).

13. Stability

Satisfactory:

The "Statistical Review and Evaluation" from HFN-715 dated 7-30-84 concludes that for the samples of 5,10,20 and 40 mg tablets suggest an expiration date of 30 months.

The "Statistical Review and Evaluation" dated 12-18-84 deals with the submission dated 10-25-84 concerning updated stability data for the 40 mg tablets. This supports the 30 month expiry date.

14. Samples and Results: Satisfactory

The Philadelphia Distric Laboratory completed its validation of NDA 18-998 as noted in the Memorandum dated February 3, 1984 from HFO-620. The deficiency issues involved were combined with those found by HFN-180. These matters were essentially resolved as noted in the Memorandum dated July 16, 1984 from Eric B. Sheinin (HFN-180).

The submission of 9/18/84 deals with a response to Dr. E. Sheinins concerns Appropriate resolution to all outstanding questions has been made in the updated amendments which are self explanatory.

The memorandum dated July 16, 1984 from HFN-180 determines that only slight problems remained agter the initial results were obtained. These matters have since been resolved by the firms in their updated amendments and by direct communication with Dr. Sheinin.

15. Labeling: Satisfactory

Carton labels are provided in the sumbission of 2-19-85. These appear to be in accord with the technical requirements.

16. Establishment Ispection: Satisfactory.

The memorandum dated 6-13-83 indicates there is no problems with GMPs and the Alert List update shows no problems.

17. Registration: Satisfactory

18. Form 356H Part 5: Satisfactory

Chemist's Part of Summary of Basis of Approval for NDA 18-998

Manufacturing and Controls:

A. Manufacturing and Controls:

The description of the synthesis is provided in sufficient detail to permit a determination of the validity of the assigned chemical structure and the suitability of the specifications and test methods for the bulk drug substance. The preparation of the new drug substance consists entirely of a synthetic process. Adeguate information is provided to explain the various steps involved and the organic chemical reactions employed are considered reasonable for the synthesis of this type of chemical compound. Raw materials and intermediates are satisfactorially characterized and sufficient attention is given to the isolation and purification of the new drug substance. The controls over the manufacturing procedures, which include specifications and test methods for the new drug substance and excipients, and the finished dosage form given sufficient assurance of the identity, strength, quality and purity of the drug.

B. Stability Studies:

The Stability data, both long-term and accelerated are satisfactory to support the proposal of a 30 month expiration date.

Proper attention is given to pertinent stability testing parameters to enable a determination that the identity, strength, guality, and purity of the drug will be preserved until it is used.

Appropriate commitments have been made for continued monitoring of representative samples.

C. Methods Validation:

Reolvant analytical methods have been independently validated by two FDA laboratories and have been found to be satisfactory for control and regulatory purposes.

D. Labeling:

All labels and labeling provided for the proposed marketed drug package are in compliance with the technical requirements of prescription drug labeling. There is no known conflict between the proposed trade name and any other drug product.

E. Establishment Inspection:

An evaluation of all the operations involved for the manufacture and packaging of the drug showed that the various firms involved are in compliance with Current Good Manufacturing Practices.

F. Environmental Impact Analysis Report (EIAR):

Satisfactory information is provided to demonstrate there is no