

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**18-998/S013**

***Trade Name:*** Vasotec Tablets

***Generic Name:*** Enalaprilat

***Sponsor:*** Merck Sharp & Dohme Research Laboratories

***Approval Date:*** August 3, 1988

***Indications:*** The treatment of hypertension.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**18-998/S013**

## CONTENTS

### **Reviews / Information Included in this NDA Review.**

<b>Approval Letter</b>	<b>X</b>
<b>Approvable Letter</b>	
<b>Labeling</b>	
<b>Medical Review(s)</b>	
<b>Chemistry Review(s)</b>	<b>X</b>
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology Review(s)</b>	
<b>Clinical Pharmacology/ Biopharmaceutics Review(s)</b>	
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH.**

*APPLICATION NUMBER:*

**18-998/S013**

**APPROVAL LETTER**



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**18-998/S013**

**CHEMISTRY REVIEW(S)**

JUL - 8 1988

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA NUMBER 18-998
3. NAME AND ADDRESS OF APPLICANT (City and State) MSD West Point, PA		4. AF NUMBER	
6. NAME OF DRUG VASOTEC		7. NONPROPRIETARY NAME Enalapril Maleate	5. SUPPLEMENT(S) NUMBER(S)   DATE(S) S-013   6/17/88
8. SUPPLEMENTS(S) PROVIDES FOR:  Packaging Tablets VASOTEC by Merck- Sharp & Dohme Caguas, at a site leased from the _____		9. AMENDMENTS AND OTHER DATES	
10. PHARMACOLOGICAL CATEGORY Antihypertensive	11. HOW DISPENSED <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		12. RELATED IND/ NDA/DMF(s) New relevant DMFs include #7286 and _____
13. DOSAGE FORM(S) Tablets	14. POTENCY(IES) 5, 10, 20 mg/tab		
15. CHEMICAL NAME AND STRUCTURE		16 RECORDS/REPORTS CURRENT     YES     NO REVIEWED     YES     NO	
17. COMMENTS  The corporate arm of MSD Caguas is a division of MSD Quimica de Puerto Rico, Inc. This part plans to conduct packaging at the site leased from the _____ Employees of MSD Caguas, in residence at the _____ will supervise all packaging.			
18. CONCLUSIONS AND RECOMMENDATIONS  Recommend an approval action pending the results of a GMP check. Action letter will be written with Chemist's Review #2.			
19. REVIEWER			
NAME Stuart Zimmerman		SIGNATURE <i>Stuart Zimmerman</i>	DATE COMPLETED 7/8/88
DISTRIBUTION	<input checked="" type="checkbox"/> ORIGINAL JACKET	REVIEWER	DIVISION FILE
R/D Init: RWalters/7/8/88		CSO c1b/7/8/88/0836C	

*MSD  
7/8/88*

AUG - 3 1988

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110		2. NDA NUMBER 18-998	
3. NAME AND ADDRESS OF APPLICANT (City and State) MSD West Point, PA				4. AF NUMBER	
				5. SUPPLEMENT(S) NUMBER(S)   DATE(S)	
6. NAME OF DRUG VASOTEC		7. NONPROPRIETARY NAME Enalapril Maleate		S-013   6/17/88	
8. SUPPLEMENTS(S) PROVIDES FOR:  Packaging Tablets VASOTEC by Merck, Sharp & Dohme Caguas, at a site leased from the _____				9. AMENDMENTS AND OTHER DATES	
10. PHARMACOLOGICAL CATEGORY Antihypertensive		11. HOW DISPENSED <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		12. RELATED IND/NDA/DMF(s) New relevant DMFs include #7286 and _____	
13. DOSAGE FORM(S) Tablets		14. POTENCY(IES) 5, 10, 20 mg/tab			
15. CHEMICAL NAME AND STRUCTURE				16 RECORDS/REPORTS	
				CURRENT <input type="checkbox"/> YES <input type="checkbox"/> NO	
				REVIEWED <input type="checkbox"/> YES <input type="checkbox"/> NO	
17. COMMENTS  The corporate arm of MSD Caguas is a division of MSD Quimica de Puerto Rico, Inc. This part plans to conduct packaging at the site leased from the _____ Employees of MSD Caguas, in residence at the _____ will supervise all packaging. This review represents Chemist's Review #2 for this S-013 and serves to report that the results of the GMP check were acceptable as noted in the memorandum dated 7/22/88 from HFN-320.  <i>Note: labeling was mistakenly included in this submission but was understandingly not to be given consideration as noted via the Record of Telephone meeting - dated 7/18/88 between Dr. Berger and Dr. Zimmerman.</i> <span style="float: right;">STS = 72</span>					
18. CONCLUSIONS AND RECOMMENDATIONS  Recommend an approval action.					
19. REVIEWER					
NAME Stuart Zimmerman		SIGNATURE <i>Stuart Zimmerman</i>		DATE COMPLETED 7/27/88	
DISTRIBUTION		ORIGINAL JACKET		REVIEWER	
DIVISION FILE		CSO			

*8-3-88*

c15/7/27/88/0900C

Comments (continued):

The same controls described in the approved NDA for Tablets VASOTEC will be used at this alternate packaging site. Tablets will be manufactured and released in full compliance with their NDA commitment and will be supplied to the contractor by MSD. The packaging operation will be performed using the same package components as approved in the NDA. Employees of MSD Caguas, in residence at the \_\_\_\_\_ will supervise all packaging activities performed in the \_\_\_\_\_. Samples of marketed packages from each lot will be forwarded to MSD's Quality Control Laboratory for performance and an identity test.

The DMFs \_\_\_\_\_ and 7286 were checked for content on 7/5/88 and they appeared to provide the required instructions, commitments and procedures involved in GMP regulations.

A request for a GMP update as made on 7/5/88 (See STS Inspection File #13 for details).

Authorizations:

Letters from \_\_\_\_\_ dated 12/30/87 \_\_\_\_\_ and from MSD Caguas (DMF 7286) of 12/18/87 are provided.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**18-998/S013**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

18-748  
56.1

7-24-90

RECORD OF TELEPHONE CONVERSATION/MEETING		DATE 8 / 6 / 90	
<p>Events of 8/6/90:</p> <p>Dr. Berger called and mentioned that he was interested in resolving the issue of which supporting information provided in the DMF 7286 serves to compete with the information held in the _____ . It may be a good idea to have the relevant information identified by page number and document date to prevent any ambiguity. I mentioned that I had called _____ and he thought that there may be a problem dealing with the DMF holder's use of their registration numbers since they both appear to be the same. This matter should be clarified as much as possible to facilitate review and inspection requests.</p> <p>Refer to Appendix I for comments about the supporting DMFs 7286 and _____ (MSD and _____)</p>		NDA NUMBER 18-998	
		IND NUMBER SCM - 013	
		TELECON/MEETING	
		INITIATED BY <input type="checkbox"/> APPLICANT/SPONSOR <input checked="" type="checkbox"/> FDA	MAD: <input type="checkbox"/> BY TELEPHONE <input type="checkbox"/> IN PERSON
		PRODUCT NAME Tablets VASOTEC (Enalapril Maleate)	
		FIRM NAME MSD	
		NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Dr. Berger (MSD)	
		TELEPHONE NO. 215-834-2310	
		cc: HFN-110 / Orig. HFN-110 / Chron File HFN-110 / CSO HFN-110 / Zimmerman	
		SIGNATURE <i>Stuart Zimmerman</i>	DIVISION HFN-110

Appendix I

DMF 7286 (MSD):

From DMF 7286 it is indicated that there is covered a description of MSD's facilities in Caguas, PR 00626. MSD, Caguas will lease portions of the \_\_\_\_\_ for the exclusive production of Merck pharmaceutical products. MSD Caguas employees at this facility will supervise the manufacturing process as well as the laboratory testing performed by \_\_\_\_\_ contracted to MSD Caguas.

DMF 7286 refers to a drug establishment registration number of \_\_\_\_\_ which is noted to be the same number used by \_\_\_\_\_ (see page 9 under section A of \_\_\_\_\_)

DMF \_\_\_\_\_

Concerning manufacturing facilities there are two solid dosage facilities. One facility has been leased to Merck Sharp and Dohme and is operated by \_\_\_\_\_ this is for the exclusive production of Merck's pharmaceutical products. MS&D, Caguas has filed a separate DMF 7283 covering this part.

The product Identification Number (NDC Number) is designed to identify a definite \_\_\_\_\_. The first five numbers consist of a five (5) digit number which is \_\_\_\_\_ NDC Labeler Code, 55370.

3159C

18-448  
561

SCM-011  
7-24-90

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 8/2/90		
<p>Concerning the need to designate the site of manufacture, it is important to have defined the following: (1) Ownership of the facility, (2) Nature of the leasing agreement between Merck Sharp and Dohme _____ In this case, it is indicated that Merck indicates that the facility in Caguas, PR is their site leased from _____</p> <p>From this, it is not quite clear to what extent FDA can make accurate assignments concerning the profile class code for this site. The basic question is to determine which corporate identity is best suited to be designated as the responsible firm which will manufacture the tablets, (3) There is the question of just what the designation, "MPMD", refers to in terms of corporate identity.</p> <p>Concerning the letter of authorization dated December 30, 1987 (Attachment III) from _____</p>	<p>NDA NUMBER 18-998/S-013</p> <p>IND NUMBER</p>		
<p>_____ IT IS noted that there is only provision for procedures and controls dealing with packaging operations. This technically means that manufacturing operations are not covered for _____ This matter needs resolution. It is also noted that this letter is outdated and needs to be updated.</p> <p>There is the question of which CFN number should be used for this inspection request; this number is on the 483 form.</p> <p>Concerning the exact designation of the site in terms of the Central File Number (CFN) it was determined that there is only one number specified for this site which is _____ It is important to be sure that this number be related to an exact corporate identity.</p> <p>There is also the question of what corporate identity the stability lots are covered under these studies. It was learned that MPMD refers to Merck Pharmaceuticals Manufacturing Division (worldwide), B:MPMD, DOC</p>	<p>TELECON/MEETING</p> <table border="1"> <tr> <td data-bbox="1089 548 1317 663"> <p>INITIATED BY</p> <p><input type="checkbox"/> APPLICANT/SPONSOR</p> <p><input type="checkbox"/> FDA</p> </td> <td data-bbox="1317 548 1510 663"> <p>MADE:</p> <p><input type="checkbox"/> BY TELEPHONE</p> <p><input type="checkbox"/> IN PERSON</p> </td> </tr> </table> <p>PRODUCT NAME VASOTEC Tablets</p> <p>FIRM NAME MS+D West Point Pa.</p> <p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Elliott T. Berger. (215) 834-2310</p> <p>TELEPHONE NO. (215) 834-2310 cc: (HFD-110) Orig. NDA Chron File S. Zimmerman CSO (Bongiovanni)</p>	<p>INITIATED BY</p> <p><input type="checkbox"/> APPLICANT/SPONSOR</p> <p><input type="checkbox"/> FDA</p>	<p>MADE:</p> <p><input type="checkbox"/> BY TELEPHONE</p> <p><input type="checkbox"/> IN PERSON</p>
<p>INITIATED BY</p> <p><input type="checkbox"/> APPLICANT/SPONSOR</p> <p><input type="checkbox"/> FDA</p>	<p>MADE:</p> <p><input type="checkbox"/> BY TELEPHONE</p> <p><input type="checkbox"/> IN PERSON</p>		
<p>SIGNATURE Stuart Zimmerman</p>	<p>DIVISION HFD-110</p>		

