CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-909

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.: 3

2. ANDA: 75-909

3. NAME AND ADDRESS OF APPLICANT:
Reddy-Cheminor, Inc.
Attention: Paul V. Campanelli
U.S. Agent for: Dr. Reddy's Laboratories Limited
66 South Maple Avenue
Ridgewood, NJ 07450
Telephone: (201)-444-4424
Facsimile: (201)-444-1456

4. LEGAL BASIS FOR SUBMISSION: See Chemistry Review #1

5. SUPPLEMENTS: N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME:
Enalapril Maleate and Hydrochlorothiazide Tablets USP

8. SUPPLEMENTS PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission: June 16, 2000
Amendment: September 20, 2000
Amendment: January 16, 2001
Amendment: March 28, 2001
Amendment: September 11, 2001
Amendment: September 26, 2001
Amendment: September 28, 2001

10. PHARMACOLOGICAL CATEGORY: Treatment of Hypertension

11. OTC/R_x: R_x

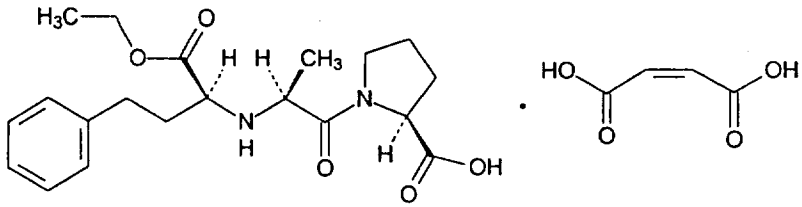
12. RELATED IND/NDA/DMF(s): See DMF Checklist

13. DOSAGE FORM: Tablet

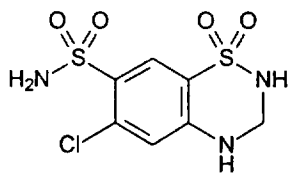
14. POTENCY: Enalapril Maleate/Hydrochlorothiazide at
5 mg/12.5 mg and 10 mg/25 mg strengths

15. CHEMICAL NAME AND STRUCTURE:

Enalapril Maleate (Antihypertensive): L-Proline, 1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (*S*)-, (*Z*)-2-butenedioate (1:1). $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$. MW = 492.53. CAS# 76095-16-4.



Hydrochlorothiazide (Diuretic): 2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide. $C_7H_8ClN_3O_4S_2$. MW = 297.75. CAS# 58-93-5.



16. RECORDS AND REPORTS: N/A

17. COMMENTS: Cheminor Drugs Limited (original applicant) has merged with Dr. Reddy's Laboratories. As of 1/2/01 the applicant is known as Dr. Reddy's Laboratories Limited.

The address and all other information remain the same. Documents have been filed to change the Registration Number and Labeler code to that of Dr. Reddy's Laboratories Limited.

On September 26, 2001, the firm requested expedited review of the ANDA, based upon the deletion of an exclusivity provision from the Orange Book.

The Labeling Review is acceptable is draft.

18. CONCLUSIONS AND RECOMMENDATIONS: **Approvable**

19. REVIEWER: ARaw DATE COMPLETED: 10/01/01

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Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem Rev. 3

10/1/01

JUL 27 2001

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-909 APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Enalapril Maleate and Hydrochlorothiazide Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg

The deficiencies presented below represent FAX deficiencies.

A. Chemistry Deficiencies:

1. Please submit an chromatogram at low attenuation for Enalapril Maleate USP (Batch RE0061) using your revised method (Related Substances). Please include a blank run and label all known and unknown impurities in your test sample.

2. Please provide a commitment that the maximum holding time for your drug product in the bulk container shall not be greater than 30 days. Otherwise we request that you provide room temperature stability data to justify a longer storage period.

3. In regard to your : impurity, we note that your accelerated and room temperature stability data do not indicate that this impurity is a viable degradant in your drug product formulation. Therefore your proposed drug product release and stability limits for this impurity should be no higher than the proposed limit for this impurity in the drug substance

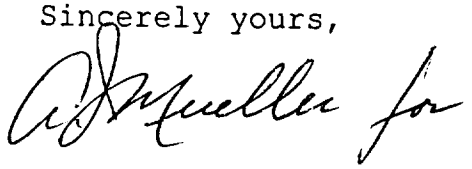
4. Please revise your release and stability specifications for impurities in the drug product to specify "Total Impurities" rather than "Sum of Enalaprilat, Enalapril and other Related Compounds".

5. We note that your updated room temperature stability data reflect your original stability specifications. Please provide updated stability data, which reflect your revised stability specifications (individual limits for enalaprilat, enalapril and unknown individual impurities). If possible, please resubmit the accelerated stability data previously acquired, which reflect these revisions to your stability specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

You have not yet responded to the labeling deficiencies communicated to you on December 14, 2000. The labeling for your drug product must be found acceptable in final print prior to approval.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

1.1

DEC 14 2000

39. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-909 APPLICANT: Cheminor Drugs Limited

DRUG PRODUCT: Enalapril Maleate and Hydrochlorothiazide Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies

1. Regarding the active ingredient, Enalapril Maleate USP, we have following comments:

   a. Please tighten your specification for petroleum based upon observed values.

   b. Please incorporate the test for Related Substances into the retest schedule.

   c. Please revise your specifications for Related Impurities and incorporate a limit for the RSS isomeric impurity of Enalapril Maleate. Please specify limits that are based upon observed values.

   d. Please provide a methods validation report for Related Substances
   Solvents (GC) according to USP 24 General Chapter <1225> Validation of Compendial Methods or the CDER Guideline. Based upon the method's accuracy, please incorporate relative response factors, if known, into your calculation of known impurities.

2. Regarding the active ingredient, Hydrochlorothiazide USP, we have following comments:

   a. Please incorporate a test for melting point. Please specify a range based upon observed values.

   b. Please provide a method validation report for Related Substances . Based upon the method's accuracy, please incorporate a relative response factor, if known, into your calculation of impurity.

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releasable.

12/14/00

2. Labeling review is pending. You will be notified on the status of the labeling review under a separate cover.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research