CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20872

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-872

Hoechst Marion Roussel, Inc.
c/o Quintiles, Inc.
P.O. Box 9708, H3-M2516
Kansas City, Mo. 64134-0708

JUL 16 1999

Attention: Wayne F. Vallee, R.Ph.
Manager
Drug Regulatory Affairs

Dear Mr. Vallee:

Please refer to your new drug application (NDA) dated July 17, 1998, received July 17, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) Tablets.

We acknowledge receipt of your submissions dated July 30, 31, August 13, 25, September 29, October 28, November 10, 20, 23, December 10, 16, 1998, February 16, May 6, 13, 14, 21, 24, June 4, 11, and 18, 1999.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to adequately address the following comments.

1. The changes to the trade name for the individual dosage strengths as proposed are not acceptable. The tradename and its representation on packaging and labeling as proposed in the original NDA submission should be utilized.

2. The data provided do not adequately support

   Specifically, efficacy throughout the entire dosing interval was not adequately shown. In order to obtain labeling for provide adequate and well-controlled data to demonstrate the efficacy of this dose, including end-of-dosing interval data. A complete, corrected report of SAR Study 0032 (protocol PJPR0032), with the electronic data, may sufficiently address this issue.

3. The pharmacokinetics data for fexofenadine indicate that the 30 mg dose in children 6 to 11 years of age would provide similar systemic exposure as the 60 mg dose in adults. There are no data that a dose higher than 30 mg twice daily provides additional benefit in the treatment of SAR in children 6 to 11 years of age. Therefore, the proposed dose not approvable. Additional data and rationale must be provided if a 60 mg twice daily dosage for the treatment of SAR is sought for children 6 to 11 years of age.

4. As the pharmacokinetics data for fexofenadine indicate that the 30 mg dose in children 6 to 11 years of age provides similar systemic exposure as the 60 mg dose in adults, and the proposed dose for the treatment of chronic idiopathic urticaria (CIU) in adults is 60 mg twice daily, and given that a dose higher than 60 mg twice daily did not provide additional clinical benefit in adults and adolescents, the proposed dosage of not approvable. Additional data and rationale must be provided if a 60 mg twice daily dose for the treatment of CIU is sought for this population.

5. Our analysis of the combined data from the two trials K-98-0093-D and K-98-0119-D using population methods indicates no difference in clearance between adults and children. Since our estimate of clearance from this analysis differs from your results, the population pharmacokinetic approach should be utilized to compare the pharmacokinetics of fexofenadine in adults with that in children using the data from K-98-0093-D and K-98-0119-D.

6. The analysis of variance with terms of sequence was not performed for each pharmacokinetic parameter in Study PJPR0045. Re-analyze the data including sequence and provide the result for the study.

The following comments pertain to the drug substance.

7. Based on actual observed data (amendment dated May 21, 1999, exhibit 2, p.60), specify a reasonable range for DSC temperature in drug substance specifications (S3380).

8. Include appropriate test(s) and acceptance criteria in drug substance specifications to control the polymorphic forms.

9. Based on the stability data submitted in the amendment dated July 30, 1998, the following acceptance criteria for the related substances are proposed. In addition, refer to the Agency's correspondence dated July 1, 1999, regarding NDA 20-625/S-008.

MDL 102,038	NMT	%
MDL 46,016	NMT	%
MDL 46,619	NMT	%
Individual Unknown	LT	%
Total related substance	NMT	%

The following comments pertain to the drug product.

10. Establish and submit a master batch record with all appropriate tests and controls for 30 mg tablets. The manufacturing process for 30 mg tablets should be validated for full commercial scale.

11. As requested in the correspondence dated April 26, 1999, include acceptance criteria for particle size distribution in the master batch record as in-process control after the final blending step.

12. The visual observation of tablets for chipping and capping, as stated in your response, do not measure the actual resistance of the tablets against the breakage or other physical defects in use. Include a test and specification for friability as in-process control.

13. We acknowledge that MDL 46,619 is a synthetic impurity and is controlled in the drug substance specifications (S3380). For completeness of the specification sheet, include MDL 46,619 in drug product specifications. A footnote may indicate that MDL 46,619 is a synthetic impurity and does not need monitoring.

14. The proposed acceptance criteria for impurities/degradation products at release and stability are unacceptable. The following acceptance criteria based on observed data are proposed.

MDL 102,038	NMT	%
MDL 46,016	NMT	%
*MDL 46,619	NMT	%
Total other degradants	NMT	%
Total degradants	NMT	%

* Refer to comment 13. above.

15. The proposed hardness range of Kp (120 mg tablets) and Kp (180 mg tablets) is not acceptable. Provide dissolution vs. hardness data for the 120 and 180

mg tablet using 0.001M HCl (as dissolution media) and propose new hardness ranges for the 120 and 180 mg tablets, respectively.

16. Submit "hardness data" for the following batches of the tablets reported in exhibit 6, amendment dated May 21, 1999, (updated stability data). Also specify the dissolution medium used for these batches.

For 30 mg tablets:	Batch Nos. RF9713, RF9714 and RF9715
For 60 mg tablets:	Batch Nos. RC9626, RD 9619, RD9620, 98057614, 98057617 and 98057619
For 120 mg tablets:	Batch Nos. 98054478, 98054529 and 98054530
For 180 mg tablets:	Batch Nos. 98058304, 98058346 and 98058362

17. The dissolution method proposed is acceptable. However, the proposed dissolution specifications of Q % at 15 minutes and Q % at 45 minutes are not sufficiently discriminatory to adequately characterize the dissolution profiles of the tablets. The following acceptance criteria are acceptable.

Q % at 10 minutes and Q % in 30 minutes

18. Specify the criteria for "the acceptable and non-acceptable changes" for the proposed grading scales No. 1 and 2 in the stability specifications for product and package appearance.

19. As previously requested, submit method validation packages that also include all updated methods.

20. Identify all packaging presentations (i.e., blister and HDPE bottles) intended for distribution that do not have child resistance closure (CRC) features. Address and justify adequately the absence of the CRC feature for such packaging.

21. Submit revised draft labeling that incorporates the following preliminary comments as well as the preliminary revisions shown in the enclosed marked-up draft package insert.

    a. Increase the size and prominence of the established name "fexofenadine hydrochloride" on all labels and labeling for Allegra tablets.

    b. Blister labels for 60 mg tablets should prominently display the statement "store at controlled room temperature 20-25°C (68-77°C)".

    c. Include the statement "protect from excessive moisture" in prominent

lettering on all labels and labeling for Allegra tablets,

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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 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.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Mr. J. Lindsay Cobbs, R.Ph., Project Manager, at (301) 827-1051.

Sincerely,

/S/

Robert J. Meyer, M.D.
Acting Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure