CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-300

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-300

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Carlos Langezaal, Ph.D.

Dear Dr. Langezaal,

Please refer to your new drug application (NDA) dated December 8, 2000, received December 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex (desloratadine) Syrup 0.5 mg/mL.

We also refer to your amendments dated March 19, and June 28, 2001, June 2, 2003, and February 27 (2), June 24, July 9, 20, 29, August 10, 12, 13(2), 30 and 31 and September 1, 2004.

The February 27, 2004, submission constituted a complete response to our October 2, 2002, action letter.

This new drug application provides for the use of Clarinex for the relief of the nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis, and the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria in patients 2 years of age and older.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below, as agreed during our telephone discussion on August 30, 2004.

1. Remove the [redacted] from the carton labeling.
2. Replace the [redacted] with the approved name, Clarinex.
3. Remove the phrase, [redacted] from the carton and container.

The final printed labeling (FPL) must be identical to, except for including the revisions listed, the enclosed labeling (text for the package insert submitted August 30, 2004) and submitted labeling (carton and container label submitted August 30, 2004). These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission "**FPL for approved NDA 21-300.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application in ages 2 years and above.

Please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Submit one market package of the drug product when it is available.

If you have any questions, call Anthony M. Zeccola, Regulatory Management Officer, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Center for Drug Evaluation and Research

Enclosure

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/s/

Badrul Chowdhury
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-300

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated December 8, 2000, received December 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex (0.5 mg/ml desloratadine) Syrup.

We acknowledge receipt of your submissions dated March 19, April 6, April 18, May 22, and July 20, 2001.

We also refer to your submission dated June 28, 2001. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

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 address the following deficiencies.

1. Provide a quantitative color specification for the drug product (e.g., APHA color test). Provide an updated drug product specification sheet.

2. Provide tightened drug product degradant specifications for individuals (e.g., [redacted] and each unknown) and total degradants. Provide an updated drug product specification sheet.

3. Provide a specification for EDTA assay in the drug product regulatory specifications (shelf-life specifications). Q6A indicates that sufficient data is needed before shelf-life testing for antioxidant preservative content may be omitted. Significant decreases in the EDTA assay are observed under accelerated conditions (up to 6.4%). Provide an updated drug product specification sheet.

4. Provide a commitment to test all parameters of the COA for the drug substance periodically from the drug substance manufacturing sites.

5. Provide an additional identification test (other than IR) for propylene glycol.

6. Add an overall yield calculation in the master batch record for the drug product manufacture and packaging. Provide an updated master batch record.

7. Assure that no reprocessing of the drug product will be done, and provide an updated master batch record that provides no reprocessing of the drug product will be done.

8. Revise the procedure to include [redacted]

9. Submit the number of bottles or bulk sampling weights/volumes tested for pH in the in-process testing of the drug product. Revise the pertinent documents accordingly.

10. Provide information in each test method procedure pertaining to number of aliquots taken of each batch or lot, number of samples measured for each method, number of analyses run on all batches used in drug product release and stability studies. Revise the pertinent documents accordingly.

11. Revise the system suitability acceptance criteria for resolution to include [redacted] and desloratadine in the "Quantitation of Degradation Products" test method (method no. [redacted]). Loratadine is not expected to be a degradant; however, the [redacted] is a degradant and [redacted] loratadine in this test method.

12. Clarify and resolve the apparent discrepancy between [redacted] and assignments for [redacted] On volume 1.2, section 4.B.6, page 62, of the December 8, 2000, submission, the [redacted] and desloratadine, while in volume 1.4, section 4.B.8, pp. 133-134, the opposite is found with similar HPLC conditions ([redacted] desloratadine). Provide data pertaining to injection of [redacted] using desloratadine as a standard using the [redacted] proposed for the "[redacted] test method (method no. [redacted])

13. Rectify the increased levels of total degradants, and each unspecified degradant found in the ¾-ounce presentation as found in the accelerated stability studies. Submit controls to decrease the levels of degradants found in the ¾-ounce bottle as compared to the other two presentations.

14. Provide, in addition to figures 5 through 9, numerical EDTA and benzoate assay results for the stress study of SCH 34117 syrup pertaining to the drug product method [redacted]

15. [redacted]

16. Provide updated drug product stability data for all batches used in stability studies.

17. Comments on the drug product stability batches acceptance criteria and expiry period proposal will be withheld until a sufficient body of data (including the addressing of comments 1-3, 13, 16) is collected and submitted to the NDA.

18. From the submitted pharmacokinetic data, it appears that a substantial number of children whose pharmacokinetic profiles were determined after administration of single doses of desloratadine had significantly higher drug exposure (AUC) than most patients to desloratadine and very low levels of 3-hydroxydesloratadine. The exposure to desloratadine resulting from multiple doses has not been determined in children, and in particular, those children with apparent poor metabolism. Moreover, there are no data provided to identify the underlying cause of these high exposure levels. Consequently, there is no means of prospectively identifying those patients who may have such high levels. If these patients are inherently slow metabolizers of desloratadine, then the number of patients who experience these high exposure levels may be much greater, particularly if there is a deficient metabolic pathway involved that may be vulnerable to inhibition with concominant medications.

    Therefore, it will be necessary for you to characterize the pharmacokinetics of repetitive-dose administration with desloratadine in a population determined to be "slow metabolizers" of desloratadine. Once an upper limit of exposure with repetitive-dosing is determined, the safety of this level of exposure will need to be adequately supported in order to gain approval.

19. You are encouraged to determine the mechanism accounting for higher levels of drug exposure observed in some patients, and to assess the potential for drug-drug interactions that might be expected based on the explanatory mechanism.

20. The information requested in comments 18 and 19 above also will be pertinent to all other NDAs for desloratadine products (currently, NDAs 21-165, 21-297, 21-300, 21-312, 21-313, and 21-363), although the relative proportion of affected patients may differ in adults compared to children.

21. Given that you are proposing a harmonized label to include Clarinex Tablets and Syrup, submit updated labeling that reflects all revisions that have been made as a result of the ongoing review of NDAs 21-165, 21-297, and 21-363. Additional comments regarding the package labeling will be forthcoming after resolution of the pending issues.

22. During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved.

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

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 314.120. 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, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
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