CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-312

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-312

Schering Corporation
Attention: Joseph Lamendola, Ph.D.
Vice President, Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated December 20, 2000, received December 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex RediTabs (desloratadine orally disintegrating tablets) Tablets.

We acknowledge receipt of your submissions dated December 22, 2000, February 7, March 1, April 6, July 19, October 5, and December 21, 2001, and May 30, June 6 and 26, 2002(2). Your submission of December 21, 2001, constituted a complete response to our October 19, 2001, action letter.

This new drug application provides for the use of Clarinex RediTabs (desloratadine orally disintegrating tablets) Tablets for 1) **Allergic Rhinitis:** CLARINEX RediTabs 5 mg are indicated for the relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal and perennial) in patients 12 years of age and older and 2) **Chronic Idiopathic Urticaria:** CLARINEX RediTabs are indicated for the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria 12 years of age and older.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 26, 2002, immediate container and carton labels submitted June 26, 2002). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-312." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27) for patients less then 12 years of age. We are deferring submission of your pediatric studies until December 7, 2002.

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 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, Maryland 20857

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

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

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Robert Meyer
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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 20, 2000, received December 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex Reditabs (5 mg desloratadine orally disintegrating tablets).

We acknowledge receipt of your submissions dated December 22, 2000, and February 7, March 1, April 6, May 22, July 19, and October 5, 2001.

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. The stability data you have submitted (3 batches out to 18 months on storage in blister foil packaging) to support your proposed 24-month expiration-dating period are incomplete. As previously requested, in addition to assay and moisture data, provide updated stability data for tensile strength and dissolution (analyzed at the 4-minute dissolution time point). Final comments on your proposed expiration-dating period are withheld until we receive and comprehensively review all of the available stability data for assay, moisture, tensile strength, and dissolution (based on the 4-minute dissolution time point).

2. Evaluate the assessment of dissolution rate using a paddle speed of — RPM instead of 50 RPM. If this speed provides better discrimination, adopt this speed for dissolution testing.

3. From the overall desloratadine pharmacokinetic database, it appears that a substantial subset of patients had significantly higher exposure to desloratadine (AUC) than most patients. These patients had very low levels of 3-hydroxydesloratadine. The exposure to desloratadine resulting from repetitive dosing in such patients is estimated to be six to nine times greater than the exposure in adult patients as a whole. There are no data to identify the mechanism for these high exposure levels, and there are no means of prospectively identifying those patients who may have such high exposure. If these patients are inherently slow metabolizers of desloratadine, then the number of patients who experience these high exposure levels in clinical use may be much greater with actual use, particularly if there is a deficient metabolic pathway

involved that may be inhibited by concominant medications.

4. You should attempt to determine the mechanism accounting for higher levels of drug exposure in some patients, and to assess the potential for drug-drug interactions that might be expected, depending on the outcome of these investigations.

5. Comments 3 and 4 are pertinent to other NDAs for desloratadine products with adult indications (NDAs 21-165, 21-297, ——— , and 21-363).

6. 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.

7. The following comments pertain to your proposed labels and labeling. Submit revised draft labeling based on these comments and to account for language agreed to under NDA 21-165. However, additional comments on labels and labeling will be forwarded following resolution of the deficiencies in this letter.

   a. The CLINICAL PHARMACOLOGY, "Pharmacokinetics: Absorption" subsection of the package insert should be revised as follows:

      Following oral administration of desloratadine ——— 5 mg once daily for 10 days to normal healthy volunteers, the mean time to maximum plasma concentrations (T_{max}) occurred at approximately 3 hours post-dose ——— mean steady-state peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) were 4 ng/mL and 56.9 ng×hr/ml, respectively. ——————————— (C_{max} and AUC) of desloratadine.

      The pharmacokinetic profile of CLARINEX Reditabs was evaluated in a three way crossover study in 30 adult volunteers. A single CLARINEX Reditab containing 5 mg of desloratadine was bioequivalent to a single 5 mg CLARINEX tablet and was bioequivalent to 10 ml of CLARINEX Syrup containing 5 mg of desloratadine ——— ——— both desloratadine and 3-OH desloratadine. In a separate study with 30 adult volunteers, food or water had no effect on the bioavailability (AUC and C_{max}) of CLARINEX Reditabs. However, food ——— desloratadine median T_{max} value from 2.5 hr to 4 hr.

   b. The DOSAGE AND ADMINISTRATION section of the package insert should be revised as follows:

      Adults and children 12 years of age and over: The recommended dose of CLARINEX Tablets is 5 mg once daily. In patients with liver failure or renal insufficiency, a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data. Administration of CLARINEX (desloratadine) Reditabs: Place CLARINEX (desloratadine) Reditabs on the tongue. Tablet disintegration occurs rapidly. Administer with or without water. Take tablet immediately after opening the blister.

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

You are reminded of your commitment under NDA 21-165 to submit the final study report for the ongoing mouse carcinogenicity study within 3 years of approval of NDA 21-165 or within 3 years of study initiation, whichever occurs first.

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 yours,

{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

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/s/

Robert Meyer
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