CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-297

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-297

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

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

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated August 30, 2000, received August 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex (desloratadine) Tablets.

We acknowledge receipt of your submissions dated October 19, and December 18, 2000, January 12, February 16, March 16, 26, and 27, May 22, July 9, August 3, 7, and 15, September 7, and 20, and October 15, 2001, January 17 and 22, and February 6, 2002. Your submission of September 7, 2001, constituted a complete response to our June 28, 2001, action letter.

This new drug application provides for the use of Clarinex (desloratadine) Tablets 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 enclosed labeling text, which includes minor revisions as discussed and agreed upon in a telephone conversations between Daniel McHugh of Schering Corporation and Anthony Zeccola of this division. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling including the minor revision.

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 21-297." 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) age. 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 studiesin patients less then 12 years of age until December 7, 2002.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product to NDA 21-165. 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-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 set forth under 21 CFR 314.80 and 314.81 for an approved NDA. To comply with these regulations, all 3-day and 15-day alert reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-165 for this drug product, not to NDA 21-297. This includes the quarterly periodic adverse drug experience reports required by this new NDA. In the future, no submissions should be made to NDA 21-297 except for the 20 copies of the final printed labeling, as requested above.

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
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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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-297

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

6-28-01

NDA 21-297

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 August 30, 2000, received August 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex (desloratadine) 5 mg Tablets.

We acknowledge receipt of your submissions dated October 19, and December 18, 2000, January 12, February 16, March 16, 26 and 27, and May 22, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved it will be necessary for you to resolve the following deficiencies:

1. During recent inspections of the manufacturing facilities in Union, New Jersey and Las Piedras, Puerto Rico, for your NDA, a number of CGMP deficiencies were noted. Satisfactory inspections will be required before this application may be approved.

2. Revise the proposed dissolution acceptance criteria for this NDA so that it is consistent with the dissolution acceptance criteria (Q=—% at 30 minutes) proposed on September 14, 2000, for NDA 21-165, Clarinex Tablets.

3. Revise and reduce the analytical error associated with the test method. [redacted] " (method no. [redacted]. The District Lab found the method unacceptable for quantitation and was unable to achieve the system suitability requirements.

We have the following preliminary comments regarding the draft labeling specific to this proposed indication. Submit revised draft labeling incorporating the revisions described below, as well as any changes (previous or subsequent) proposed under NDA 21-165.

4. Revise the first paragraph of the Pharmacodynamics subsection of the **CLINICAL PHARMACOLOGY** section to read as follows:

   Wheal and Flare: *Human histamine skin wheal studies following single and repeated 5 mg doses of desloratadine have shown that the drug exhibits an antihistaminic activity by 1 hour; this activity may persist for as long as 24 hours. There was no evidence of histamine-induced skin wheal tachyphylaxis within the desloratadine 5 mg group over the 28 day treatment period. The clinical relevance of histamine wheal skin testing is unknown.*

5. Add the following sentence to the end of the second paragraph of the Pharmacodynamics subsection of the **CLINICAL PHARMACOLOGY** section:

   *See **OVERDOSE** section for information on human QTc experience.*

6. Revise the fourth paragraph of the Pharmacodynamics subsection of the **CLINICAL PHARMACOLOGY** section to read as follows:

   The efficacy and safety of CLARINEX Tablets 5 mg once daily was studied in 416 chronic idiopathic urticaria patients 12 to 84 years of age, of whom 211 received CLARINEX. In two double-blind, placebo-controlled, randomized clinical trials of six weeks duration, at the pre-specified one-week primary time point evaluation, CLARINEX Tablets reduced the severity of pruritus when compared to placebo. Draft

7. Revise the **INDICATIONS AND USAGE** section to read as follows:

   DRAFT

8. List the incidence of adverse events reported by ≥ 2% of subjects in the two placebo-controlled, multiple-dose CIU clinical trials separately in the **ADVERSE REACTIONS** section of the label (i.e. not pooled with the seasonal allergic rhinitis data). Preferably, this can be done as text following a revised Table 3, which includes only adverse events reported by ≥2% of SAR patients.

9. Expand the information regarding the human QTc evaluation study in the **OVERDOSAGE** section to include the mean heart rate values and mean QTc values (using both Fridericia and Bazett's methods of correction). Provide comment on the technical limitations of interpretation for both Fridericia and Bazett's corrections and comment on the clinical relevance of the findings from this study.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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 314.110. 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.
Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

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 Dr. Craig Ostroff, Regulatory Management Officer, at 301-827-5585.

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

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/s/

Robert Meyer
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