CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-641/SE5-007

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-641/S-007

12-4-00

Schering Corporation
US Regulatory Affairs
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 supplemental new drug application dated November 24, 1999, received November 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Claritin (loratadine) Syrup.

We acknowledge receipt of your submissions dated February 14, March 15, and October 3, 2000. Your submission of October 3, 2000, constituted a complete response to our September 26, 2000, action letter.

This supplemental new drug application provides for the use of Claritin (loratadine) Syrup for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 2 years of age and older.

We have completed the review of this supplemental 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 and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

1. In the first paragraph of the Pediatric section, the number 13 is to be added as the number of pediatric volunteers for subjects ages 8 to 12 years old, and the number 13 is to be removed as the number of pediatric volunteers for subjects ages 2 to 5 years old.

2. The expression of the age groups is to be consistent throughout the labeling (e.g., "2 to 5 years old" instead of "2-5 years old").

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted October 3, 2000, immediate container and carton labels submitted October 3, 2000). These revisions are terms of the approval of this application.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled

Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-641/S-007." 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 fulfilled the pediatric study requirement at this time.

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-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 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 Vicky Borders, Pharm.D., Regulatory Project Manager, at (301) 827-5580.

Sincerely,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

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SEP 26 2000

Schering Corporation
2000 Galloping Hill Road
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Attention: Joseph F. Lamendola, Ph.D.
Vice President
US Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your supplemental new drug application dated November 24, 1999, received November 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Claritin (loratadine) Syrup.

We acknowledge receipt of your submissions dated February 14 and March 15, 2000.

This supplemental new drug application proposes the use of Claritin (loratadine) Syrup for the nasal and non-nasal symptoms of seasonal allergic rhinitis and the treatment of chronic idiopathic urticaria in patients 2 to 5 years of age.

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 submit draft labeling revised as follows.

1. Revise the CLINICAL PHARMACOLOGY section to read as follows.

> **CLINICAL PHARMACOLOGY:** Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.
>
> Human histamine skin wheal studies following single and repeated 10 mg oral doses of CLARITIN have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with CLARITIN.
>
> Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H_1 receptors

indicate that there was preferential binding to peripheral versus central nervous system H_1- receptors.

Repeated application of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) to the hamster cheek pouch did not cause local irritation.

Pharmacokinetics: **Absorption:** Loratadine was rapidly absorbed following oral administration of 10 mg tablets, once daily for 10 days to healthy adult volunteers with times to maximum concentration (T_{max}) of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. Based on a cross-study comparison of single doses of loratadine syrup and tablets given to healthy adult volunteers, the plasma concentration profile of descarboethoxyloratadine for the two formulations is comparable. The pharmacokinetics of loratadine and descarboethoxyloratadine are independent of dose over the dose range of 10 to 40 mg and are not altered by the duration of treatment. In a single-dose study, food increased the systemic bioavailability (AUC) of loratadine and descarboethoxyloratadine by approximately 40% and 15%, respectively. The time to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour. Peak plasma concentrations (C_{max}) were not affected by food.

Pharmacokinetic studies showed that CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) provide plasma concentrations of loratadine and descarboethoxyloratadine similar to those achieved with CLARITIN Tablets. Following administration of 10 mg loratadine once daily for 10 days with each dosage form in a randomized crossover comparison in 24 normal adult subjects, similar mean exposures (AUC) and peak plasma concentrations (C_{max}) of loratadine were observed. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) mean AUC and C_{max} were 11 % and 6% greater than that of the CLARITIN Tablet values, respectively. Descarboethoxyloratadine bioequivalence was demonstrated between the two formulations. After 10 days of dosing, mean peak plasma concentrations were attained at 1.3 hours and 2.3 hours (T_{max}) for parent and metabolite, respectively.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), food increased the AUC of loratadine by approximately 48% and did not appreciably affect the AUC of descarboethoxyloratadine. The times to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine were delayed by approximately 2.4 and 3.7 hours, respectively, when food was consumed prior to CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) administration. Parent and metabolite peak concentrations (C_{max}) were not affected by food.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in 24 subjects, the AUC of loratadine was increased by 26% when administered without water compared to administration with water, while C_{max} was not substantially affected. The bioavailability of descarboethoxyloratadine was not different when administered without water.

Metabolism: *In vitro* studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome P450 2D6 (CYP2D6). In the presence of a CYP3A4 inhibitor ketoconazole, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with substantially increased plasma concentrations of loratadine (See **Drug Interactions** section).

Elimination: Approximately 80% of the total loratadine dose administered can be found equally distributed between urine and feces in the form of metabolic products within 10 days. In nearly all patients, exposure (AUC) to the metabolite is greater than to the parent loratadine. The mean elimination half-lives in normal adult subjects (n =54) were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for descarboethoxyloratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. There was considerable variability in the pharmacokinetic data in all studies of CLARITIN Tablets and Syrup, probably due to the extensive first pass metabolism.

Special Populations:
Pediatric: The pharmacokinetic profile of loratadine in children in the 6- to 12-year age group is similar to that of adults. In a single-dose pharmacokinetic study of pediatric volunteers (age 8-12 years) given 10 mL of CLARITIN Syrup containing 10 mg loratadine, the range of individual subject values of pharmacokinetic parameters (AUC and Cmax) were comparable to those following administration of a 10 mg tablet or syrup to adult volunteers.

The pharmacokinetic profile of loratadine in children in the 2- to 5-year age group (n=18) is similar to that of adults. In a single-dose pharmacokinetic study of 13 pediatric subjects (age 2-5 years) given 5 mL of CLARITIN Syrup containing ~~10~~ 5 mg loratadine, the range of individual subject values of pharmacokinetic parameters (AUC and C_{max}) were comparable to those following administration of a 10 mg tablet ~~or syrup~~ to adult volunteers or children eight years of age and older.

Geriatric: In a study involving twelve healthy geriatric subjects (66 to 78 years old), the AUC and peak plasma levels (C_{max}) of both loratadine and descarboethoxyloratadine were approximately 50% greater than those observed in studies of younger subjects. The mean elimination half-lives for the geriatric subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for descarboethoxyloratadine.

Renal Impairment: In a study involving 12 subjects with chronic renal impairment (creatinine clearance ≤ 30 mL/min) both AUC and C_{max} increased by approximately 73% for loratadine and by 120% for descarboethoxyloratadine, as compared to 6 subjects with normal renal function (creatinine clearance ≥80 mL/min). The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not substantially different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or descarboethoxyloratadine in subjects with chronic renal impairment.

Hepatic impairment: In seven patients with chronic alcoholic liver disease, the AUC and C_{max} of loratadine were double while the pharmacokinetic profile of descarboethoxyloratadine was not substantially different from that observed in other trials enrolling normal subjects. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

2. Revise the first paragraph of the Carcinogenesis, Mutagenesis, Impairment of Fertility section to read as follows.

   In an 18-month carcinogenicity study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (descarboethoxyloratadine) times the exposure in adults and 5 (loratadine) and 20 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times the exposure in adults and 40 (loratadine) and 80 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and males and females given 25 mg/kg. Exposure of rats given 10 mg/kg of loratadine was 10 (loratadine) and 15 (descarboethoxyloratadine) times the ~~exposure~~ in adults and 15 (loratadine) and 20 (descarboethoxyloratadine) times the ~~exposure~~ in children given the maximum recommended daily oral dose. The clinical significance of these findings during long-term use of CLARITIN is not known.

3. Revise the phrase "The safety and tolerance of CLARITIN syrup..." to "The safety and tolerability of CLARITIN syrup..." in the Pediatric Use subsection of the PRECAUTIONS section.

4. The following comments pertain to the ADVERSE REACTIONS section.

   a. Revise the text regarding 2 to 5 year old patients as follows and delete the table of adverse events for this age group:

      Sixty pediatric patients 2 to 5 years of age received 5 mg loratadine once daily in a double-blind, placebo-controlled clinical trial for a period of 14 days. No unexpected adverse events were seen given the known safety profile of loratadine and the likely adverse reactions for this patient population. The following adverse events occurred with a frequency of 2 to 3 percent in the loratadine syrup-treated patients (2 to 5 years old) during the placebo-controlled trial and more frequently than in the placebo group: diarrhea, epistaxis, pharyngitis, influenza-like symptoms, fatigue, stomatitis, tooth disorder, earache, viral infection and rash.

   b. Include "thrombocytopenia" in the list of events reported during marketing of loratadine.

5. Revise the third paragraph of the OVERDOSAGE section to read as follows.

   No deaths occurred at oral doses up to 5000 mg/kg in mice (approximately 1200 and 1400 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m^2 basis). No deaths occurred at oral doses up to 5000 mg/kg in matured rats (approximately 2400 and 2900 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m^2 basis). However, lethality occurred in juvenile rats at an oral dose of 125 mg/kg (approximately 100 and 70 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m^2 basis). No deaths occurred at oral doses up to 1280 mg/kg in monkeys (approximately 2100 and 1500 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m^2 basis).

6. Revise the third paragraph of the DOSAGE AND ADMINISTRATION section to read as follows.

   In adults and children 6 years of age and over with liver failure or renal insufficiency (GFR < 30 mL/min), the starting dose should be 10 mg (one tablet or two teaspoonfuls) every other day. In children 2 to 5 years of age with liver failure or renal insufficiency, the starting dose should be 5 mg (one teaspoonful) every other day.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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 supplemental 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.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Sandy Barnes, Chief, Project Management Staff, at (301) 827-1055.

Sincerely,

/S/

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