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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-641/SE5-007

Medical Review(s)

Medical Officer Review

Division of Pulmonary Drug Products (HFD-570)

Application #:	NDA 20-641	**Category of Drug:**	Antihistamine
Sponsor:	Schering Corporation	**Route of Administration:**	Oral
Proprietary Name:	Claritin Syrup	**Medical Reviewer:**	Susan Johnson, Pharm.D., Ph.D.
USAN/Established Name:	Loratadine	**Review Date:**	September 21, 2000

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
November 24, 1999	November 26, 1999	SE5-007, Pediatric Labeling Supplement	
March 15, 2000	March 16, 2000	Safety Update	

Related Applications (if applicable)

Overview of Application and Review:
Safety data from pharmacokinetic and safety studies based on designs specified in pediatric Written Request are reviewed. Supplement may be approved pending acceptance of the sponsor of labeling changes.

Outstanding Issues:

Recommended Regulatory Action

New Clinical Studies: _____ Clinical Hold
_____ May Proceed

NDA/Supplements: __X__ Approval
_____ Approvable

Signature: /S/ Medical Reviewer **Date:** 9-21-00

Concurrence: /S/ Team Leader **Date:** 22 sept 2000

cc: ~~Div File~~
NDA 20-641
HFD-570/Trout, Borders

I. Background

This submission contains a supplemental application in partial response to the Written Request (WR) for pediatric studies issued by DPADP on October 15, 1998, asking that four studies be submitted:

Study 1: Conventional PK study in pediatric subjects 2-5 years old
Study 2: Safety study in pediatric subjects 2-5 years old
Study 3: Population PK study in pediatric subjects 6 months to 2 years of age
Study 4: Safety study in pediatric subjects 6 months to 2 years of age

This submission contains reports of the studies required for children age 2 to 5 years, i.e., Study 1 and Study 2.

Amendments were made to the WR on November 17 and November 19, 1999 and May 17, 2000. Only the November 19, 1999 amendment contained comments relevant to the studies in children age 2 to 5 years.

The WR stated that information on dosing and safety in children age 2 to 5 years with seasonal allergic rhinitis or chronic idiopathic urticaria may be placed in labeling as a result of the requested studies.

II. Study 1 (per Written Request)

Per the WR, this study was designed as a **single dose bioavailability study** in normal pediatric volunteers. Doses of 5 mg were administered to 18 subjects between the ages of 2 and 5 years and plasma levels were collected over the subsequent 72 hour timeperiod. Patients were confined to the study clinic during the 24 hours prior to treatment and for 24 hours following treatment. Dr. Young Moon Choi of OCPB has reviewed the pharmacokinetic findings of this trial.

Safety assessments included physical examinations, electrocardiograms and clinical laboratory tests, which were conducted at screening and at 72 hours following dosing. Vital signs were obtained daily and subjects were observed and questioned regarding adverse events throughout the study.

No patients discontinued from the trial due to adverse events or other reasons. There were no adverse events reported during this trial. Laboratory findings revealed that six of the 18 patients had an elevated glucose concentration at discharge. However, none of the cases was felt to be clinically significant and were attributed to a breakfast meal (off-site) preceding the clinic visit. No formal analyses of ECG data were conducted, but review of individual data did not appear to show trends in the difference between screening and post-study assessments in ventricular rate or PR, QRS, QT or QTc intervals. Tachycardia was reported in eight patients at one or both timepoints. Vital signs and physical examinations did not appear to show clinically significant trends.

III. Study 2 (per Written Request)

Per the written request, this study was designed as a randomized, double blind, placebo-controlled, parallel group safety study. It was carried out at a single center by the principal investigator Jerry M. Herron, M.D. The duration of treatment was two weeks plus a screening day and a follow-up day (WR specified at least one week) with 5 mg QD (WR specified an age- or weight-appropriate single dose level) or placebo. The WR specified that it was "allowable to study at least 50 subjects per treatment arm (i.e. total ≥ 100) if the study duration is 15 days." Accordingly, sixty patients received active treatment and 61 received placebo. The WR specified that the sponsor enroll an approximately equal representation of patients in each age group, which was achieved as shown in the demographic summary below.

The WR denoted that children should be enrolled "with allergic rhinitis or urticaria or with a medically documented history of allergic rhinitis or urticaria, who are free of any other clinically significant disease." Actual entry criteria fulfilled these specifications.

Endpoints were specified in the WR as adverse events, physical and clinical monitoring with appropriately timed chemistries, hematology profiles and ECGs:

- Adverse reactions in daily diaries.
- Laboratories (clinical chemistry and hematology) at screening and end of study.
- Vital signs at screening, baseline and end of study.
- If studying 100 subjects for 2 weeks, 12-lead ECG at screening and study days 8 and 15.

Study Design

Per the protocol for Trial C98-566, developed based on the WR, patients age 2 to 5 years were **eligible** for the study if they had a documented history of allergic rhinitis or chronic idiopathic urticaria (CIU) and were otherwise in good health. Subjects with a diagnosis of allergic rhinitis must have had either a positive RAST or a positive skin test (prick or intradermal) response to an appropriate allergen. Patients were **excluded** if they had had an upper respiratory infection tract or sinus infection in the seven days prior to screening, were intolerant of antihistamines or had current evidence of clinically significant disease.

Patient enrollment was stratified by age group (2 to <3, 3 to <4, 4 to <5 and 5 to < 6), with a minimum of 10 subjects per strata.

Medications other than the study treatment were required to be washed out prior to the study and withheld for the duration of the study, including all forms of corticosteroids, antihistamines, cromolyn sodium and nedocromil, decongestants and topical anti-inflammatories. Stable doses of systemic antibiotics and maintenance immunotherapy were allowed.

At the **Screening Visit**, procedures were explained to the patient and parent/guardian and written informed consent was obtained from parent/guardian. A medical history was obtained, skin testing was performed, if needed, a physical examination was conducted, vital signs and body weight and height were recorded, a standard 12-lead ECG was obtained and samples were collected for assessment of laboratory parameters (CBC, blood chemistry, urinalysis). At the subsequent Baseline Visit (may have been simultaneous with Screening), the first dose of medication was administered and patient diaries were dispensed. Adverse events were recorded beginning at the Baseline Visit, and were subsequently recorded by parent/guardians in the daily diary.

There were two additional clinic visits, on **Days 8 and 15** of treatment administration. Vital signs measurement, ECGs and adverse event assessments were repeated at each of these visits. Physical examinations, laboratory assessments and recording of body weight and height were repeated at the final visit (Day 15).

No efficacy assessments were made during this trial.

Sample size was based on the Written Request; 100 subjects with 50 in the loratadine group and 50 in the placebo group. It was estimated that the probability that one or more of the 50 subjects in the loratadine group would report an adverse event with an underlying incidence of 5 percent was 92 percent.

Disposition of Subjects

There were 121 patients enrolled in the trial, 60 in the loratadine group and 61 in the placebo group. None of the patients dropped out of the trial. Mean age was 3.6 years, 55 percent of participants were female and 87 percent of the patients were Caucasian. Mean weight was approximately 38 pounds and mean height was approximately 40 inches. The two treatment groups did not differ substantially with respect to these parameters. The number of patients in each age group were as follows:

	Loratadine 5 mg (N = 60)	Placebo (N = 61)
2 to <3 yrs	12	15
3 to < 4 yrs	14	14
4 to < 5 yrs	17	17
5 to < 6 yrs	16	15
6 yrs	1	0

Safety Outcomes

No deaths or serious events occurred during the trial and **no patients were discontinued due to adverse events**. Treatment was interrupted due to adverse events in two loratadine patients and eight placebo patients. These interruptions were due to various gastrointestinal complaints, some associated with flu symptoms or fever. No difference between the loratadine and placebo patients was observed with respect to causes of treatment interruptions.

All treatment-emergent adverse events that occurred during the trial are reported in the table on the following page. Those events with an incidence rate of two percent or greater, which occurred at a higher rate among the loratadine patients than placebo patients, are proposed for inclusion in labeling: diarrhea, epistaxis, pharyngitis, influenza-like symptoms, fatigue, stomatitis, tooth disorder, earache, viral infection and rash.

Two placebo patients experienced clinically meaningful laboratory abnormalities post-baseline, as defined by a priori criteria (Pt # 083 WBC and Pt # 109 SGOT/AST & SGPT/ALT). There appeared to be no trends in distribution of subjects above, within or below the pre-specified reference range for either treatment.

ECGs were conducted at Screening and on Days 8 and 15. There were no statistical differences between groups at any timepoint with regard to change from baseline in mean ventricular rate, or PR, QRS, QT, and QTc intervals (both Bazett and Fridericia calculations). No subject had a QTc of > 440 msec. Percent change from baseline in each parameter was analyzed categorically and appeared to show no meaningful trends within or between treatment groups.

Vital sign and body weight changes between screening and the final study visit did not appear to suggest a treatment difference.

Physical examinations did not appear to show trends of changes between screening and the end of the study for either treatment group.

Age, race and gender did not appear to have observable treatment effects on outcomes of adverse events, laboratory data, ECG, vital signs, body weight, or physical examination findings. However, there were too few pediatric patients of races other than Caucasian to consider these data conclusive.

Incidence of Treatment-Emergent Adverse Events, Number (%) of Subjects

	Loratadine 5 mg (N = 60)	Placebo (N = 61)
Any Adverse Event	19 (32)	25 (41)
Autonomic Nervous System	0	1 (2)
Lacrimation	0	1 (2)
Body as a Whole	7 (12)	9 (15)
Fatigue	1 (2)	0
Fever	4 (7)	5 (8)
Headache	3 (5)	4 (7)
Influenza-like symptoms	1 (2)	0
Central and Peripheral Nervous System	0	2 (3)
Hyperkinesia	0	2 (3)
GI System	7 (12)	10 (16)
Constipation	1 (2)	1 (2)
Diarrhea	2 (3)	0
Dyspepsia	1 (2)	4 (7)
Loose stools	1 (2)	2 (3)
Nausea	0	2 (3)
Stomatitis	1 (2)	0
Tooth disorder	1 (2)	0
Vomiting	3 (5)	3 (5)
Hearing/Vestibular	1 (2)	0
Earache	1 (2)	0
Musculoskeletal	0	2 (3)
Body aches	0	2 (3)
Psychiatric	4 (7)	5 (8)
Appetite increased	0	1 (2)
Drowsiness	4 (7)	4 (7)
Resistance Mechanism	1 (2)	0
Infection, viral	1 (2)	0
Respiratory System	7 (12)	8 (13)
Allergic rhinitis	1 (2)	2 (3)
Coughing	2 (3)	3 (5)
Epistaxis	2 (3)	0
Nasal congestion	0	1 (2)
Pharyngitis	2 (3)	1 (2)
Sinus congestion	0	1 (2)
Sneezing	0	1 (2)
Skin and Appendages	1 (2)	0
Rash	1 (2)	0
Urinary System	0	1 (2)
Nocturia	0	1 (2)

IV. Integrated Summary of Safety

The ISS contained information from Study 1 and Study 2, as discussed above, as well as summary data from three placebo controlled trials and six active controlled trials which were submitted with the original NDA. Among the previously reported trials, patients between the ages of two and five were exposed to various doses of loratadine syrup: 25 patients received 2.5 mg, 127 patients received 5 mg and 1 patient received 10 mg. The total number of patients between the ages of two and five who have been exposed to loratadine syrup during any of the trials was 231 and their age distribution was:

2 to < 3 years	36
3 to < 4 years	49
4 to < 5 years	65
5 to < 6 years	80
6 years	1

The majority of these patients were exposed to treatment for between 8 and 15 days.

Only adverse event safety data were reported in the ISS for the previously submitted trials. No patients who received loratadine were discontinued from these trials due to adverse events. There were two discontinuations due to treatment failure. The adverse event profile from these trials was consistent with that seen in Trial C98-566. Of note, one patient who had received loratadine 5 mg QD reported hyperkinesia. There were no severe adverse events reported. Age, race and gender did not appear to affect reporting rates, however, there were few non-Caucasian patients enrolled in these trials.

Eight post-marketing reports were received through May 15, 1999. Three cases reported thrombocytopenia (in addition to other events such as rash and purpura). This term should be added to labeling. Behavioral changes, e.g. "aggressive reaction" were reported in two cases and should also be reflected in the labeling. Bradycardia was reported in two cases and extrasystoles/arrhythmia was also reported. These cardiac events are currently described in the labeling.

V. Safety Update

A safety update was submitted March 15, 1999, which contained no additional information.

VI. Labeling

The following comments should be provided to the sponsor regarding their proposed labeling.

PRECAUTIONS section, Pediatric Use subsection:

Change the phrase

ADVERSE REACTIONS section:

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

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

DOSAGE AND ADMINISTRATION section:

Revise the sentence beginning "In patients with liver failure..." to read as follows.

VII. Conclusion

This supplement should be approved, pending acceptance by the sponsor of the labeling changes noted above.

DEPT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products

MEDICAL TEAM LEADER MEMORANDUM

DATE: 22 September 2000

FROM: Mary Purucker, MD, PhD
Medical Team Leader

/S/ 7 sept 00 — 9/22/00

/S/

SUBJECT: NDA 20-641 SE5-007
Claritin Syrup (Loratadine, 1 mg/ml)
Pediatric Labeling Supplement (age 2 – 5 years)

TO: Robert Meyer, MD
Director, DPADP

Introduction: This submission contains a partial response to the Written Request for Pediatric Studies for Loratadine, issued 15 October 1998, and as amended. The submission is intended to satisfy the request for studies for children age 2 – 5 years, inclusive, and to extend the indication for loratadine down to age 2 years at a recommended dose of 5 mg once daily. The proposed indication for this pediatric population would be the treatment of allergic rhinitis and chronic idiopathic urticaria.

The medical reviewer for both submissions is Dr. Susan Johnson.

Submission SE5-007 is comprised of the results of two studies:

- C97-033, an open label, single dose study intended to characterize the pharmacokinetic profiles of loratadine and its active metabolite desloratadine, following a single 5 mg dose of loratadine syrup, 1 mg/ml, administered to 18 children age 2 to 5 years, inclusive. This trial was primarily reviewed by Dr. Y.M. Choi of the Office of Clinical Pharmacology and Biopharmaceutics. The safety assessments performed during this trial, comprised of adverse events and ECGs, were reviewed by Dr. Susan Johnson.
- C98-566, a randomized, double-blind, placebo controlled, parallel group, single center safety study of atopic children age 2 – 5 years, inclusive. Safety endpoints

included adverse events, ECGs, physical exams, and laboratory studies. There were no efficacy endpoints. The medical reviewer is Dr. Susan Johnson.

Clinical Issues: Please refer to Dr. Johnson's review for comprehensive coverage of the important clinical/safety issues and (clinical) labeling recommendations for the sponsor, to which I concur.

Secondary review of this supplement generated a few additional questions, which if answered may add to the overall yield of information from Study C98-566, but which would not be considered approvability issues:

1. Inclusion criteria specified allergic rhinitis or chronic idiopathic urticaria, by history, RAST or other documentation. A breakdown by working diagnosis under "Patient Demographics" would have provided some confidence that there was reasonable representation of both diagnoses among the group.
2. The sponsor's analysis of the ECG data would have benefited by more background, that is, a discussion of expected "normals" for this age range with supportive references. Although there was no difference between the placebo and loratadine groups in mean change-from-baseline in QTc, it is unclear how much variability is ordinarily present among young children and therefore if the study was adequately powered to detect a true difference. This could lead to a false sense of reassurance.

   On the other hand, the sponsor did perform a categorical analysis of the data which showed, among other things, that no child developed a QTc > 440 msec at the proposed therapeutic dose. In addition, individual values of the change-from-baseline in QTc showed that twice as many children treated with placebo had QT prolongation >20% as children treated with loratadine.

Additional comment:

3. Dr. Johnson's recommendation to include "thrombocytopenia" in the "Adverse Reactions" Section is appropriate. This recommendation is based on 3 newly submitted case reports, the inadequate coverage presently in the label ("thrombocytopenia" is not synonymous with "purpura"), and similar reactions/marrow toxicity reported with several of the first generation antihistamines (see Soleymanikashi Y, Weiss NS *Annals of Allergy* 1970; 28 (10) 486-90).

[redacted]

APPEARS THIS WAY
ON ORIGINAL