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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-641/SE5-007

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-641, SE5-007	**REVIEWER:** Young-Moon Choi, Ph.D.
DRUG: Claritin (loratadine) Syrup	**SUBMISSION :** 11/24/99
SPONSOR: Schering Corporation	**STAMPED :** 11/26/99
TYPE OF SUBMISSION: Pediatric labeling supplement for 2-5 years old age group	**ASSIGNED :** 12/13/99
	REVIEWED: 9/19/00

1. SYNOPSIS

Loratadine is an orally active, selective peripheral H1-antagonist. A major metabolite of loratadine, desloratadine (DCL), appeared to be more potent than parent compound.
Currently, loratadine is indicated (10 mg once daily) for the treatment of the nasal and non nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticardia in patients 6 years of age and older. The present submission (Supplement 007) is a labeling supplement for pediatric (2-5 years of age) use.

The supplement 007 includes one pharmacokinetic study (C97-033) and a safety study (C98-566). Therefore, it is a partial response to the 'Official Written Request for Pediatric Studies' dated 10/15/98 as amended 11/17/99 and 11/19/99, in which the following four studies were requested by the Agency:

Study 1: Conventional pharmacokinetic (PK) study in pediatric subjects 2-5 years old (C97-033)
Study 2: Safety study in pediatric subjects 2-5 years old (C98-566),
Study 3: Population PK study in pediatric subjects 6 months to 2 years old, and
Study 4: Safety study in pediatric subject's 6 months to 2 years of age.

. Overall, the four studies fulfilled the Pediatric Exclusivity requests and the Pediatric Exclusivity has been granted to the sponsor.

For S007, the Office of Clinical Pharmacology and Biopharmaceutics reviewed the Study 1 (C97-033) and Division of Pulmonary and Allergic Drug Products (DPADP) reviewed the Study 2 (C98-566).

From a pharmacokinetic perspective, the review is mainly focused on the comparison of the systemic exposures of loratadine as well as DCL in pediatric subjects to those in adults. The pharmacokinetics of loratadine and DCL in children 2-5 years of age (Study C98-033) after administration of 5 mg loratadine were compared to the respective pharmacokinetics in older children (8-12 years; Study C90-187) and adults obtained using 10 mg loratadine syrup (Study C92-025) and the approved 10 mg loratadine tablet (Study C91-339). Also, the above values were compared to the pharmacokinetics of loratadine and DCL when given as a 40 mg of loratadine (Study C86-070-01) since this is the maximum safe dose in adults.

The arithmetic mean or median values of the pharmacokinetic parameters of loratadine and desloratadine

appeared substantially higher in pediatric patients 2-5 years of age group (Tables 1 and 2). However, the degree of the systemic exposure was 17-33 % of that after 40-mg single dose of loratadine, of which the safety has been evaluated and found acceptable. As observed in the older age group, the pharmacokinetics of loratadine and DCL in pediatric subjects 2-5 years of age were highly variable: the intersubject variability as expressed as coefficient of variation (CV) of Cmax and AUC_{0-t} for loratadine (n=18) were 90% and 80%, respectively; for DCL, the CVs were 36 % for Cmax and 88 % for AUC_{0-t}. Furthermore, the distribution of the individual data indicates that the substantially high arithmetic mean value of pharmacokinetic parameters of pediatric subjects 2-5 years of age is due to the few extremes, especially for Cmax of loratadine and AUC of DCL.

Therefore, considering

(1) the large variability of pharmacokinetic parameters in pediatric subjects 2-5 years of age as observed in the older age group,
(2) the similar range of distribution of the individual data (rather than arithmetic mean or median values; please refer to the following Box-whisker Plots), and
(3) the much lower exposure in pediatric subjects 2-5 years of age than that after a 40 mg dose in adults,

This reviewer is of the opinion that the study results of 5-mg dose for pediatric subjects 2-5 years old supported a pediatric indication from a pharmacokinetic perspective.

Accordingly, the following sections of labeling need to be changed appropriately:

Clinical Pharmacology: Pharmacokinetics; Clinical Trials
Indications and usage
Precautions: Pediatric use
Adverse reactions
Dosage and Administration

It is noted that the proposed labeling under the pharmacokinetic section is not divided by the subtitle. The sponsor needs to revise/rearrange the structure of the "Clinical Pharmacology Section of the labeling" by subtitle (Please refer to the "Labeling comments"). The contents of the original labeling under pharmacokinetic section should not be changed, except for the labeling of pediatric subjects.

Table 1. Loratadine pharmacokinetic parameters (% CV)

Parameters	**StudyC92-025** 10mg syrup in adults	**Study C91-339** 10 mg tablet in adults	**Study C90-187** 10 mg syrup in pediatrics 8-12 yrs old	**Study C86-070** 40 mg syrup in adults	**Study C97-033** 5 mg syrup in pediatrics 2-5 years old
Cmax (ng/ml)	3.62 (150)	2.11 (90)	4.38 (72)	41.74 (78)	7.78 (99)
AUC0-t (ngxh/ml)	10.1 (147)	4.64 (106)	8.98 (69)	97.45 (73)	16.7 (80)
AUCinf (ngxh/ml)				103.8 (71)	
Tmax (hr)	0.86 (44)	1.00 (34)	1.00 (0)	1.19 (59)	1.17 (33)
T1/2 (hr)				5.19 (65)	

Table 2. Desloratadine pharmacokinetic parameters (% CV)

Parameters	**StudyC92-025** 10mg syrup in adults	**Study C91-339** 10 mg tablet in adults	**Study C90-187** 10 mg syrup in pediatrics 8-12 yrs old	**Study C86-070** 40 mg syrup in adults	**Study C97-033** 5 mg syrup in pediatrics 2-5 years old
Cmax (ng/ml)	3.65 (35)	3.66 (45)	3.79 (26)	21.38 (48)	5.09 (36)
AUC0-t (ngxh/ml)	35.1 (30)	53.36 (89)	51.66 (49)	264.6 (57)	87.2 (88)
AUCinf (ngxh/ml)	38.8 (27)	48.4 (44)	55.59 (48)		
Tmax (hr)	0.94 (17)	1.97 (98)	1.69 (56)	3.24 (117)	2.33 (75)
T1/2 (hr)	19.0 (23)	24.9 (35)	13.79 (22)		25.1 (94)

2. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has completed the review of NDA 20-641 (SE5-007) submitted on 11/24/99 and found that from a clinical pharmacology and biopharmaceutic perspective, the submission is acceptable, supporting the 5-mg dose for pediatric subjects 2-5 years of age. The following "Labeling comments" needs to be conveyed to the sponsor, as appropriate.

3. LABELING COMMENTS

3-1. The sponsor is asked to revise/rearrange the structure of the "Clinical Pharmacology Section of the labeling" by following subtitle:

Clinical pharmacology
Pharmacokinetics
- Absorption
- Distribution
- Elimination
- Metabolism

Special population
- Geriatric subjects
- Pediatric subjects
- Renal impaired
- Hepatically impaired

Drug interaction

3-2. The following is the Agency's recommendation of the label under the Clinical Pharmacology section.

Draft

1 pages redacted from this section of the approval package consisted of draft labeling

Draft

9/22/00

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Concurrence

/S/ 9/20/00

Shiew-Mei Huang, Ph.D.
Acting Division Director
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Office of Clinical Pharmacology and Biopharmaceutics

CC: HFD-570 NDA 20-641; DIV FILE; /Trout; Borders
HFD-870 Huang; Choi
CDR Attn: Barbara Murphy

Appendix 1. Study summary and reviewer's comments

Appendix 1.

Title of the Study: SCH 29851: Single-Dose Bioavailability of Loratadine Syrup in Normal Pediatric Volunteers (Protocol No. C97-033).

Investigator(s): Jerry M. Herron, M.D.

Studied Period: 26 Sep 1997 to 05 OCT 1997

Objective(s): To characterize the pharmacokinetic profiles of loratadine (SCH 29851) and its active metabolite, desloratadine (DCL; SCH **34117),** following a single 5 mg dose of loratadine syrup) (1 mg/ml) administered orally to healthy pediatric subjects ranging in age from 2 to 5 years, inclusive.

Methodology: Open-label, single-dose study. Eighteen volunteers were assigned to receive SCH 29851. Blood and urine samples were collected at pre-specified times for safety. Additional blood was collected for pharmacokinetic evaluation. Subjects were continually observed and questioned throughout the study for possible occurrence of adverse events. All plasma samples were assayed for loratadine and DCL concentrations using validated [redacted] methods.

Reviewer's comment on assay: Assay performance was acceptable (Refer to the following table). Plasma concentrations of loratadine and desloratadine were determined using [redacted]

	Loratadine	**Desloratadine**
Linearity	Standard curve linear in the range of [redacted]	Standard curve linear in the range of [redacted]
Accuracy	Satisfactory [redacted]	Satisfactory [redacted]
Precision	Satisfactory [redacted]	Satisfactory [redacted]
Sensitivity	LOQ: [redacted]	LOQ: [redacted]
Specificity	Satisfactory [redacted]	Satisfactory [redacted]

Number of Subjects: Eighteen healthy pediatric subjects.

Diagnosis and Criteria for Inclusion: Pediatric male and female subjects between 2-5 years of age, inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology and urinalysis) were empanelled for this study.

Test Product, Dose, and Mode of Administration, Batch No(s): Loratadine syrup, 5 mg, oral, Batch No. 7-RUD-2.

Duration of Treatment: Single dose was administered in the morning at approximately 8 a.m. and each subject was followed for 72 hours postdose.

Criteria for Evaluation: Physical examinations, electrocardiograms, clinical laboratory tests were performed at screening and at the conclusion of the study and adverse events throughout the study were to be recorded for safety evaluation. Blood samples were collected over 72 hours for determination of pharmacokinetic parameters (Cmax, Tmax, AUC and t1/2).

Statistical Methods: The pharmacokinetic parameters were listed and summarized using means, standard deviations and coefficients of variation.

Results:

Safety: There were no adverse events reported in this study. Loratadine 5 mg was well tolerated in children 215 years of age.

Blood pressure, pulse rate, respiratory rate, oral body temperature evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy pediatric male and female subjects.

Pharmacokinetics: Mean Cmax values for loratadine and its metabolite DCL were 7.8 ng/mL and 5.1 ng/mL, respectively; mean Tmax values were 1.2 hours and 2.3 hours, respectively. Mean extent of absorption estimated by AUC(tf) for loratadine and DCL were 16.7 ngxhr/mL and 87.2 ngxhr/mL, respectively; therefore, systemic exposure to DCL was 8-fold greater than loratadine. Plasma concentrations of loratadine decreased rapidly. There were an insufficient number of quantifiable plasma concentrations during the elimination phase to determine its elimination half-life. The mean elimination half-life for DCL was 25.1 hours in this pediatric population (n=18).

Sponsor's conclusions: Plasma concentrations and pharmacokinetic profiles of loratadine and DCL achieved in 2-5 year old children following administration of loratadine syrup 5 mg are similar to those achieved following 10 mg loratadine administered to adults and children eight years of age and older. The well-established efficacy and safety associated with oral administration of loratadine 10 mg to adults, therefore, should be achieved with oral administration of loratadine syrup 5 mg to children aged 2 to 5 years.

Reviewer's comments:

The arithmetic mean or median values of the pharmacokinetic parameters of loratadine and desloratadine in pediatric patients 2-5 years of age after administration of 5 mg loratadine syrup appeared substantially higher than that in older age group after 10 mg dose of loratadine (Please refer to the Tables 1 and 2 on page 2).

However, considering

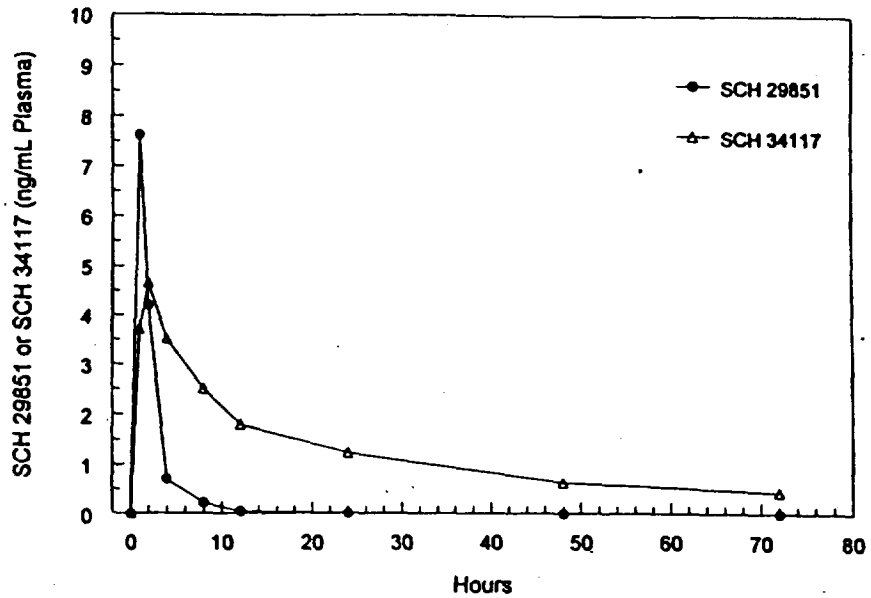
(1) high variability of the Pharmacokinetics parameters as observed in older age groups,
(2) the similar range of distribution of individual data (Refer to the Figures 1, 2 and 3 on page 8, 9, and 10), and
(3) much lower systemic exposure than that after 40 mg of loratadine dose,

This reviewer is of the opinion that the study results of 5-mg dose for pediatric subjects 2-5 years old satisfactorily support a pediatric indication, provided the favorable safety profile from the safety study in this age group with 5 mg dose (C-98-566).

It should be also noted that the higher systemic exposure of loratadine (Cmax and AUC) and desloratadine (AUC) in pediatric subjects 2-5 years of age appeared to be due to a few extremes (Refer to the Figures 2 and 3 on page 9, 10).

[redacted]

Linear-Linear



Log-Linear

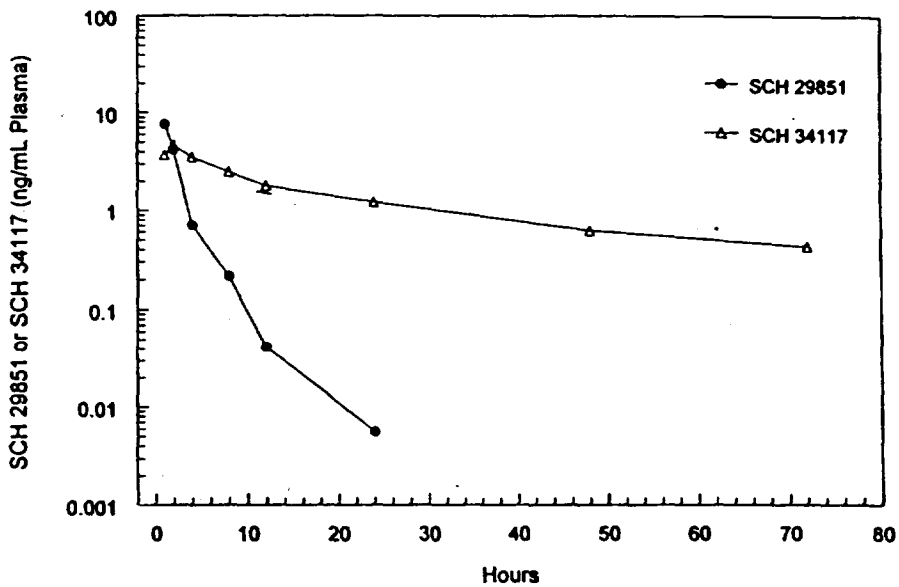


Figure 1 Mean Plasma Concentrations of Loratadine and DCL Following a Single 5 mg Dose of Loratadine Syrup to Pediatric Volunteers.

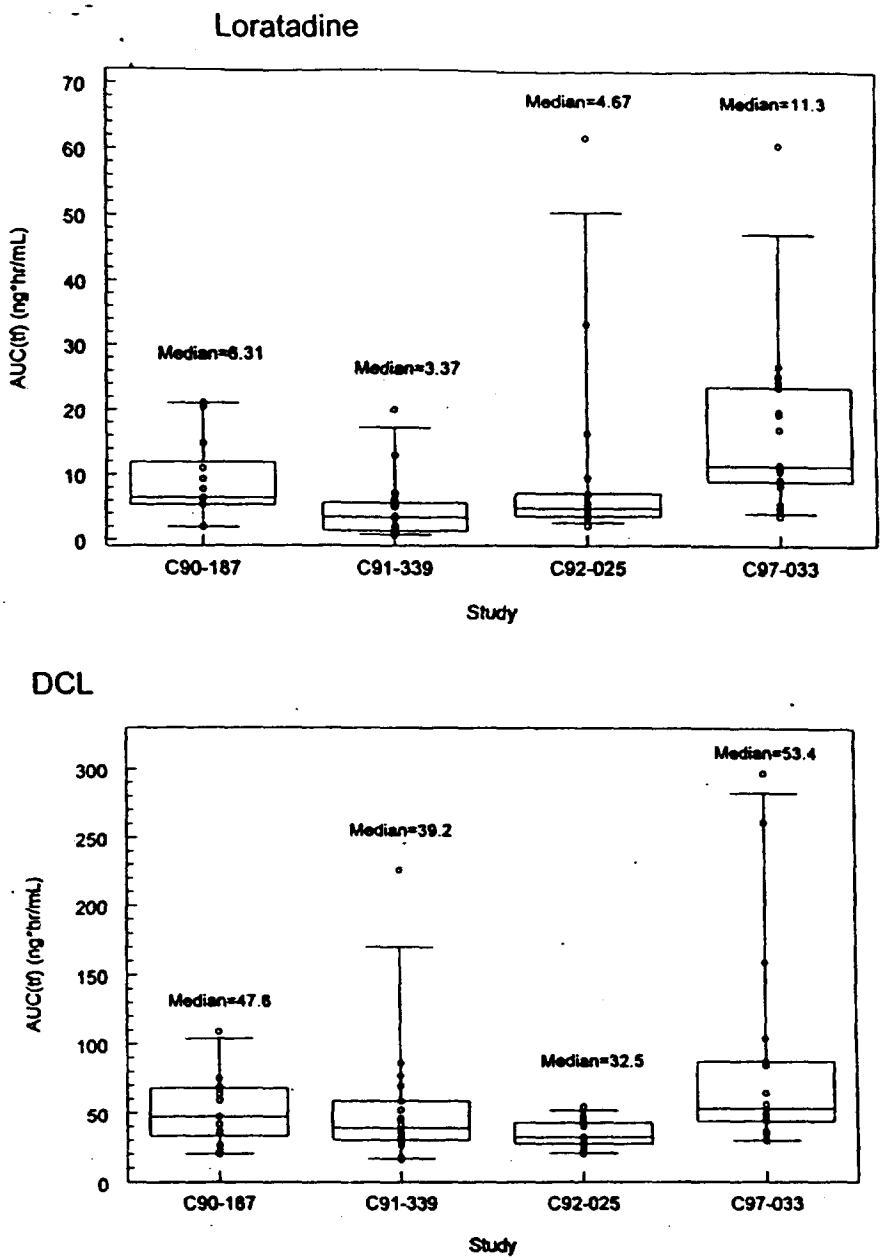


Figure 2. Comparison of AUC Data in Pediatric (C97-033, C90-187) and Adult (C92-025, C91-339) Subjects Administered 5 mg (C97-033), 10 mg (C90-187, C92-025) Loratadine Syrup, or 10 mg (C91-339) Loratadine Conventional Tablet.

Box-Whisker Plots: Line represents median, box represents from the 25th to 75th percentile of the data, whiskers represent 5th and 95th percentile.

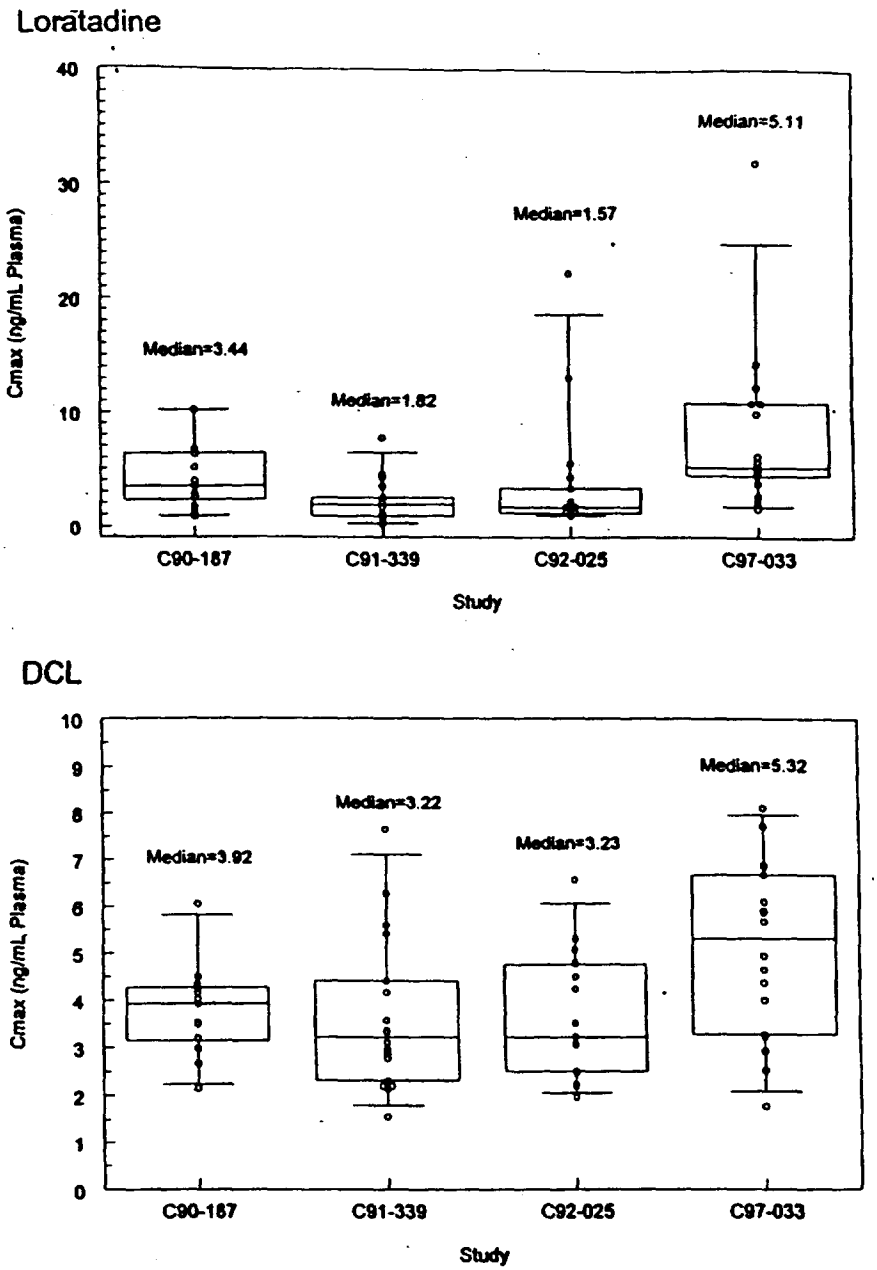


Figure 3. Comparison of Cmax Data in Pediatric (C97-033, C90-187) and Adult (C92-025, C91-339) Subjects Administered 5 mg (C97-033), 10 mg (C90-187, C92-025) Loratadine Syrup, or 10 mg (C91-339) Loratadine Conventional Tablet.

Box-Whisker Plots: Line represents median, box represents from the 25th to 75th percentile of the data, whiskers represent 5th and 95th percentile.