

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-658 S005

FINAL PRINTED LABELING

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO  
ENSURE ONLY CORRECT AND CURRENT INFORMATION IS  
DISSEMINATED TO THE PUBLIC.

SEP 14 1995

August 17, 1995

NDA 19-658/S-003, S-005, S-007  
Claritin (loratadine 10 mg) Tablet  
Schering Corporation

**CSO LABELING REVIEW**

**BACKGROUND INFORMATION**

S-003 was originally submitted on February 14, 1995 to provide for the use of Claritin in the management of idiopathic chronic urticaria. It was NA'd on July 3, 1995 because several administrative documentation problems and protocol violations were detected. In the NA letter, three labeling comments were included. The first two labeling comments requested that the sentence dealing with onset-of-action be deleted and also the reference to  
Our third comment recommended that the labeling be brought up to date with regard to the loratadine-relevant labeling contained in the labeling supplements S-005 and S-007. Schering's major amendment dated June 30, 1995 was reviewed and found to be approvable. Since this submission includes revised labeling to reflect the labeling supplements of S-005 & S-007, the approval of S-003 should supersede S-005 & S-007.

S-005 was originally submitted on October 3, 1994 to provide for dosing instructions, "Take 1 tablet once-a-day on an empty stomach.", on the blister backing for professional samples. In the May 2, 1995 teleconference, Mr. Kyoung Lee informed Mr. Michael Belman of Schering that the dosing instructions must be complete if they wish to add it to the blister package and that the phrase "on an empty stomach" should be omitted. Schering submitted an amendment on May 9, 1995 with the revised dosing instruction "~~Adults and children 12 years of age and over: Take 1 tablet daily.~~ Please note that the phrase, "on an empty stomach" has been deleted per Biopharm's March 9, 1995 review of the loratadine-food interaction study (C9 281-01). This Biopharm review was for NDA 20-470 (loratadine 10 mg/PSE 240 mg) but applies to NDA 19-658 and NDA 19-670 because of the loratadine component. This change also applies to the package insert. This supplement has been reviewed by the chemist, Dr. Sung Kim, and the medical officer (MO), Dr. Peter Honig, and is acceptable as amended. Please refer to chemistry review dated April 18, 1995 and MO Reviews dated March 28 and May 15, 1995.

S-007 was originally submitted on November 30, 1994 to provide for revised labeling to include "supraventricular tachyarrhythmias" as an additional adverse event. Additional labeling changes were requested by Dr. Peter Honig on January 31, 1995 via telephone conference. Schering submitted an amendment on April 11, 1995 with the requested changes and was found to be acceptable by Dr. Honig. Please refer to MO review dated May 4, 1995.

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This labeling review compares the proposed labeling submitted on June 30, 1995 to the last approved labeling (approved on January 21, 1994). The following changes have been made to the labeling submitted on June 30, 1995

## 1. DESCRIPTION Section

The only change that has been made is the addition of a colon after the heading DESCRIPTION. Please note that a colon has been added after the headings of all the sections as recommended by Dr. Honig in his January 31, 1995 teleconference.

## 2. CLINICAL PHARMACOLOGY Section

- a. In the last sentence of the second paragraph, the word "tablets" has been deleted.
- b. In the third paragraph, the sentence "*The specific enzyme systems responsible for metabolism have not been identified.*" has been deleted. The sentences, "*Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. The pharmacokinetics of loratadine and descarboethoxyloratadine are dose independent over the dose range of 10 to 40 mg and are not significantly altered by the duration of treatment.*" have been added to the end of the paragraph. The first sentence that was added is a revised version of the first sentence of the fifth paragraph of the last approved labeling. The second sentence that was added is identical to the second sentence of the fifth paragraph of the last approved labeling.
- c. The fourth paragraph is new.  

*"In vitro studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by P450 CYP3A4 and, to a lesser extent, by P450 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 significantly increased plasma concentrations of loratadine (See Drug Interactions section)."*

- d. In the sixth paragraph, the sentence "*Although these differences would not be expected to be clinically important, CLARITIN Tablets should be administered on an empty stomach*" has been deleted.
- e. In the first sentence of the seventh paragraph, the letter "c" in "*creatinine clearance*" is no longer capitalized.
- f. In the third sentence of the tenth paragraph, the percentage sign has been deleted after 73.
- g. The thirteenth paragraph is new.

*"Among those patients involved in double-blind randomized controlled studies of CLARITIN Tablets, approximately 1000 patients were enrolled in studies of idiopathic chronic urticaria. In placebo-controlled clinical trials, CLARITIN Tablets 10 mg once daily were superior to placebo in the management of idiopathic chronic urticaria, as demonstrated by reduction of associated itching, erythema, and hives." In these studies, the incidence of somnolence seen with CLARITIN Tablets was similar to that seen with placebo."*

3. **INDICATIONS AND USAGE Section**

The phrase "*and for the management of idiopathic chronic urticaria.*" has been added.

4. **CONTRAINDICATIONS Section**

No changes were made.

5. **PRECAUTIONS Section**

- a. In the **General** subsection, the phrase "*or renal insufficiency (GFR < 30 mL/min)*" has been added

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b The Drug Interactions subsection has been replaced by the following.

*"Loratadine (10 mg once daily) has been safely coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n=24 in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on QT<sub>c</sub> intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 55% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in the following table.*

**Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers**

	<u>Loratadine</u>	<u>Descarboethoxyloratadine</u>
Erythromycin (500 mg Q6h)	+ 10%	+ 16%
Cimetidine (500 mg QID)	+ 103%	+ 6%
Ketoconazole (200 mg Q12h)	+ 30%	+ 7%

*There does not appear to be an increase in adverse events in subjects who received oral contraceptives and CLARITIN Tablets compared to placebo."*

It appears that the word "Descarboethoxyloratadine" has been misspelled as "Descarboethoxylaratadine" in the table

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CSO Labeling Review  
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- c. No changes have been made to the **Carcinogenesis, Mutagenesis and Impairment of Fertility** subsection
- d. In the **Pregnancy Category B** subsection, the phrase "*at oral doses up to 96 mg/kg (75 times and 150 times, respectively the recommended daily human dose on a mg/m<sup>2</sup> basis)*" has been added to the end of the first sentence.
- e. No changes have been made to the **Nursing Mothers** subsection
- f. No changes have been made to the **Pediatric Use** subsection

## 6. **ADVERSE REACTIONS** Section

- a. In the second sentence of the first paragraph, "2" and "3" have been spelled out and the apostrophes after the words "weeks" and "months" have been deleted
- b. The sentence "*Adverse events reported in placebo-controlled idiopathic chronic urticaria trials were similar to those reported in allergic rhinitis studies.*" has been added after the Reported Adverse Events Table
- c. The order of the adverse events have been alphabetized in all the subsection and in the last paragraph
- d. The word " " has been deleted from the **Body As A Whole** subsection
- e. The word " " has been deleted from the **Respiratory System** subsection
- f. The word "*supraventricular tachyarrhythmias*" has been added to the last paragraph

## **DRUG ABUSE AND DEPENDENCE** Section

No changes have been made

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### 8. OVERDOSAGE Section

In the third paragraph, the comma after mice has been deleted.

### 9. DOSAGE AND ADMINISTRATION Section

The phrase, "*on an empty stomach*" has been deleted from the first sentence.

In the second sentence, the phrase "*or renal insufficiency (GFR < 30 mL/min)*" has been added after "*liver failure*".

### 10. HOW SUPPLIED Section

The 500 tablet bottle has been added.

## CSO COMMENTS/RECOMMENDATION

According to the chemist's and MO's reviews, the labeling revisions are acceptable.

Although the labeling for the blister package was not submitted in the June 30, 1995 submission, the amendment to S-005 dated May 9, 1995 contains the dosing instructions, "*Adults and children 12 years of age and over Take 1 tablet daily.*" I think the blister package should be revised as "*Adults and children 12 years of age and over: One 10 mg tablet daily*" to be consistent with the package insert.

The addition of the 500 tablet container appears to be acceptable according to the chemistry reviews numbers 1 and 2 dated January 28 and July 29, 1987 respectively.

The sponsor should be notified that the spelling of "*Descarboethoxyloratadine*" is misspelled if it is indeed misspelled. I think the correct spelling is Descarboethoxyloratadine.

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An approval letter should be drafted for S-003 with labeling comments regarding consistent dosing instructions for the blister package and package insert and correct spelling of Descarboethoxyloratadine if the MO and Chemist agree to them. This approval letter should be used to supersede S-005 and S-007 since it covers the labeling changes contained in both supplements.

**ISI** 8/28/95  
Koung Lee, CSO

- cc: Original NDA 19-658
- HFD-155/Divison Files
- HFD-155/C.Schumaker
- HFD-155/M.Himmel
- HFD-155/P.Honig
- HFD-155/S.Kim
- HFD-155/R.Wood
- HFD-155/K.Lee

**ISI**  
9-14-95

Since the blister pack  
insert was never incorporated  
into S-003, S-005 should  
be approved separately.

**ISI**  
9-14-95

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-658 S005

MEDICAL REVIEW(S)

D.F.

MAY 12 1995

MEDICAL OFFICER REVIEW

DATE REVIEWED: May 12, 1995  
NDA# 19-658;Amendment of Supplement #005  
REVIEWER: Peter Honig, M.D.  
PRODUCT: loratadine 10mg tablet (Claritin)  
CATEGORY of DRUG: antihistamine  
ROUTE of ADMINISTRATION: oral tablet  
SPONSOR: Schering Corporation  
MATERIAL REVIEWED: Amended supplement-revised labeling component.

The following dosing instructions are being proposed to be added to the blister backing for loratadine professional samples: "Adults and children over 12 years of age: Take 1 tablet daily".

Reviewer comment and recommendations:

This is acceptable and in concordance with dosing recommendations contained in approved loratadine labeling.

Comments to be forwarded to the sponsor:

The proposed text for the blister backing "Adults and children 12 years of age and over: Take 1 tablet daily" is acceptable and approved.

/S/

Peter K Honig, MD  
Medical Review Officer

/S/ 5/12/95

Martin H. Himmel, MD  
Medical Group Leader

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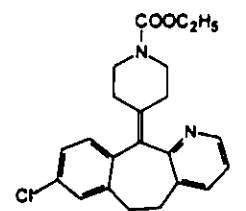
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RESEARCH**

**APPLICATION NUMBER: 19-658 S005**

**CHEMISTRY REVIEW(S)**

DF

APR 10 1995

<b>CHEMIST'S REVIEW</b>		1. ORGANIZATION HFD-150 DOPDP	2. NDA NUMBER <u>19-658</u>
3. NAME AND ADDRESS OF APPLICANT (City and State) Schering Corporation 2000 Galloping Hill Road Kenilworth, New Jersey 07033		4. AF NUMBER	
6. NAME OF DRUG Claritin Tablets	7. NONPROPRIETARY NAME Loratadine		5. SUPPLEMENT (S) NUMBER(S) DATE(S) S-005, SLR, 10/3/94
8. SUPPLEMENT PROVIDES FOR: Revised text for the blister backing for professional samples ( additional dosing information " Take one tablet once-a-day			9. AMENDMENT (S) NUMBER(S) DATE(S) Correspondence, 3/22/95
10. PHARMACOLOGICAL CATEGORY Antihistamine for seasonal allergic rhinitis	11. HOW DISPENSED RX <u>XX</u> OTC <u>   </u>		12. RELATED IND/NDA/DMF  DMF <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px; vertical-align: middle;"></span>
13. DOSAGE FORM(S) Tablets	14. POTENCY 10 mg		
15. CHEMICAL NAME AND STRUCTURE  <div style="text-align: center;">  <p>Loratadine Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate</p> </div>			16. RECORDS AND REPORTS CURRENT YES <u>   </u> NO <u>   </u> REVIEWED YES <u>   </u> NO <u>   </u>
17. COMMENTS:  CC: Orig. NDA # 19-658 HFD-150/Div. File HFD-150/SKKim HFD-150/PHonig HFD-150/KLee HFD-150/RHWood R/D Init. by: <span style="border: 1px solid black; border-radius: 50%; padding: 2px;">5</span> 3-29-95			
18. CONCLUSIONS AND RECOMMENDATIONS The proposed labeling is not adequate. This supplement may be approvable pending satisfactory responses to our comments in a draft letter. The CSO will draft a letter for Dr. Hoiberg's signature.			
19. REVIEWER NAME Sung K. Kim, Ph.D.		SIGNATURE <span style="border: 1px solid black; padding: 5px; font-size: 2em;">/S/</span>	DATE COMPLETED March 29, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-658 S005

CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)

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MAR - 9 1995

NDA 20-470

Submission Dates: 4/15/94  
7/11/94Loratadine 10/Pseudoephedrine  
240 SR (CLARITIN ADD<sup>®</sup>)Type of Submission:  
NDASchering Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033Reviewer:  
Brad Gillespie, PharmD

Synopsis Designed for once daily administration, each CLARITIN ADD<sup>®</sup> (All-Day-Decongestant) tablet contains 10 mg of loratadine in its immediate release coating and an extended release core which contains 240 mg pseudoephedrine sulfate. The sponsor already markets CLARITIN-D<sup>®</sup>, a twice-daily product containing 120 mg pseudoephedrine and 5 mg loratadine.

This NDA is based on pharmacokinetic studies as well as pivotal clinical trials.

In this review, the following five bio studies were evaluated: Multiple-dose bioequivalence study; Single-dose interaction study; two Single-dose food effect studies; and a Single-Dose bioequivalence study comparing formulations with differing rates of *in vitro* dissolution. The multiple-dose study assay validation for loratadine and descarboethoxyloratadine was unsatisfactory. The pseudoephedrine data from this study<sup>2</sup> indicated that the  $C_{max}$  and AUC from CLARITIN ADD were equivalent to that from AFRINOL but the fluctuation index was greater (Day 8 mean test/reference point estimate 127%, 90% CI: 113 - 141) and  $C_{min}$  was lower (Day 8 mean test/reference point estimate 74.4%, 90% CI: 63 - 86) for CLARITIN ADD than AFRINOL. Dosage forms were equivalent with respect to descarboethoxyloratadine AUC and  $C_{max}$  on day 8, while loratadine was equivalent with respect to AUC on day 8, only. Therefore, the products can not be considered bioequivalent. The results of the interaction study indicated that neither loratadine nor pseudoephedrine adversely affected the pharmacokinetics of each other. The results of the food effect study (C87-031-01), in which only pseudoephedrine, was evaluated indicated that food increased the  $C_{max}$  and AUC of pseudoephedrine by 22% and 12%, respectively. The results of the second food effect study (Study C92-281-01), which evaluated loratadine, descarboethoxyloratadine and pseudoephedrine, indicated that the  $C_{max}$  of pseudoephedrine increased by 7% while for loratadine, the  $C_{max}$  and AUC increased by 80% and 125%, respectively. Finally, an *in vitro-in vivo* Type A correlation was developed based on the study comparing the pseudoephedrine bioavailability of formulations with differing dissolution rates.

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Recommendations

The biopharmaceutical portion of this NDA has been reviewed by the Division of Biopharmaceutics and the results have indicated that pseudoephedrine was not bioequivalent between the CLARITIN ADD and CLARITIN/AFRINOL treatment groups.

The pseudoephedrine dissolution specifications proposed by the sponsor and outlined in attachment 1, are acceptable. Loratadine dissolution specifications are unsatisfactory. The sponsor has been requested to submit full dissolution profiles for loratadine so that appropriate specifications may be set. In the interim, the same loratadine dissolution specification is recommended for CLARITIN ADD as CLARITIN-D, i.e., Q=

The recommendations and comments of this review should be forwarded to the sponsor.

Also, as stated by the sponsor, if this NDA is approved, it would mean approval of the product manufactured using only the method since the product manufactured using the alternate method, i.e., the method has not been evaluated in this NDA.

**/S/** 3/9/95  
Bradley K. Gillespie, PharmD  
Pharmacokinetics Evaluation Branch I

Biopharm Day. February 24, 1995 (Drs Ludden, Malinowski, Fleischer, Chen and Mehta)

FT **/S/** 3/9/95  
Mehul U. Mehta, PhD, Section Head (Acting)

cc:

- HFD-150 (NDA-20-470)
- HFD-150 (Division File)
- HFD-151 (Schumaker)
- HFD-151 (Lee)
- HFD-150 (Barron)
- HFD-150 (Poochikian)
- HFD-426 (Mehta)
- HFD-426 (Fleischer)
- HFD-427 (Chen, Mei Ling)
- HFD-426 (Chron)
- HFD-426 (Gillespie, Brad)
- HFD-340 (Viswanthan)
- HFD-019 (FOI)

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ON ORIGINAL**



## BACKGROUND

Designed for once daily administration, each CLARITIN ADD\* (All-Day-Decongestant) tablet contains 10 mg of loratadine in its immediate release coating and an extended release core which contains 240 mg pseudoephedrine sulfate, USP. Proposed indications are the relief of seasonal allergic rhinitis including nasal congestion, and nasal congestion associated with the common cold.

The sponsor submitted 7 pharmacokinetic studies in support of this NDA. The Division of Biopharmaceutics has reviewed all of these studies with the exception of one food study (Study C87-094-01: Did not examine effect on loratadine) and a multiple-dose study comparing CLARITIN-ADD to CLARITIN-D (Study C92-278-01: not relevant to this NDA).

## FORMULATIONS

The sponsor used the to-be-marketed formulation for all clinical trials. It should be noted, however, that batches used in the different pharmacokinetic studies were manufactured using two different methods. The clinical batch (21536-143: see Attachment 2) utilized a system. The pharmacokinetic study batches used a combination of the above and an and the Compositionally, the core is the same between the processes but coating components vary. Originally, the sponsor stated that tablet cores used in the interaction study (study C89-339-01) were manufactured using the different methods, thus providing a direct comparison. As a result, they requested a waiver to allow manufacturing of to-be-marketed batches using the method not studied clinically. At the time of submission, the sponsor realized that this claim was erroneous, and that in fact, both cores were manufactured using the same method. At this time, they withdrew their request to manufacture the product using the method.

## SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS

### **I. Bioavailability/Bioequivalence**

A. **Bioequivalence:** Study C87-030-01 compared the to-be-marketed Claritin ADD tablet to a reference treatment consisting of a conventional 10 mg loratadine tablet given once daily and a 120 mg pseudoephedrine sulfate REPETAB given every 12 hours. Loratadine and descarboethoxyloratadine assay validation was unsatisfactory (Loratadine: unsatisfactory assay precision throughout concentration ranges [CV-3.8 - 23.4]; descarboethoxyloratadine: no standard curve data submitted, unsatisfactory assay precision throughout concentration ranges [CV- 1.6% - 25.17%]). Dosage forms were equivalent ( $C_{max}$  and AUC) with respect to pseudoephedrine on both days 6 and 8.

However, pseudoephedrine failed  $C_{min}$  (Day 8 mean test/reference point estimate 74.4%, 90% CI: 63 - 86) and percent fluctuation (Day 8 mean test/reference point estimate 127%, 90% CI: 113 - 141). Dosage forms were equivalent with respect to descarboethoxyloratadine AUC and  $C_{max}$  on day 8, while loratadine was equivalent with respect to AUC on day 8, only.

**B. Food Effect:** The effect of food on the absorption of pseudoephedrine administered as a single, to-be-marketed, ADD tablet was evaluated in Study C87-031-01 (N=12). While a food effect is evident, differences between the fed (high fat breakfast) and fasted groups were statistically significant only with respect to the  $C_{max}$  (+21.7%) but not extent (AUC +11.9%) of absorption. Study C92-281-01 (N=24) examined the effect of food on the bioavailability of loratadine and descarboethoxyloratadine in addition to pseudoephedrine. As in the first study, statistically significant pseudoephedrine differences were present with respect to  $C_{max}$  (+7%,  $p=0.009$ ). However the low variability observed (90% CI: 103 - 112) suggests that this effect is not clinically important. A significant loratadine food effect was detected in terms of both  $C_{max}$  (+81%) and AUC (+126%). No significant food effect on descarboethoxyloratadine was detected. This contrasts with the proposed labeling, which states that food increased loratadine and SCH 34117 AUCs by 40% and 15%, respectively. While the labeling should be adjusted to reflect the results of this study, these data should be considered in light of the parent/metabolite AUC ratio of ~ 0.20 (parent and metabolite are approximately equipotent). Thus, the recommendation to take this product on an empty stomach should be removed.

## II. Pharmacokinetics

**Pseudoephedrine** After a single CLARITIN ADD dose (Study C89-339-01), the mean  $C_{max}$  was 337 ng/mL (CV 14%), the mean  $AUC_{0-\infty}$  was 6867 ng hr/mL (CV 22%) and the mean  $T_{max}$  6.1 hr (CV 24%). On multiple dose administration of CLARITIN ADD (Study C87-087-01) for 8 days, the mean  $C_{max}$  was 582 ng/mL and the mean  $C_{min}$  was 224 ng/mL. The mean terminal elimination half-life across studies was 7.4 hr (range: ).

**Loratadine** After a single CLARITIN ADD dose (Study C89-339-01), the mean  $C_{max}$  was 2.79 ng/mL (CV 127%), the mean  $AUC_{0-\infty}$  was 6.36 ng hr/mL (CV 120%) and the mean  $T_{max}$  1.2 hr (CV 21%). On multiple dose administration of CLARITIN ADD (Study C87-087-01) for 8 days, the mean  $C_{max}$  was 3.40 ng/mL.

**Descarboethoxyloratadine** After a single CLARITIN ADD dose (Study C89-339-01), the mean  $C_{max}$  was 2.28 ng/mL (CV 24%), the mean  $AUC_{0-\infty}$  was 34.1 ng hr/mL (CV 96%) and the mean  $T_{max}$  3.00 hr (CV 136%). On multiple dose administration of CLARITIN ADD (Study C87-087-01) for 8 days, the mean  $C_{max}$  was 4.07 ng/mL and the mean  $C_{min}$  was 1.37 ng/mL.

### III. Drug Interactions

Since both components of this combination product are approved drug products, the only required interaction study (C89-339-01) was of the components, pseudoephedrine and loratadine.

Co-administration of loratadine and pseudoephedrine did not significantly alter the pharmacokinetics of either pseudoephedrine or descarboethoxyloratadine. However a statistical difference was detected with respect to loratadine ( $C_{max}$ : +9.41%, 90% CI 88 - 131;  $AUC_{0-\infty}$ : +8.35%, 90% CI 93 - 124).

### IV. Dissolution

The proposed dissolution method

and the dissolution specifications proposed by the sponsor for pseudoephedrine seem to be acceptable. However, the dissolution specifications proposed for loratadine are unsatisfactory. The sponsor has been asked to submit full loratadine dissolution profiles so that more appropriate specifications may be set by the agency. In the interim, the same dissolution specification is recommended for CLARITIN ADD as CLARITIN-D, i.e., Q=

Based on the unvalidated *in vitro-in vivo* correlation (see Appendix IV), The Division of Biopharmaceutics has attempted to attach clinical relevance (*in vivo* performance) to *in vitro* dissolution behavior. Predicted pseudoephedrine plasma concentration vs time data suggest that lots performing within the proposed dissolution specifications would produce lots bioequivalent to the clinical formulation.

See Table A, below, for dissolution data submitted by the sponsor for production-sized lots.

Figure 4 represents the pseudoephedrine dissolution profiles of 7 production-sized lots relative to the proposed specifications.

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Table A. Dissolution Data from 7 Production-Sized Lots

## COMMENTS

1. Results of Study C87-030-01 indicated that with regard to pseudoephedrine  $C_{min}$ , CLARITIN ADD and AFRINOL were not bioequivalent (Day 8 mean CLARITIN ADD/AFRINOL point estimate 74.4%, 90% CI: 63 - 86). Also the fluctuation index was higher for CLARITIN ADD than AFRINOL (Day 8 mean CLARITIN ADD/AFRINOL point estimate 127%, 90% CI: 113 - 141).
2. Assay validation for Study C87-030-01 is unsatisfactory. The loratadine (CV- 3.8% - 23.4%) and descarboethoxyloratadine (CV- 1.6% - 25.17%) assays both lacked precision throughout the concentration ranges. Also, no standard curve or recovery data were provided for the descarboethoxyloratadine assay.
3. No single-dose bioequivalence study was submitted in support of this application.
4. Sponsor proposed dissolution specifications for pseudoephedrine are acceptable. Appropriate specifications for loratadine will be set after dissolution profiles are submitted by the sponsor. In the interim, the same loratadine dissolution specification is recommended for CLARITIN ADD as CLARITIN-D, i.e.,  $Q=$
5. **Labeling Changes**
  - (a) The food effect observed in C92-281-01 should be reflected.

[In a single dose study, food increased the AUC of loratadine by approximately 125% and  $C_{max}$  by approximately 80%]

[In a single dose food study, food did not significantly affect the pharmacokinetics of pseudoephedrine of descarboethoxyloratadine]

The recommendation to take this product on an empty stomach should be omitted.
  - (b) Precautions section should be changed to state that this product should be avoided in patients with hepatic impairment since doses of this fixed combination product cannot be individually titrated and in cases of hepatic impairment, a reduction of loratadine clearance would be expected to be greater than that of pseudoephedrine.
  - (c) The drug interactions section should reflect the confirmed interacting effect of erythromycin and cimetidine.

## APPENDIX I

### Multiple Dose Bioequivalence Study

Study C87-030-01 Volumes 1.11-1.12 Pages 60 - 401

#### INVESTIGATOR AND LOCATION

**OBJECTIVE** To determine steady-state bioequivalency of the SCH 434 SR tablets given once daily for 8 days (Treatment A) compared to a conventional loratadine 10 mg tablet given once daily with 120 mg pseudoephedrine tablets administered twice daily for 8 days (Treatment B).

**FORMULATIONS** LORATADINE ADD Tablet, Batch 20124-055; Lot Size Conventional 10 mg loratadine tablet, Batch 19595-097. Pseudoephedrine (Afrinol) 120 mg REPETABS, Lot No. 6CRD103.

**STUDY DESIGN** Randomized two-way crossover with 18 subjects and a one week washout. Subjects fasted the night before assay days (1, 6 and 8) and 4 hours after AM dosing. Blood samples were collected each morning prior to (zero hour), and 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hours after dosing on days 6 and 8. Additionally, 36 and 48 hour samples were collected on day 8.

**ASSAY** Pseudoephedrine: Loratadine: Descarboethoxyloratadine:  
For validation details, see Appendix II.

**DATA ANALYSIS**  $C_{max}(t)$ ,  $C_{min}$ , AUC(t), terminal phase  $t_{1/2}$  and fluctuation indices (pseudoephedrine) were calculated.

**RESULTS** Bioequivalence data (Tables 1 - 4) and mean plasma time-concentration curves below (Figures 1-3).

**COMMENTS** The loratadine and descarboethoxyloratadine assays lacked satisfactory precision.

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**Table 1 Pseudoephedrine Bioequivalence Data**

Parameter	Mean (%CV)		p-Value <sup>a</sup>	Power <sup>b</sup>	Ratio(%) <sup>c</sup>	
	Treatment A (SCH 434 SR)	Treatment B (REFERENCE)			Point Estimate	Confidence Interval
AUC6	8117 (37)	8373 (32)	0.51	99%	96.9	89 - 105
AUC8	10161 (37)	9643 (30)	0.32	98%	105.4	97 - 113
Cmax6	512 (25)	489 (28)	0.32	97%	104.9	96 - 113
Cmax8	582 (28)	571 (23)	0.78	98%	101.9	94 - 110
Cmin6	166 (57)	251 (46)	<0.01	83%	66.4	55 - 78
Cmin7	163 (58)	232 (51)	<0.01	53%	70.2	54 - 86
Cmin8	190 (66)	255 (43)	<0.01	84%	74.4	63 - 86
Cmin9	224 (62)	298 (40)	<0.01	87%	75.1	64 - 86

a p-Value for treatment effect from ANOVA

b Power to detect 20% difference from Treatment B

c Confidence interval calculated using two one-sided t-tests at  $\alpha=0.05$ .

%CV - Coefficient of variation, expressed as a percent

AUC6 (ng·hr/ml) = Area under the plasma concentration-time curve on Day 6 from time zero to 24 hr

AUC8 (ng·hr/ml) = Area under the plasma concentration-time curve on Day 8 from time zero to 24 hr

Cmax6 (ng/ml) = Maximum plasma concentration on Day 6

Cmax8 (ng/ml) = Maximum plasma concentration on Day 8

Cmin6 (ng/ml) = Minimum plasma concentration on Day 6

Cmin7 (ng/ml) = Minimum plasma concentration on Day 7

Cmin8 (ng/ml) = Minimum plasma concentration on Day 8

Cmin9 (ng/ml) = Minimum plasma concentration on Day 9

**Table 2 Pseudoephedrine % Fluctuation SCH 434 vs REPETAB**

	SCH 434	REPETAB	Confidence Interval
% FI-6	115.1	79.1	124 - 167
% FL <sub>90</sub> -8	93.0	73.1	113 - 141

**Table 3 Loratadine Bioequivalence Data**

Parameter	Mean (%CV)		p-Value <sup>a</sup>	Power <sup>b</sup>	Ratio(%) <sup>c</sup>	
	Treatment A (SCH 434 SR)	Treatment B (REFERENCE)			Point Estimate	Confidence Interval
AUC6	16.7 (109)	18.5 (162)	0.59	18%	90.1	58 - 122
AUC8	17.0 (132)	17.5 (126)	0.56	85%	97.2	86 - 108
Cmax6	3.28 (66)	3.58 (133)	0.73	12%	91.6	49 - 134
Cmax8	3.40 (102)	3.03 (74)	0.47	19%	112.3	82 - 143

a p-Value for treatment effect from ANOVA

b Power to detect 20% difference from Treatment B

c Confidence interval calculated using two one-sided t-tests at  $\alpha = 0.05$

%CV - Coefficient of variation, expressed as a percent

AUC6 (ng·hr/ml) = Area under the plasma concentration-time curve on Day 6 from time zero to 24 hr

AUC8 (ng·hr/ml) = Area under the plasma concentration-time curve on Day 8 from time zero to 24 hr

Cmax6 (ng/ml) = Maximum plasma concentration on Day 6

Cmax8 (ng/ml) = Maximum plasma concentration on Day 8

**Table 4 Descarboethoxyloratadine Data**

Parameter	Mean (%CV)		p-Value <sup>a</sup>	Power <sup>b</sup>	Ratio(%) <sup>c</sup>	
	Treatment A (SCH 434 SR)	Treatment B (REFERENCE)			Point Estimate	Confidence Interval
AUC6	48.3 (50)	56.3 (35)	0.04	100%	85.9	79 - 93
AUC8	42.9 (35)	46.0 (31)	0.58	68%	93.2	80 - 107
Cmax6	5.02 (65)	5.76 (60)	0.51	45%	87.1	69 - 105
Cmax8	4.07 (39)	4.32 (38)	0.81	62%	94.2	80 - 109
Cmin6	0	0	-	-	-	-
Cmin7	0.62 (54)	0.83 (39)	0.07	33%	75.2	54 - 97
Cmin8	0.78 (78)	0.87 (61)	0.56	30%	89.7	67 - 113
Cmin9	1.37 (70)	1.44 (75)	01.00	12%	95.8	53 - 139

a p-Value for treatment effect from ANOVA

b Power to detect 20% difference from Treatment B

c Confidence interval calculated using two one-sided t-tests at  $\alpha = 0.05$

%CV - Coefficient of variation, expressed as a percent

AUC6 (ng·hr/ml) = Area under the plasma concentration-time curve on Day 6 from time zero to 24 hr

AUC8 (ng·hr/ml) = Area under the plasma concentration-time curve on Day 8 from time zero to 24 hr

Cmax6 (ng/ml) = Maximum plasma concentration on Day 6

Cmax8 (ng/ml) = Maximum plasma concentration on Day 8

Cmin6 (ng/ml) = Minimum plasma concentration on Day 6

Cmin7 (ng/ml) = Minimum plasma concentration on Day 7

Cmin8 (ng/ml) = Minimum plasma concentration on Day 8

Cmin9 (ng/ml) = Minimum plasma concentration on Day 9

Figure 1 Mean Loratadine Plasma Concentration Data

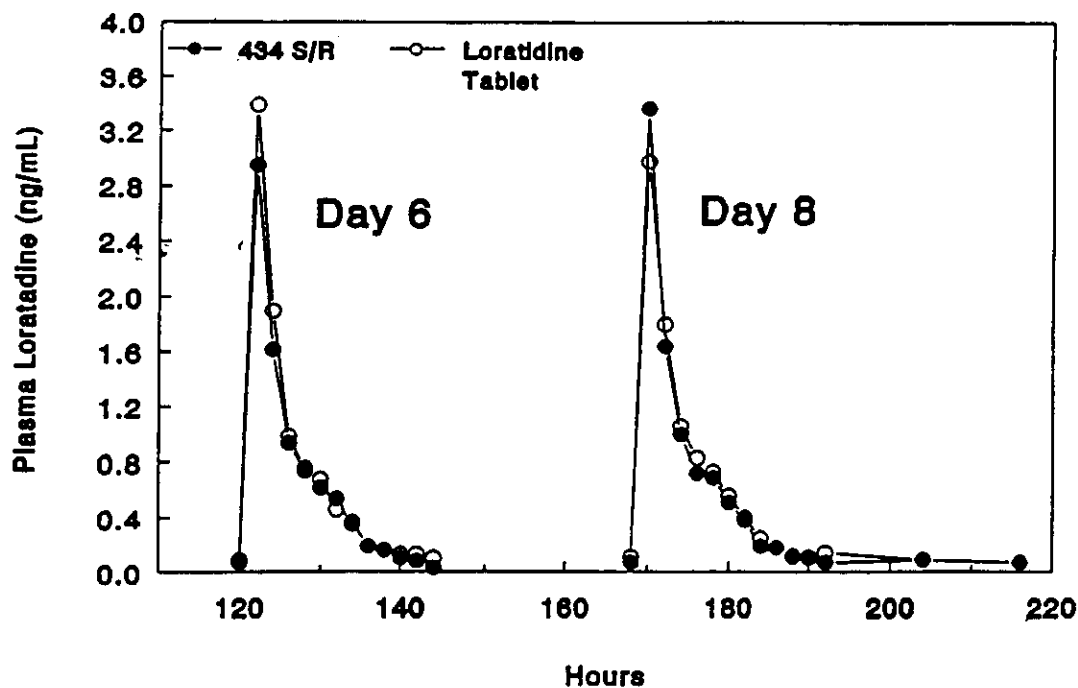


Figure 2 Mean Descarboethoxyloratadine Plasma Concentration Data

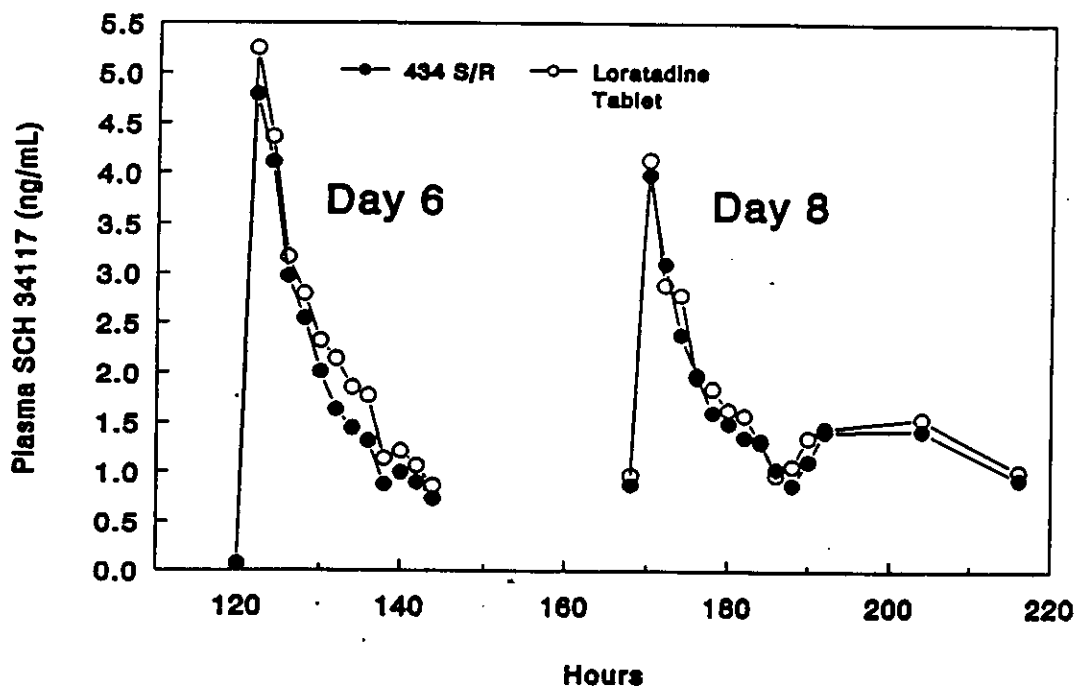
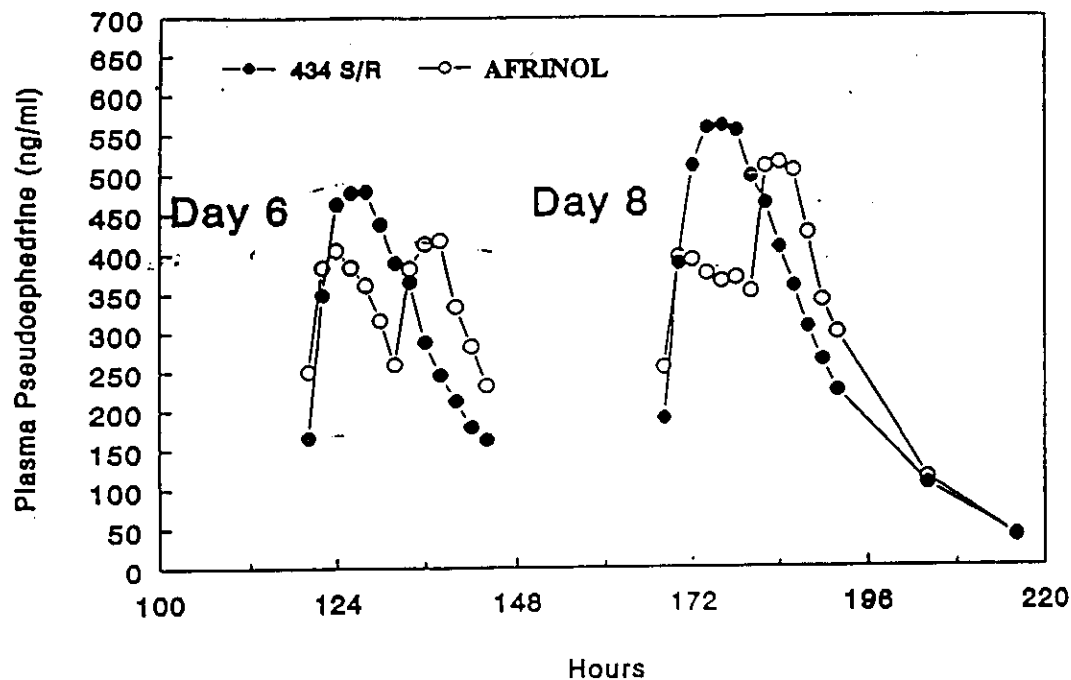




Figure 3 Mean Pseudoephedrine Plasma Concentration vs Time



**CONCLUSIONS** (a) Dosage forms were equivalent with respect to pseudoephedrine AUC and  $C_{max}$  on days 6 and 8. (b) Pseudoephedrine  $C_{min}$  was bioequivalent on days 6, 7, 8 and 9, as well as percent fluctuation on days 6 and 8. (c) Dosage forms were equivalent with respect to descarboethoxyloratadine AUC and  $C_{max}$  on day 8. (d) Loratadine was equivalent with respect to AUC on day 8, only.

### Single Dose Food Study

Study C87-031-01

Volume

1.12

Pages 402 - 528

### INVESTIGATOR AND LOCATION

**OBJECTIVE** To evaluate the bioavailability of pseudoephedrine from SCH 434 SR and pseudoephedrine SR tablets when given in the presence of food.

**FORMULATIONS** CLARITIN ADD Tablet, Batch 20124-055; Lot Size  
Pseudoephedrine 240 mg SR tablet, Batch 20757-003; Lot Size

**STUDY DESIGN** Randomized three-way crossover with 12 healthy male subjects and a one-week washout. Subjects in treatment group A received one CLARITIN ADD tablet with a standard breakfast, subjects in treatment B received one CLARITIN ADD tablet after a ten-hour fast, while treatment C consisted of one pseudoephedrine SR tablet (ADD core with placebo coating) administered with a standard breakfast. Subjects were confined to the study area 12 hours prior to the start of the study and maintained an overnight fast until immediately after the four-hour blood sample collection. Blood samples were collected immediately prior to drug administration (zero-hour) and then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36 and 48 hours after dosing.

**ASSAY** Pseudoephedrine Only:

For validation data, see Appendix II

**DATA ANALYSIS**  $C_{max}$ ,  $T_{max}$ ,  $AUC(t)$ , terminal phase  $t_{1/2}$ .

**RESULTS** See Tables 5 and 6, below

**Table 5** Bioavailability of Pseudoephedrine from CLARITIN ADD Tablet (Treatment A = Fed; Treatment B = Fasting)

<u>Parameter</u>	<u>Unit</u>	<u>Treatment A</u>	<u>Treatment B</u>	<u>% Change</u>	<u>p-Value</u>	<u>CI<sub>90</sub></u>
AUC(t)	ng-hr/mL	6040.2	5509.4	+9.6	0.159	99 - 120
AUC <sub>∞</sub>	ng-hr/mL	6413.2	5729.6	+11.9	0.095	102 - 122
C <sub>max</sub>	ng/mL	370.6	304.5	+21.7	0.002	111 - 133
T <sub>max</sub>	hr	7.08	6.42			

**Table 6** Bioavailability of Pseudoephedrine from Pseudoephedrine SR Tablet (Treatment C = Fed Pseudoephedrine SR Tablet; Treatment B = Fasting SCH 434 Tablet)

<u>Parameter</u>	<u>Unit</u>	<u>Treatment B</u>	<u>Treatment C</u>	<u>% Change</u>	<u>p-Value</u>	<u>CI<sub>90</sub></u>
AUC(t)	ng-hr/mL	5509.4	6145.7	+11.6%	0.076	100.9 - 122.2
AUC <sub>∞</sub>	ng-hr/mL	5729.6	6392.5	+11.6%	0.063	101.4 - 121.7
C <sub>max</sub>	ng/mL	304.5	382.5	+25.6%	0.001	114.4 - 136.8
T <sub>max</sub>	hr	6.42	6.00			

**COMMENT** The sponsor has not studied the effect of food on loratadine or its metabolite.

**CONCLUSIONS** (1) While a pseudoephedrine food effect is evident, differences between the fed and fasting groups are statistically significant only with respect to the rate (C<sub>max</sub>: +21.7%) and not extent (AUC<sub>0-∞</sub> 90% CI: 102 - 122) of absorption. (2) Wagner-Nelson plots show a similar absorptive pattern for treatments A, B and C.

# Drug Interaction Study Comparing CLARITIN ADD to its Components: Loratadine and Pseudoephedrine Sulfate

Study C89-339-01      Volume      1.14      Pages      742 - 1067

## INVESTIGATOR AND LOCATION

**OBJECTIVE** To determine if there is a significant drug interaction between the active components of a CLARITIN ADD tablet.

**FORMULATIONS** CLARITIN ADD Tablet, Batch 21536-143; Lot Size  
Modified ADD Tablet (pseudoephedrine core, with placebo coating), Batch 23819-073;  
Lot Size      Modified ADD Tablet (placebo core, with loratadine coating), Lot  
Size

**STUDY DESIGN** Randomized three-way crossover with 18 subjects and a one week washout. Subjects fasted 10 hours prior to the study onset and until the 4 hour blood sample was obtained. Patients in Treatment A received one CLARITIN ADD tablet. Patients receiving Treatment B received a modified tablet containing a 10 mg loratadine coating and placebo core. Treatment C consisted of a modified tablet containing only a 240 mg pseudoephedrine core matrix and no loratadine coating. All study participants were confined to the study area until after the 48-hour blood specimen was obtained. Blood samples were collected immediately prior to drug administration (zero hour) and then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after dosing.

**ASSAY** Pseudoephedrine:      Loratadine and descarboethoxyloratadine:  
Assay validation data in Appendix II.

**DATA ANALYSIS**  $C_{max}$ ,  $T_{max}$ ,  $AUC_t$ ,  $AUC_{0-\infty}$  and terminal phase  $t_{1/2}$  (pseudoephedrine and descarboethoxyloratadine) were calculated.

**RESULTS** Pharmacokinetic data from Study C89-339-01 follows.

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**Table 7 Pharmacokinetic Data From C89-339-01**

Treatment	Unit	Test	Reference	Parameter	% Change	CI <sub>90</sub>	p-value
SCH 434 vs. PSE Alone	ng-hr/mL	6645.5	6628.2	AUC(t)	+0.26	93.7 - 106.8	0.947
	ng-hr/mL	6866.8	6838.6	AUC <sub>0-∞</sub>	+0.41	94.0 - 106.8	0.914
	ng/mL	337.1	339.5	C <sub>max</sub>	- 0.71	94.1 - 104.5	0.824
(Pseudoephedrine)	hours	6.1	6.4	T <sub>max</sub>			
	hours	6.9	6.6	t <sub>1/2</sub>			
.....							
SCH 434 vs. Lorat. Alone	ng-hr/mL	6.36	5.87	AUC(t)	+8.35	92.5 - 124.2	0.675
	ng/mL	2.79	2.55	C <sub>max</sub>	+9.41	87.8 - 131.0	0.690
	hours	1.2	1.1	T <sub>max</sub>			
(Loratadine)							
.....							
SCH 434 vs. Lorat. Alone (SCH 34117)	ng-hr/mL	29.1	27.7	AUC(t)	+5.05	95.7 - 114.4	0.364
	ng-hr/mL	34.1	35.5	AUC <sub>0-∞</sub>	- 3.94	88.0 - 104.1	0.446
	ng/mL	2.28	2.14	C <sub>max</sub>	+6.54	99.1 - 114.0	0.165
hours	3.00	2.22	T <sub>max</sub>				
hours	15.5	16.5	t <sub>1/2</sub>				

**CONCLUSION** Co-administration of loratadine and pseudoephedrine did not significantly affect the pharmacokinetics of pseudoephedrine or descarboethoxyloratadine. Statistical differences were not detected with respect to the bioavailability of the parent compound, loratadine (p > 0.675). However, characteristically high loratadine variability may have caused the difference observed in the confidence interval analysis (90% CI AUC: 92.5 - 124.2; C<sub>max</sub>: 87.8 - 131.0).

**Influence of Food on the Oral Bioavailability of CLARITIN ADD Tablets;  
Two-way Crossover Design**

Study C92-281-01

N(IM)050

Pages 1 - 475

**INVESTIGATOR AND LOCATION**

**OBJECTIVE** To evaluate the effect of food on the bioavailability of loratadine, descarboethoxyloratadine and pseudoephedrine.

**FORMULATIONS** CLARITIN ADD Tablet, Batch 26477-090; Lot Size

**STUDY DESIGN** Randomized two-way crossover with 24 healthy male subjects and a one-week washout. Subjects were confined to the study area 12 hours prior to the start

of the study and maintained an overnight fast until commencement of the study. Subjects in Treatment A then received one CLARITIN ADD tablet within 5 minutes of completion of a standard high-fat breakfast. Those in Treatment B received one CLARITIN ADD tablet after an overnight fast. Both treatment s were administered with 180 mL of tap water. After dosing, no food or fluids (except water) were permitted. All volunteers received a regular lunch immediately after the four-hour blood sample collection. Regular meals were resumed for all volunteers 8 hours after drug administration. Blood samples were collected immediately prior to drug administration (zero-hour) and then at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 20, 24, 36 and 48 hours after dosing.

ASSAY Loratadine and Descarboethoxyloratadine: Pseudoephedrine:  
Assay validation data in Appendix II.

DATA ANALYSIS  $C_{max}$ ,  $T_{max}$ ,  $AUC_t$ ,  $AUC_{0-\infty}$  and terminal phase  $t_{1/2}$  (pseudoephedrine and descarboethoxyloratadine) were calculated.

RESULTS: See Table 10, below.

Table 10 Pharmacokinetic Data for C92-281-01

Treatment	Unit	Test*	Reference	Parameter	% Change	CI <sub>90</sub>	p-value
Fed	ng-hr/mL	7054	7074	$AUC_{0-\infty}$	-0.3%	94 - 106	0.939
vs.	ng/mL	407	381	$C_{max}$	+7%	103 - 112	0.009
Fasted (Pseudoephedrine)							
Fed	ng-hr/mL	8.75	3.88	$AUC(t)_b$	+126%	193 - 265	0.001
vs.	ng/mL	3.12	1.72	$C_{max}$	+81%	150 - 222	0.001
Fasted (Loratadine)							
Fed	ng-hr/mL	44.2	41.1	$AUC_{0-\infty}$	+8%	101 - 113	0.064
vs.	ng/mL	2.95	2.75	$C_{max}$	+7%	98 - 116	0.164
Fasted (SCH 34117)							

CONCLUSIONS No significant food effect was detected with respect to either pseudoephedrine or descarboethoxyloratadine. However administration of a single SCH

\*Geometric Mean

<sup>b</sup>Elimination  $t_{1/2}$  could not be determined, so  $AUC_{0-\infty}$  was not calculated

434 SR tablet with food significantly increased mean loratadine bioavailability ( $C_{max}$  +81%, AUC +126%) compared to fasting.

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# Influence of Dissolution on the Bioequivalency of SCH 434 SR Tablets

Study C89-037-01      Volume      1.13      Pages      529 - 741

## INVESTIGATOR AND LOCATION

**OBJECTIVE** To determine the bioequivalency of pseudoephedrine from four different SCH 434 formulations with different *in vitro* dissolution profiles to validate the limits of the dissolution specifications of this product.

**FORMULATIONS** Treatment A:      Batch No. 23819-095;  
Lot Size      Treatment B:      Batch No. 23819-083; Lot  
Size      Treatment C:      Batch No. 23819-104; Lot  
Size      Treatment D: *Standard dissolution formulation,* Batch No. 21536-143;  
Lot Size

**STUDY DESIGN** Randomized four-way crossover with 20 subjects and a one-week washout period. Subjects fasted the night before drug administration and until after the 4-hour blood sample was obtained. Blood was drawn immediately prior to dosing (zero-hour and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing.

**ASSAY** Pseudoephedrine Only:      Assay validation data in Appendix II

**DATA ANALYSIS**  $C_{max}$ ,  $T_{max}$ ,  $AUC_{17}$ ,  $AUC_{0-\infty}$  and terminal phase  $t_{1/2}$  were calculated.

**RESULTS** See Table 11, below. Figure 4 for Wagner-Nelson Plots.

**CONCLUSIONS** Bioequivalence was demonstrated with respect to  $AUC(t_f)$ ,  $AUC_{0-\infty}$  and  $C_{max}$  between: (1) the      and standard dissolution formulations; (2) the      and      dissolution formulations; (3) the      and      dissolution formulations.  $AUC(t_f)$  and  $AUC_{0-\infty}$  equivalence was demonstrated between: (1) the      and standard dissolution formulation; (2) the      and      dissolution formulations. A positive correlation is evident between pseudoephedrine *in vitro* dissolution and *in vivo* absorption rates. Development of this unvalidated correlation is outlined in Appendix IV.

**COMMENT** % Recovery was not documented over the range of concentrations found in the study (      ng/mL).



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### Appendix III<sup>1</sup>

#### Development of *in vitro-in vivo* Correlation

The sponsor modified their formulation by varying the amount of \_\_\_\_\_ in the pseudoephedrine core (see Table 1). The resultant *in vitro* dissolution behavior is described below, in Table 2, and graphically represented in Figure 1.

The sponsor then directly compared each formulation to each other in a Single-Dose bioequivalence study. The results of this study are shown below, in Table 3.

Bioequivalence was demonstrated with respect to  $AUC(t)$ ,  $AUC_{0-\infty}$  and  $C_{max}$  between: (1) the \_\_\_\_\_ and standard dissolution formulations; (2) the \_\_\_\_\_ and standard dissolution formulations; (3) the \_\_\_\_\_ and \_\_\_\_\_ dissolution formulations. All parameter point estimates in the \_\_\_\_\_ vs \_\_\_\_\_ dissolution formulation comparison fell outside the 90% Confidence Interval 80 - 120% range.

*In vivo* data were then deconvoluted (Wagner-Nelson method) and expressed as percent absorbed at each time point (see Figure 2 for mean Wagner-Nelson data and plot). Originally, deconvolution was performed using the elimination rate constant observed with each formulation. It was immediately evident that the absorption rate (and thus also elimination rate) in the \_\_\_\_\_ formulations were dissolution rate dependent (flip-flop effect). Therefore, individual elimination rate constants obtained in the \_\_\_\_\_ treatment arm were utilized when calculating individual Wagner-Nelson data.

Next, observed *in vivo* (%absorbed) data from all 4 formulations were pooled and plotted against the percentage of dose dissolved *in vitro* at each common time point (see Figure 3). Points were fitted with simple regression yielding a linear equation of:

$$y=1.066986x-14.3617$$

Based on this relationship, we can conclude that a Type A correlation is present between the *in vivo* performance of pseudoephedrine and its *in vitro* dissolution behavior in the Loratadine ADD product.

Next, the dissolution data (independent variables T; dependent variable D; Parameters  $D_{max}$ ,  $D_{50}$  and  $\gamma$ ) were fitted to a sigmoidal  $D_{max}$  model.

$$D = \frac{D_{max} \cdot T^\gamma}{D_{50}^\gamma + T^\gamma}$$

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**Table 4 Simulated PK Parameters**

	Lower	Target	Upper	Lower/Target	Target/Upper
$D_{max}$	110	110	110		
$D_{50}$	6.18	4.34	3.01		
$\gamma$	0.929	1.096	1.067		
<hr/>					
$C_{max}$	328.7	378.2	440.8	0.87	0.86
$T_{max}$	7.4	6.5	5.7	1.14	1.14
AUC	5988	6621	7336	0.90	0.90

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 19-658 S005**

**ADMINISTRATIVE DOCUMENTS**

SK-005

# SCHERING CORPORATION

CALLOPING HILL ROAD

KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH

TELEX: 138318  
138280

TELEPHONE: (908) 296-4000

## BEST POSSIBLE COPY

October 3, 1994

Gregory P. Burke, M.D., Ph.D., Director  
Division of Oncology-Pulmonary Drug Products  
Center for Drug Evaluation and Research  
HFD-150  
1451 Rockville Pike  
Rockville, Maryland 20852

NDA 19-658  
CLARITIN (loratadine) Tablets

**SUBJECT: Supplement - Revised Labeling Component**

Dear Dr. Burke:

Submitted for your approval is revised text for the blister backing for professional samples. We would like to add the following dosing instructions:

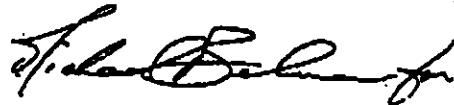
"Take 1 tablet once-a-day on an empty stomach."

No dosing information is currently reflected on the blister.

Enclosed are twelve (12) copies of the proposed labeling component.

Please be advised that material and data contained in this submission are considered confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331 (j), as well as the FDA regulations.

Sincerely,



Richard N. Spivey, Pharm.D., Ph.D.  
Senior Director  
U.S. Regulatory Affairs

MB:js  
Attachment

NDA 19-658  
Claritin Tablets  
Blister Backing for Professional Samples

**BEST POSSIBLE COPY**

CODE AREA CODE AREA  
1 CLARITIN® 10 mg  
brand of loratadine Tablet  
Schering Corporation  
Kenilworth, NJ 07033 USA  
Take 1 tablet once-a-day  
on an empty stomach.

**APPEARS THIS WAY  
ON ORIGINAL**



SCHERING-PLOUGH RESEARCH INSTITUTE



SK-005

SCHERING CORPORATION

CALLOPING HILL ROAD

KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH  
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138180  
TELEPHONE: (908) 298-4000

**BEST POSSIBLE COPY**

October 3, 1994

Gregory P. Burke, M.D., Ph.D., Director  
Division of Oncology-Pulmonary Drug Products  
Center for Drug Evaluation and Research  
HFD-150  
1451 Rockville Pike  
Rockville, Maryland 20852

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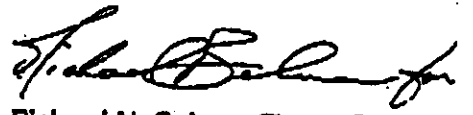
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Sincerely,



Richard N. Spivey, Pharm.D., Ph.D.  
Senior Director  
U.S. Regulatory Affairs

MB:js  
Attachment

**NDA 19-658**  
**Claritin Tablets**  
**Blister Backing for Professional Samples**

**BEST POSSIBLE COPY**

**CODE AREA CODE AREA**  
**1 CLARITIN® 10 mg**  
**brand of loratadine Tablet**  
Schering Corporation  
Kenilworth, NJ 07033 USA  
Take 1 tablet once-a-day  
on an empty stomach.

**APPEARS THIS WAY  
ON ORIGINAL**



**SCHERING-PLOUGH RESEARCH INSTITUTE**