CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-605

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
(FINAL)

NDAs: 21-605	**Date of Submission:** April 30, 2004
Generic Name	Desloratadine 5mg/Pseudophedrine sulfate 240 mg
Brand Name:	**CLARINEX-D® 24 HOUR**
Formulations:	Tablet
Route of Administration:	Oral
Indication:	Allergic Rhinitis and Nasal Congestion
Type of Submission:	Original NDA
Sponsor:	Schering Corporation, Kenilworth, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.
Date of Submission:	April 30, 2004
Date Received:	May 10, 2004
Review Date:	November 15, 2004
First Draft	December 28, 2004
Briefing Draft	January 12, 2005
DFS Version (Final)t:	February 1, 2005

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1. Executive Summary:

1.1 Recommendation:

Although the product was found to be **not** bioequivalent to the reference, the Office of Clinical Pharmacology and Biopharmacetuics found this NDA acceptable provided that:

1) The safety and efficacy of the new product are established in Phase III clinical studies submitted to this NDA and
2) A satisfactory agreement can be reached between the Agency and sponsor regarding the language in the package insert.

1.1.2 Comments to the sponsor

For *in vitro* dissolution, the following specifications are recommended:

For PSE (ER):

1 h	Q
2h	Q
4 h	Q
8 h	Q
16h	

For DL (IR):

30 min	Q

1.2 Phase 4 Commitments

No Phase IV commitment is applicable for this application.

1.3 Summary of Clinical Pharmacology and Biopharmacetuics Findings

This is an original NDA for Clarinex-D® 24 hour "combination" product tablets containing 5 mg immediate release desloratadine (DL) layer and 240 mg extended release pseuduoephedrine (PSE) layer. The proposed indications are for the relief of symptoms of allergic rhinitis and nasal congestion.

What is the new Formulation?

The DL component of the tablet is formulated as immediate release coating, whereas the PSE is as extended release tablet core.

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What is the Rationale of the Combination Product?

This is a combination drug product of DL and PSE. DL is the major active metabolite of loratadine (Claritin). The pharmacological activity of loratadine is primarily due to its metabolite, DL. From the PK perspective, DL appears to exhibit a better systemic bioavailability and a longer plasma elimination half-life than loratadine. No major safety issues are of concern from PSE as it is widely used as an over-the counter (OTC) containing product.

Therefore, the sponsor believes that the proposed combination of DL and PSE (Clarinex-D® 24) would be an ideal combination product for the proposed indication. The safety, efficacy, and PK of DL were submitted to Clarinex NDA # 21-165. The current NDA further characterizes the PK and safety of DL and PSE following administration of DL D-24 (DL 5mg/PSE 240 mg), DL, and PSE.

What Studies Are Submitted in the Current NDA:

In this NDA five clinical pharmacology studies were submitted which enrolled 154 adult subjects and two Phase III clinical studies. In all clinical pharmacology/PK studies, the plasma levels of DL, 3-OH DL (major metabolite), and PSE were monitored. These studies are grouped as follows:

- One bioequivalent (BE) study for the clinical formulation of DL D-24 (pivotal Study # P00439).
- One BE study of DL D-24 components and both the clinical DL D-24 formulation and a D-24 formulation containing 6 mg of DL and 240 mg PSE (study # P01813).
- One bioavailability study for DL D-24 formulation containing PSE cores with altered *in vitro* dissolution rate (Study # P01981).
- One effect of food study on DL D-24 (Study # P00441).
- One multiple (repetitive) dose study to characterize the PK of DL D-24 (Study # P00884).

The focus of this review will be mainly on the clinical pharmacology studies and specifically on the pivotal bioequivalent, effect of food, and multiple dose studies.

What are the Main Findings?

From the submitted studies, the following conclusions can be made:

- Following a single dose administration of one DL D-24 (5 mg DL/240 mg PSE), DL 5 mg, or PSE 240 mg tablets, the 90% CI for both Cmax and AUC of DL and 3-OH DL were **outside** the bioequivalence (BE) limits of 80%-125% (**Table 1.3.1**). However, the 90% for the PSE was within 80%-125% for both Cmax and AUC. In the same study, the exposure for DL and 3-OH DL as determined by Cmax and AUC following DL D-24 tablet was lower by approximately 15% to 20% than that after DL 5 mg tablet.

Table 1.3.1. Relative Bioavailability and 90 % Confidence Interval for DL and 3-OH DL (Study # P00439)

Treatment Ratio	Parameter	Estimate of Bioavailability (%)[a]	Confidence Interval[b]
	DL		
DL D-24 (5 mg/240 mg) tablet / 5 mg DL tablet	AUC(tf)	85.0	78-92
	Cmax	80.2	75-86
	3-OH DL		
DL D-24 (5 mg/240 mg) tablet / 5 mg DL tablet	AUC(tf)	81.2	72-92
	Cmax	80.3	75-86

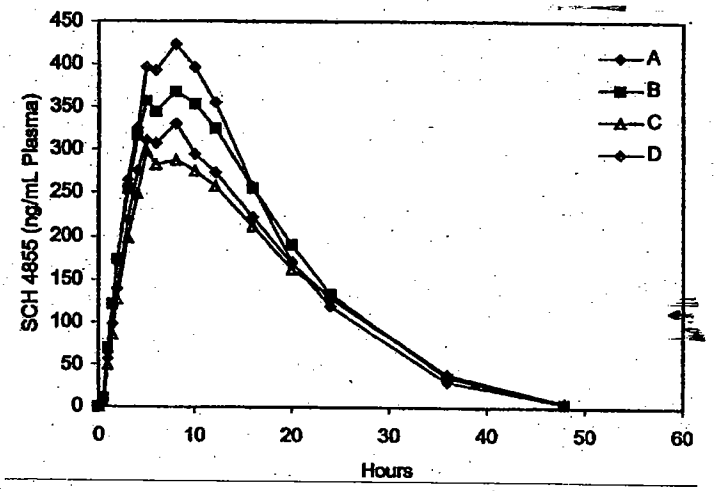
a: Expressed as a percent ratio of Treatments (DL D-24/DL).

b: Ninety percent two-tailed confidence interval.

- In another single dose study (**Study # P01813**) using two different tablet strengths: 5 mg DL/240 mg PSE (Treatment A) and 6 mg DL/240 mg PSE (Treatment B), the 5 mg DL/240 mg PSE tablet met the 80%-125% bioequivalence limits for AUC **but not for Cmax** (% CI =75-91) when compared to the reference products (5 mg DL tablet and 240 mg ER PSE tablet, treatment C). However, the DL and 3-OH DL components of the 6mg/240-mg tablet were bioequivalent to the reference (5 mg DL tablet) based on both Cmax and AUC values. Similarly, for 3-OH DL, the 90% CI was within 80%-125% for AUC, **but not for Cmax** as compared to reference (Cmax %CI =77-90). As found in the previous study, the 90% CI for the PSE was within 80%-125% for both Cmax and AUC.

- There was some relationship between the *in vitro* dissolution rates and *in vivo* performance for certain PSE formulations (**Study P01981, Figure 1.3.2**). However, the 90% CI for the Cmax for the very fast formulation was **outside** the 80%-125% limits, whereas the AUC passed. The 90% CI for the Cmax for the very fast failed at the upper end (112-129).

Figure 1.3.2. Mean PSE Plasma Profiles from Different in vitro Release Rate Formulations: A = standard, B = fast, C = slow and D = very fast (Study # P01981)



- Food did not show any effect on the bioavailability of any of the determined components in the plasma: DL, 3-OH, and PSE (**Study P00441**) . Accordingly, the 90% CI for both Cmax and AUC for the three components were within 80%-125% limits.

- Following multiple dose administration, the steady state for both DL and 3-OH DL was attained on Day 12, while for PSE was after 10 days (**Study # P00884, Figures 1.3.3**).

Mean Plasma Profiles after Multiple Dose Administration (Study # P00884)

Figure 1.3.3. DL (close circles) and 3-OH DL (open circles)

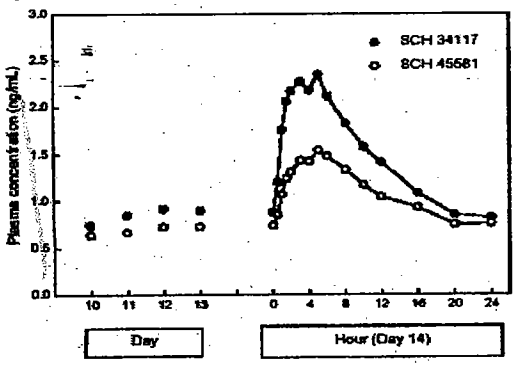
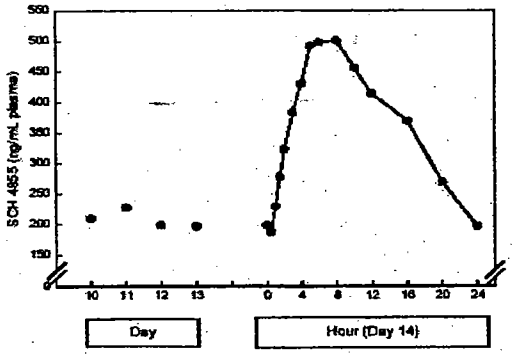


Figure 1.3.15. PSE



Overall Summary and Conclusions:

Based on all the information submitted, the following main conclusions can be made:

- Food had no effect on the absorption of Clarinex D-24
- Steady state of all 3 analytes (DL, 3-OH DL, and PSE) were reached within 12 days of dosing.
- The percent fluctuation in multiple-dose study was consistent with that of a once-daily formulation.
- The combination product was **not bioequivalent** to the monoproduct with respect to DL (5 mg).
- The combination product was bioequivalent to the monoproduct with respect to PSE.
- No gender differences in PK of DL.
- In terms of *in vitro* dissolution rates for PSE, the formulation with the very fast *in vitro* rate was **not bioequivalent** to the standard formulation at Cmax level..

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Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaulation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

2.0
Clinical Pharmacology and Biopharmaceutics Review (Question Based Review-QBR)

2.1 What are the General Attributes of Clarinex-D 24

This is an original NDA for Clarinex-D® 24 hour "combination" product tablets containing 5 mg immediate release desloratadine (DL) and 240 mg extended release Pseuduoephedrine (PSE). The proposed indications are for the relief of symptoms of allergic rhinitis and nasal congestion.

The DL component of the tablet is formulated as immediate release coating, whereas the PSE is as extended release tablet core.

2.1.1 What is the Rationale of the Combination Product?

Desloratadine (DL) is a major active metabolite of loratadine. It is currently marketed under the trade name Clarinex for the relief of the nasal and non-nasal symptoms of allergic rhinitis and chronic idiopathic urticaria in patients 12 years of age and older.

It is believed that DL is considered to be primarily responsible for loratadine activity. Loratadine (Claritin) is currently marketed as tablet and syrup. DL appears to exhibit less first-pass metabolism and a longer plasma elimination half-life than loratadine. On the other hand, PSE is widely used as over-the counter (OTC) oral and nasal decongestant products. Its safety and efficacy profiles are well established.

Claritin® D-24 (loratadine 10 mg/PSE 240 mg) is currently marketed worldwide, including the US, for the treatment of seasonal allergic rhinitis. Based on the favorable PK characteristic and safety profiles of DL over loratadine, the sponsor believes that the proposed combination of DL and PSE (Clarinex-D® 24) would be an ideal combination product for the proposed indication. The safety, efficacy, and PK of DL were submitted in Clarinex NDA # 21-165.

The current NDA further characterizes the PK and safety of DL and PSE following administration of DL D-24 (DL 5mg/PSE 240 mg), DL, and PSE.

2.2 What is the General Clinical Pharmacology?

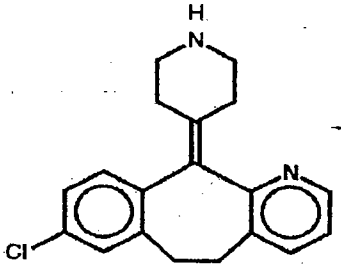
From the clinical pharmacology and biopharmaceutics perspective, the main finding in this submission is that the proposed to-be-marketed formulation is **not bioequivalent** to the reference products. Therefore, a clinical study was conducted to establish the safety and efficacy of the combination product. In addition, based on results from food effect study, the drug could be taken with or without food. Furthermore, a multiple dose PK study shows the steady-state concentration of the product components attained by approximately 12 days.

Therefore, the approval of this NDA will be based mainly on the data from the clinical trials to establish its safety and efficacy. In this case, the PK data will be used to support the decision making process for its approval and in labeling.

What is DESLORATADINE (DL) as Drug Substance?

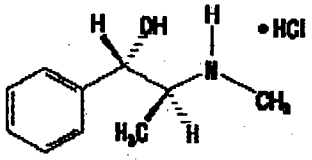
DL is a long-acting tricyclic histamine antagonist with selective H_1-receptor histamine antagonist activity. It has an empirical formula: $C_{19}H_{19}ClN_2$, a molecular weight of [redacted] and the following structure.

Desloratadine Structure



What is PSE as Drug Substance?

PSE is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. PSE is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. PSE produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. The molecular weight of PSE is [redacted] and its chemical structure is as follows:



PSE HCl

2.2.1 What are the PK Characteristics of DL and PSE?

The PK and bioavailability (BA) of DL and PSE have been evaluated in the previous NDAs within the Division and in the literature. For the purpose of this review, the following is a summary of the relevant PK characteristics for each component of Clarinex-D.

DL:

- The Tmax occurs at approximately 3 hours post dose
- Neither food nor grapefruit juice had an effect on the bioavailability (Cmax and AUC) of DL. However, food increased the Tmax from 2.5 to 4 hr.
- It is highly bound to plasma protein (~82%)
- It is extensively metabolized to 3-hydroxydesloratadine (3-OH DL), an active metabolite, which is subsequently glucuronidated.

- The enzyme(s) responsible for the formation of 3-OH DL have not been identified (see also OCPB review for NDA 21-300, Clarinex syrup).
- It should be noted that a subset of the general patient population has a decreased ability to form 3-OH DL, and are slow metabolizers of DL. This range from ~5% to 20% depending on race and other unknown variability factors (see also OCPB review of NDA 21-300).
- The exposure (AUC) to DL in the slow metabolizers was approximately 6-fold greater than the subjects who are not slow metabolizers (see also OCPB review of NDA 21-300).
- According to the sponsor's labeling, patients who are slow metabolizers may be more susceptible to dose-related adverse events.
- The elimination half-life of DL is ~ 25-30 hours.
- There is dose proportionality over doses of 5 to 20 mg.
- A total of 87% of the ^{14}C-DL was recover in urine and feces combined.
- The exposure in elderly is approximately 20% higher than adults.
- The exposure to DL may increase by ~2.5 fold in patients with sever renal and/or hepatic impairment.
- ketoconazole was shown to produce a greater exposure of DL (~40%) and 3-OH DL (~70%) compared to other tested drugs and/or control.
- Studies have shown no QTc prolongation was associated with DL.

B. PSE

- One compartment PK
- Percent of plasma protein binding is unknown.
- Extensively distributed into extravascular sites (apparent volume of distribution between 2.6 and 3.5 L/kg).
- Minimal hepatic metabolism (less than 1%)
- Mainly undergo N-demethylation to the active metabolite norpseudoephedrine.
- Excreted mainly unchanged in urine (43% to 96%).
- Half life depends on urine pH as follows. The half life range from approximately 2 hours at a pH 5 to 20 hours at pH 8.

2.2.3 What Studies are submitted in the Current NDA?

A. PK Studies

The sponsor submitted five clinical pharmacology/PK studies in this NDA.
These studies are listed in **Tables 2.2.3.1**

From the BE perspective, study # P00439 is a pivotal study comparing Clarinex-D (5 mg DL/240 mg PSE) to its individual components (5 mg DL and 240 mg PSE) after a single dose administration. Two other important studies were included in this submission: effect of food study (#P00441) and multiple dose study #P00884). These studies will be summarized in the following sections and will be presented in more detail in the appendix.

Table 2.2.3.1 List of Studies Submitted in this NDA

Study Title/Description	Protocol Number Investigator (Starting Date)	Number of Subjects	Age Range (yr) Sex Distr. (M/F)[a] Ethnic Distr.[b]	Treatment, Dose and Dosing Frequency
A. Bioavailability/Bioequivalence Studies				
SCH 483: Bioequivalence of Desloratadine and Pseudoephedrine Following Single-Dose Administration of DL D-24, Desloratadine 5-mg, and Pseudoephedrine 240-mg **Type of Study:** Single-dose, randomized, open-label, three-way crossover study. **Report Location:** Vol.: 1.14 **Data Listings:** Vol: N/A	P00439 J. Herron, MD (8/4/1999)	36	21-45 36M 24B/12C	• Single dose of DL D-24 (SCH 483) (5-mg/240-mg) extended release tablet. • Single dose of DL (SCH 34117) (5 mg) tablet. • Single dose of pseudoephedrine (SCH 4855) (240 mg) extended release tablet.
SCH 483: Bioequivalency of Desloratadine and Pseudoephedrine Following Single-Dose Administration of DL D-24 (5-mg), DL D-24 (6-mg), and Desloratadine 5-mg and Pseudoephedrine 240-mg Given Concomitantly **Type of Study:** Single-dose, randomized, open-label, three-way crossover. **Report Location:** Vol.: 1.23 **Data Listings:** Vol.: N/A	P01813 J. Herron, MD (3/2/2000)	42	19-45 21M/21F 37C/4B/1H	• Single dose of DL D-24 (SCH 483) (5-mg/240-mg) extended release tablet. • Single dose of DL D-24 (SCH 483) (6-mg/240-mg) extended release tablet. • Single dose of DL (SCH 34117) (5-mg) tablet plus a single dose of pseudoephedrine sulfate (SCH 4855) (240 mg) extended release tablet.
SCH 483: The Bioavailability of Pseudoephedrine From Controlled-Release (24-Hour) Formulations: A single-Dose Four-Way Crossover Study **Type of Study:** Single-dose, randomized, open-label, four-way crossover study. **Report Location:** Vol: 1.28 **Data Listings:** Vol: N/A	P01981 K. Lasseter, MD (8/25/2000)	20	18-45 13M/7F 5C/1B/14H	• Single dose of DL D-24 (SCH 483) (5-mg/240-mg standard dissolution batch) extended release tablet. • Single dose of DL D-24 (SCH 483) (6-mg/240-mg fast dissolution batch) extended release tablet. • Single dose of DL D-24 (SCH 483) (5-mg/240-mg slow dissolution batch) extended release tablet. • Single dose of DL D-24 (SCH 483) (6-mg/240-mg very fast dissolution batch) extended release tablet.

Table 2.2.3.1 (continued): List of Studies Submitted in the NDA

Study Title/Description	Protocol Number Investigator (Starting Date)	Number of Subjects	Age Range (yr) Sex Distr. (M/F)[a] Ethnic Distr.[b]	Treatment, Dose and Dosing Frequency
B. Bioavailability/Human Pharmacokinetic Studies				
SCH 483: Influence of Food on the Oral Bioavailability of DL D-24 Administered to Healthy Subjects: A Two-Way Crossover Study **Type of Study:** Single-dose, randomized, open-label, two-way crossover study **Report Location:** Vol.: 1.18 **Data Listings:** Vol: N/A	P00441 T. Marbury, MD (8/2/1999)	38	19-44 27M/11 F 24C/11B/3H	• Single dose of DL D-24 extended release tablet (SCH483) (5-mg/240-mg) under fed or fasted conditions.
SCH 483: The Multiple-Dose Pharmacokinetics of DL D-24 **Type of Study:** Multiple-dose, open-label study **Report Location:** Vol.: 1.21 **Data Listings:** Vol: N/A	P00684 C. Johnson, MD (11/22/1999)	18	21-45 15M/3F 14C/4B	• One DL D-24 (SCH 483) (5-mg/240-mg) extended-release tablet once daily x 14 days.

a: M=Male, F=Female.

b: C=Caucasian, B=Black, H=Hispanic, O=Other.

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B. Clinical Studies:

For detail of the Phase III clinical trials, please see the Medical Officer's review. The sponsor conducted **two identical** Phase III studies as summarized in **Table 2.2.3.2.**

Table 2.2.3.2 Phase III Clinical Trials

Study Number Study Dates Study Centers	Study Design	Numbers of Subjects: (Randomized/Efficacy -Evaluable)[a] Age Range (Years) Sex Distribution
P01875 Aug 2000 to Dec 2000 47 centers in United States	Multicenter, Double-Blind, Double-Dummy, Active-controlled, Parallel-group, Efficacy and Safety Study: DL D-24 QD and DL D-24 AF QD versus DL 5-mg QD and PSE 240-mg QD for 15 days	1495/1410 12-78 527 M, 968 F
P01884 Aug 2000 to Dec 2000 47 centers in United States	Multicenter, Double-Blind, Double-Dummy, Active-controlled, Parallel-group, Efficacy and Safety Study: DL D-24 QD and DL D-24 AF QD versus DL 5-mg QD and PSE 240-mg QD for 15 days	1357/1270 11-78 516 M, 841 F

AF=Alternate Formulation; QD=Once Daily; M=Male; F=Female.
a: All analyses of efficacy included all randomized subjects who received at least one dose of study medication and had both Baseline and some postbaseline data. Confirmatory analyses of primary efficacy included all subjects in the efficacy-evaluable subset.

The primary objective of these two studies was to evaluate the efficacy of the two Clarinex-D 24 formulations compared to the active comparators; 5-mg DL and 240 mg PSE. Safety was also monitored as a secondary objective.

Briefly, these two clinical studies were virtually identical in terms of the design. They both randomized, multicenter, double-blind, double-dummy, active-controlled, parallel-group studies in approximately 1300 to 1400 subjects each. However, the two formulations (DL D-24 and DL D-24 AF [alternative formulation]) evaluated in these studies differed only by a slight modification in the quantity of some of the excipients in the film coat, although the qualitative formula remained the same. The placebo tablets were identical in appearance to the 5.0-mg DL tablets and the other placebo tablets were identical to both the DL D-24 and 240-mg PSE tablets (which themselves were identical in appearance).

Each subjects received treatment at approximately the same times in the morning for the duration of 15 days. Each treatment consisted of two tablets; one active and one placebo. The efficacy endpoint was the average of 15 days treatments.

For detailed analysis of the safety and efficacy data, please see the Medical Officer's review. However, based on the sponsor's summary reports the safety and efficacy data for Clarinex-D 24 appears to be reasonable and comparable to the comparator. However, it should be emphasized again that these data has not been reviewed by OCPB.

2.2.4 Does this Drug Prolong the QT or QTc Interval?

No signals for prolongation in QTc intervals prolongation were noted in this submission (see also the Medical Officer's Review).

In addition, an analysis of the data for QTc was performed by OCPB in the previous NDA for syrup (21-300) in a subset of poor metabolizers. Briefly, from the analysis of the data, no apparent signal of QTc prolongation has been observed in poor metabolizers compared to normal metabolizers and placebo treatments.

2.3 Are there any Intrinsic Factors?

DL is converted to 3-OH DL. From OCPB review of NDA 21-300 it was concluded that the enzymes responsible for its conversion are not known. In a subgroup of population the conversion of DL to 3-OH DL was markedly reduced. Subjects were classified based on their metabolic status as poor or normal metabolizers. This was based on the ratio of 3-OH DL to DL. Those with a ratio of <10% were classified as poor metablizers, whereas those with a ratio of >10% were considered normals. However, those with a ratio of >25% were enrolled in further safety study. In NDA 21-300, the safety and PK profiles of DL have been further characterized in the poor metabolizers sub-population following repeated doses of DL. No major safety concerns were noted (see also OCPB review for NDA 21-300).

2.3.1. Is there any Intrinsic Factor Affecting Exposure?

From NDA 21-300, it was concluded that the prevalence of poor metabolizers appears to be dependent on race and/or ethnic background. For example, the prevalence in Blacks was approximately 10% to 20 % higher than in Caucasians (1% to 5%). Therefore, the exposure to DL in Blacks is expected to be higher than in Caucasians.

Also, considering the variability in the data submitted in NDA 21-300, the exposure to DL appears to be independent of age. In other word, the DL exposure in pediatric population appears to be comparable to adults.

2.4 Is there any Extrinsic Factors?

As stated above, the main factor affecting exposure is the polymorphism status in the conversion of DL to 3-OH DL.

2.5 Biopharmaceutics Issues

2.5.1 What is the Drug Product/Formulation?

The composition of each layer of the formulation is shown in **Tables 2.5.1.1 and 2.5.1.2.** The formulation lot numbers used in each study are listed in **Tables 2.5.1.3 and 2.5.1.4.**

Table 2.5.1.1 Components of Extended Release Core Portion

The Components of the Extended Release Tablet Core are:

Pseudoephedrine Sulfate USP
Hypromellose
Ethylcellulose NF
Dibasic Calcium Phosphate USP Dihydrate
Povidone USP
Silicon Dioxide NF
Magnesium Stearate NF

The Components of the Immediate Release Coating are:

Desloratadine, I
Polyacrylate Dispersion
Polyethylene Glycol NF
Hypromellose

Blue Lake Blend 50726[b]
Simethicone USP

Ink, imprinting, black (Opacode® S-1-4159)[c]

Table 2.5.1.2 Components of Immediate Release Coating

Immediate Release Coating

Ingredient	Theoretical Calculated mg/tablet
Desloratadine,	5.00
Polyacrylate Dispersion	
Polyethylene Glycol NF	
Hypromellose	
Blue Lake Blend 50726[b]	
Simethicone USP	
Ink, imprinting, black (Opacode® S-1-4159)[d]	
Theoretical Coating Weight	
Theoretical Total Coated Tablet Weight	842.38

Table 2.5.1.3: Formulations Used in Clinical Pharmacology Studies

PROTOCOL NUMBER	DRUG PRODUCT BATCH NUMBER	DATE OF MANUFACTURE	TABLET CORE LOT NUMBER	BATCH SIZE APPROX. TABLET	DRUG SUBSTANCE* LOT NUMBER
P00439	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRQ-98-13M1 / DL
P00441	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRQ-98-13M1 / DL
P00584	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRQ-98-13M1 / DL
P01813	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRQ-98-13M1 / DL
P01881	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRQ-98-13M1 / DL

Table 2.5.1.4: Formulations Used in Phase III Studies

PROTOCOL NUMBER	DRUG PRODUCT BATCH NUMBER	DATE OF MANUFACTURE	TABLET CORE LOT NUMBER	BATCH SIZE APPROX. TABLET	DRUG SUBSTANCE* LOT NUMBER
P01875	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRQ-98-13M1 / DL
P01884	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRQ-98-13M1 / DL

*Note: PSE = Pseudoephedrine Sulfate USP and DL = Desloratadine

According to the sponsor, the two formulations, DL D-24 and DL D-24 AF (alternative formulation), used in these studies differed only by a slight modification in the quantity of some of the excipients in the film coat. For details on these differences and on all formulations, please see the CMC review.

2.5.3 What is the Relative Bioavailability of the Proposed to-be-marketed Formulation Following a Single Dose Administration Compared to the Reference Products?

The sponsor submitted 5 clinical pharmacology studies to this NDA. Among these was Study # P00439 which is considered pivotal to investigate the relative bioavailability of the proposed to-be-marketed formulation following a single dose administration compared to the reference. It should be noted that the formulation used in all clinical pharmacology and Phase III studies is of the same lot (i.e., lot # 75882-056, **Tables 2.5.1.3 and 2.5.1.4**). This study is briefly described below:

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Study # P00439 (Single Dose BE):

Objectives:

The primary objective of this study was to determine the BE of DL, 3-OH DL, and PSE following a single dose administration of DL D-24, DL- 5mg, and PSE 240 mg.

Design:

This was three-way crossover study as follows:

Treatment A (Test): One DL D-24 (5mg DL/240 mg PSE) (lot # 75882-056)

Treatment B (Reference): One DL 5 mg tablet

Treatment C (Reference): One 240 mg PSE tablet (oval extended-release PSE cores from Claritin ® D 24 coated with placebo Claritin® D-24 coat).

Population:

36 healthy subjects (males only)

Results:

- The plasma concentration-time profiles of DL and 3-OH DL and their exposure (**Figures 2.5.2.1, 2.5.2.2 and Table 2.5.2.1**) were consistently higher in treatment B (5 mg Dl tablet) compared to treatment A (combination product).
- The 90% CI limits for both DL and 3-OH DL were outside the 80-125 regulatory BE acceptable limits (**Table 2.5.2.2**).
- For PSE, the mean Cmax was slightly higher following the reference (treatment C) compared to combination product (treatment A) but the total AUC is slightly lower (**Figure 2.5.2.3 and table 2.5.2.3**).
- The 90% CI for PSE, however, was within 80%-125% (**Table 2.5.2.4**)

Figure 2.5.2.1. Mean DL Plasma Profiles (Study # P00439)

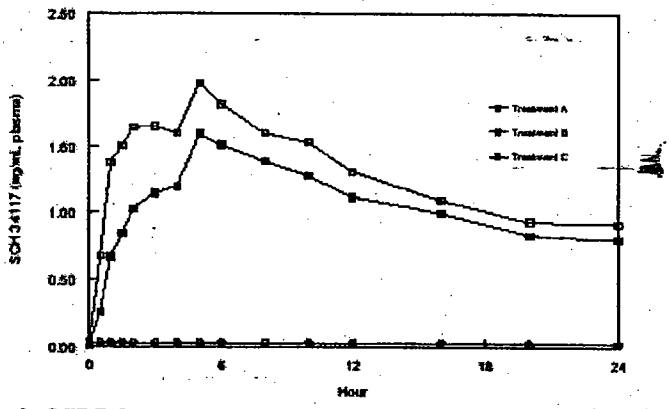

Figure 2.5.2.2 Mean 3-OH DL Plasma Profiles (Study # P00439)

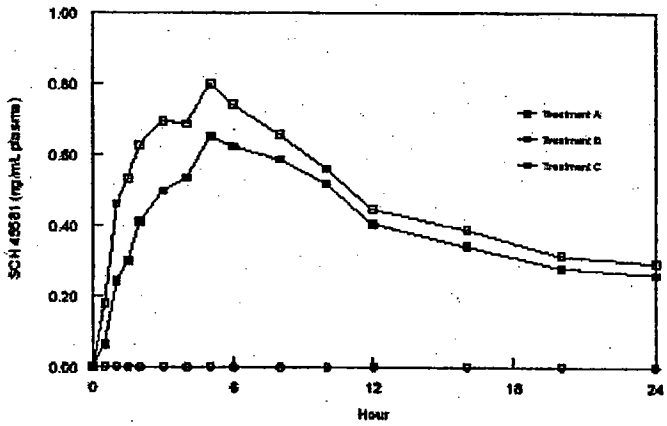

Figure 2.5.2.3 Mean PSE Plasma Profiles (Study # P00439)

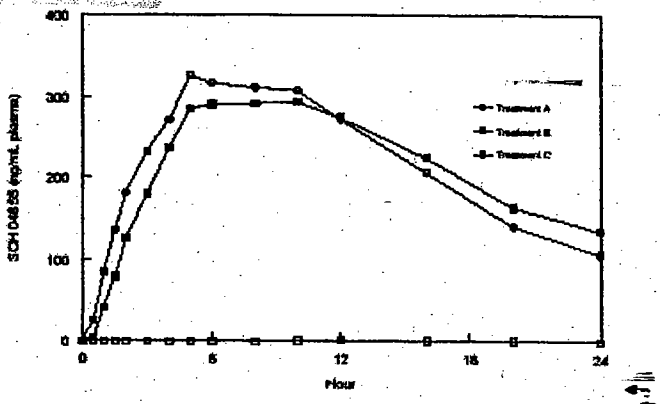

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Table 2.5.2.1. PK of DL and 3-OH DL (Study # P00439)

		DL			
		DL D-24 5-mg/240-mg (Treatment A)		DL 5-mg (Treatment B)	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	1.79	36	2.23	35
Tmax	hr	6.78	57	5.10	53
AUC(tf)	ng·hr/mL	61.1	95	72.5	95
tf	hr	105	19	105	20
AUC(I)	ng·hr/mL	54.8[a]	121	63.3[a]	114
t½	hr	23.7[a]	37	23.5[a]	35
		3-OH DL			
		DL D-24 5-mg/240-mg (Treatment A)		DL 5-mg (Treatment B)	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	0.695	59	0.832	55
Tmax	hr	6.09[b]	33	4.96[b]	31
AUC(tf)	ng·hr/mL	19.8	51	22.6	49
tf	hr	103	30	103	26
AUC(I)	ng·hr/mL	24.4[c]	33	28.0[c]	30
t½	hr	29.6[c]	13	29.5[c]	14

a: n=32.

b: n=35 (all 3-OH DL concentrations for subject 36 were below the LOQ).

c: n=30.

Table 2.5.2.2. Relative Bioavailability and 90 % Confidence Interval for DL and 3-OH DL (Study # P00439)

Analysis With All Subjects Included			
Treatment Ratio	Parameter	Estimate of Bioavailability	90% Confidence Interval
DL (n=36)			
DL D-24 tablet/ DL 5-mg tablet	AUC(tf)	85.0	78-92
	Cmax	80.2	75-86
3-OH DL (n=36)			
DL D-24 tablet/ DL 5-mg tablet	AUC(tf)	81.2	72-92
	Cmax	80.9	75-86

Table 2.5.2.3. PK of PSE (Study # P00439)

		Pseudoephedrine			
		DL D-24 5-mg/240-mg		Oval-Extended Release PSE Cores from Claritin D-24	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	328	25	349	18
Tmax	hr	8.42	34	7.36	36
AUC(tf)	ng·hr/mL	6438	42	6225	39
tf	hr	44.0	37	40.0	26
AUC(I)	ng·hr/mL	6780	40	6452	37
t½	hr	10.3	148	7.25	22

Table 2.5.2.4. Relative Bioavailability and 90 % Confidence Interval for PSE (Study # P00439)

Analysis With All Subjects Included			
Treatment Ratio	Parameter	Estimate of Bioavailability (%)	90% Confidence Interval
Pseudoephedrine (n=36)			
DL D-24 tablet/ 240-mg pseudoephedrine sulphate extended-release core	AUC(tf)	102	94-112
	Cmax	93	89-97

What are the Main Conclusions from Study # P00439?

- The 90% CI for both Cmax and AUC of DL and 3-OH DL were outside the bioequivalence (BE) limits of 80%-125% (**Figures 2.5.2.1, 2.5.2.2 and Tables 2.5.2.1**).
- The exposure for DL and 3-OH DL as determined by Cmax and AUC following DL D-24 tablet was lower by approximately 15% to 20% than that after DL 5 mg tablet.
- The 90% for the PSE was within 80%-125% for both Cmax and AUC (**Table 2.5.2.4**)
- It appears that there is data integrity issue with this study. PSE was detected in relatively high concentrations in two subjects who received 5 mg DL only containing tablets (Treatment B). The PSE plasma concentration ranged from approximately 14 ng/ml to 63 ng/ml. The sponsor stated that the reason for these measurable concentrations of PSE is unknown.

Conclusions:

The formulation is considered **not bioequivalent** to the reference. Therefore, the final decision of the approval of this formulation will depend on both the safety and efficacy data from Phase III study and with additional consideration of the BE data (see also the Medical Officer's review).

2.5.3 What is the Effect of Food on the Bioavailability of the Proposed to-be-marketed Formulation?

Study # PO0441 (Effect of Food):

Objectives:

The primary objective of this study is to determine the food effect on the bioavailability of DL, 3-OH DL, and PSE following DL D-24.

Design:

This was two arms crossover study as follows:

Treatment A (Reference): DL D-24 after overnight fast

Treatment B (Test): DL D-24 after high fat, high-caloric breakfast

Population:

38 healthy subjects (male and females)

Results:

- The plasma concentration-time profiles for D and 3-OH Dl show some variability in the plasma levels following either treatment (**Figures 2.5.3.1 and 2.5.3.2**). However, PSE plasma levels are less variable (**Figure 2.5.3.3**).
- The % CV for DL data ranges from 54% to 118% and for 3-OH data from 26% to 123% in both treatments (**Table 2.5.3.1**). However, for PSE the %CV ranges from 15% to 24% (**Table 2.5.3.1**).
- The 90% CI limits for all components were within 80% to 125% (**Table 2.5.3.2**).

Figure 2.5.3.1. Mean DL Plasma Profiles (Fed/fasted, Study # P00441)

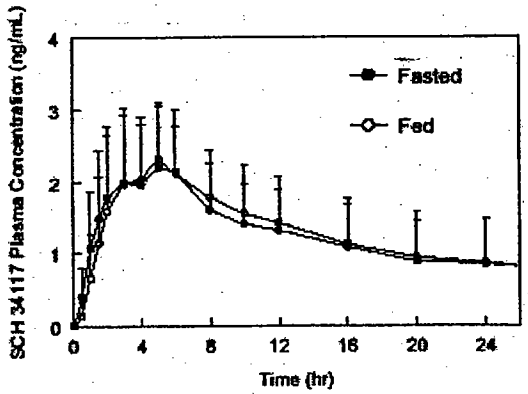

Figure 2.5.3.2. Mean 3-OH DL Plasma Profiles (Fed/fasted, Study # P00441)

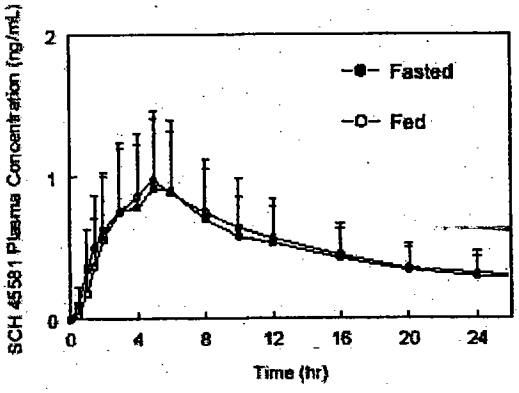

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Figure 2.5.3.3. Mean PSE Plasma Profiles (Fed/fasted, Study # P00441)

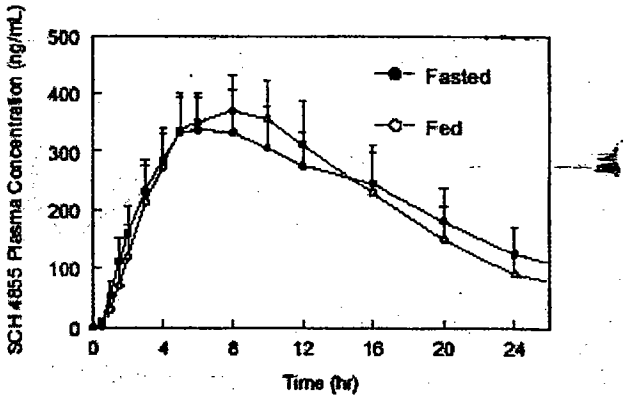

Table 2.5.3.1. PK of DL, 3-OH, and PSE (Study # P00441)

Treatment	Mean (%CV) Pharmacokinetic Parameters (n=36)				
	Cmax (ng/mL)	Tmax (hr)	AUC(if) (ng·hr/mL)	AUC(i) (ng·hr/mL)	t½ (hr)
DL					
Fasted	2.50 (39)	5.69 (84)	84.9 (79)	83.8 (118)	29.6 (79)
Fed	2.55 (36)	5.39 (54)	86.6 (82)	83.7 (111)	29.0 (74)
3-OH DL					
Fasted	0.980 (56)	5.53 (26)	24.6 (45)	27.4 (39)	44.3 (123)
Fed	1.01 (50)	5.14 (26)	25.3 (46)	28.8 (36)[a]	40.3 (69)[a]
Pseudoephedrine					
Fasted	358 (19)	7.04 (19)	6842 (24)	7072 (23)	7.04 (19)
Fed	386 (17)	5.92 (15)	6313 (22)	6475 (22)	5.92 (15)

a: n=35.

Table 2.5.3.2. 90 % Confidence Interval for PSE (Study # P00441)

Comparison		Relative Bioavailability (%)	90% Confidence Interval
DL (n=36)			
Fed/Fasted	AUC(I)	102	97.0-107
Fed/Fasted	Cmax	104	96.0-113
3-OH DL (n=36)			
Fed/Fasted	AUC(I)[a]	102	97.0-107
Fed/Fasted	Cmax	106	99.0-114
Pseudoephedrine (n=36)			
Fed/Fasted	AUC(I)	92.0	87.0-97.0
Fed/Fasted	Cmax	108	104-113

a: n=35.

What are the Main Conclusions from Study # P00441?

- Food did not have any effect on the bioavailability of the formulation components **(Figures 2.5.3.1-2.5.3.3 and Table 2.5.3.1 and 2.5.3.2).**
- Accordingly, the 90% CI for both Cmax and AUC for the three analytes were within 80%-125% limits **(Table 2.5.3.2).**
- There was a noticeable variability in the data as the %CV for Cmax and AUC ranged from 15% to 123% for both DL and 3-OH DL **(Table 2.5.3.1)**

2.5.4 What is the PK Characteristics of Clarinex Components Following Multiple Dose Administration?

Study # PO0884 (Multiple Dose):

Objectives:

The primary objective of this study is to determine the PK profile of DL, 3-OH DL, and PSE following daily administration of DL D-24 for 14 days.

Design:

Open label, multiple-dose, and steady-state study.

Population:

18 healthy subjects (male and females)

Results:

- From the plasma concentration-time profiles, it can clearly be concluded that the steady state level achieved by approximately Day 10 (**Figure 2.5.4.1**). The average Cmin on Day 10 for DL level is approximately 0.8 ng/ml and for 3-OH Dl is approximately 0.7 ng/ml (**Table 2.5.4.1**).
- The DL level is approximately 1.3-1.5 fold higher than 3-OH DL (**Figure 2.5.4.1 and table 2.5.4.2**).
- Similarly, the steady state level of PSE achieves on approximately Day 10 to Day 12 (**Figure 2.5.4.2 and Tables 2.5.4.3 and 2.5.4.4**). The average Cmin for PSE was approximately 200 ng/ml on Day 10 throughout Day 14 (**Table 2.5.4.3**).

Figure 2.5.4.1. Mean DL (close circles) and 3-OH DL (open circles) Plasma Profiles after Multiple Dose Administration (Study # P00884)

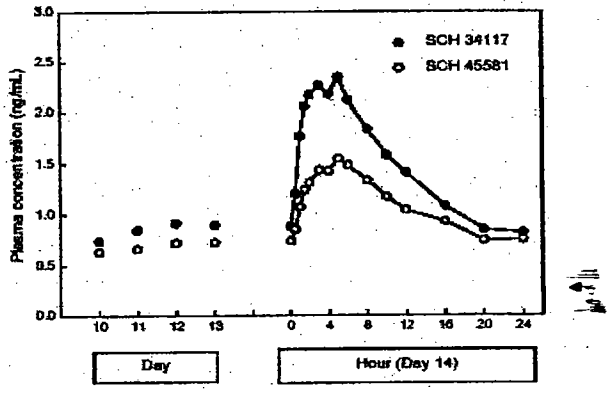

Figure 2.5.4.2. Mean PSE Plasma Profile after Multiple Dose Administration (Study # P00884)

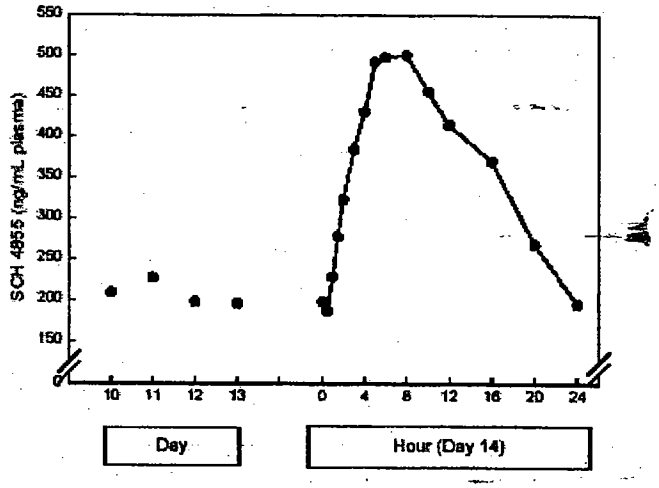

Table 2.5.4.1. Mean Plasma Cmin of DL and 3-OH DL after Multiple Dose Administration (Study # P00884)

Days[a]	Mean Cmin (ng/mL)	%CV
DL		
10	0.739	39
11	0.847	35
12	0.917	32
13	0.896	37
14	0.880	39
3-OH DL		
10	0.635	32
11	0.664	30
12	0.724	24
13	0.725	28
14	0.739	31

a: Predose.

Table 2.5.4.2. Mean PK Parameters of DL and 3-OH DL at Steady State (Day 14) (Study # P00884)

Cmax (ng/mL)		Tmax (hr)		Cmin (ng/mL)		Cavg (ng/mL)		AUC(0-24 hr) (ng·hr/mL)		% Fluctuation	
Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
DL											
2.44	35	3.68	39	0.788	39	1.45	34	34.8	34	115	14
3-OH DL											
1.56	20	4.65	26	0.689	27	1.07	21	25.7	21	82.9	18

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Table 2.5.4.3. Mean Plasma Cmin of PSE after Multiple Dose Administration (Study # P00884)

Day[a]	Mean Cmin (ng/mL)	%CV
t0	209	44
t1	227	37
t2	198	36
t3	196	37
t4	198	46

a: Predose.

Table 2.5.4.4. Mean PK Parameters of PSE at Steady State (Day 14) (Study # P00884)

Cmax (ng/mL)		Tmax (hr)		Cmin (ng/mL)		Cavg (ng/mL)		AUC(0-24 hr) (ng·hr/mL)		% Fluctuation	
Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
523	27	6.65	21	161	51	366	29	8795	29	102	22

What are the Main Conclusions from Study # P00884?

- Steady state concentration for DL and 3-OH was attained on Day 12
- Steady state concentration for PSE was attained on Day 10

2.5.5 What are the Proposed *In Vitro* Dissolution Methods and Specifications?

The summary of the proposed **in vitro** dissolution methods and specifications are shown **Tables 2.5.5.1-2.5.5.3 and Figures 2.5.5.1 and 2.5.5.2.** From OCPB perspective, these methods and specifications are acceptable. For detail analysis and discussion, see also the chemistry review.

Table 2.5.5.1. Proposed *In Vitro* Dissolution Methods and Specifications for PSE 24 mg Extended Release Tablets

PROPOSED PRODUCT DISSOLUTION METHOD SPECIFICATIONS AND RESULTS

Dissolution Data for SCH 4855 Extended Release Tablets 240 mg

Time (Minutes)	Dissolution Profile Results Percent 4855 Dissolved/Dosage Form Avg. (range)
0.5	
0.75	
1	
2	
4	
8	
10	
16	

Dissolution Procedure

Apparatus:
Dissolution Medium:
Temperature:
Detection:
Recommended Dissolution Specification:

a: Revolutions per minute.

Table 2.5.5.2 Proposed *In Vitro* Dissolution Methods and Specifications for DL 5 mg Tablets (Formulation # 98564D02, Batch # 38833-142)

PROPOSED PRODUCT DISSOLUTION METHOD SPECIFICATIONS AND RESULTS	
Dissolution Data for SCH 34117 Tablets 5 mg,	
Time (Minutes)	Dissolution Profile Results Percent 34117 Dissolved/Dosage Form
	Avg. (range)
15	
30	
45	
60	
Dissolution Procedure	
Apparatus:	
Dissolution Medium:	
Temperature:	
Detection:	
Recommended Dissolution Specification:	

a: Revolutions per minute.

Table 2.5.5.3 Proposed *In Vitro* Dissolution Methods and Specifications for Products DL D-24 Extended Release Tablets (5 mg/240 mg) (Formulation # 99630D02, Batch # 75882-056)

PROPOSED PRODUCT DISSOLUTION METHOD SPECIFICATIONS AND RESULTS	
Dissolution Data for SCH 483 DL D-24 Extended Release Tablets, 5 mg/240 mg,	
Time (Hours)	Dissolution Profile Results Percent Pseudoephedrine Sulfate Dissolved/Dosage Form
	Avg. (range)
0.5	
0.75	
1	
2	
4	
8	
10	
16	
	Dissolution Profile Results Percent SCH 34117 Dissolved/Dosage Form
0.5	
0.75	
1	
Dissolution Procedure	
Apparatus:	
Dissolution Medium:	
Temperature:	
Detection:	
Recommended Dissolution Specification:	

a: Revolutions per minute.

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b Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Conclusions:

Based on these data, the following specifications are recommended:
For PSE (ER):

1 h	Q
2 h	Q
4 h	Q
8 h	Q
16h	

For DL (IR):

30 min	Q

2.6 Are There any Analytical Issues?

The plasma concentration of DL and 3-OH DL were determined by a validated LC/MS/MS method. The lower limit of quantitation (LOQ) was 25.0 pg/mL and the calibration curve was linear over a high range of concentrations of approximately for both DL and 3-OH DL. The %CV at LOQ ranges from approximately for both DL and 3-OH DL.

PSE plasma concentration was determined by HPLC coupled with mass spectrometry detection. The method was validated with LOQ of . The calibration curve was linear over a range of . The %CV ranged from established over a range of concentrations within the calibration curve.

3. Detailed Labeling Recommendation

All labeling comments will be made directly into the proposed label in conjunction with the other members of the review team after the briefing.

Comment Related to Renal and Hepatic Impairment:

The main labeling comment is related to the patients with renal and hepatic impairment. In the current Clarinex labeling, the starting dose is 5 mg **every other day** in patients with renal and hepatic impairment. This is based on the PK data that showed the Cmax and AUC increased by approximately 2 fold in patients with renal and hepatic impairment (Clarinex labeling).

Therefore, this issue was discussed at OCPB briefing held on January 28, 2005 and also at the wrap up meeting held on February 1, 2005. Based on the discussion with the review team members, it was recommended that Clarinex-D 24 should not be used in patients with renal or hepatic impairment. This warning statement should be included in the Contraindication Section of the labeling. The exact language will be included in the labeling after further discussion with members of the review team.

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6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

4.2 Individual Study Review

The pertinent information from all studies is sufficiently covered in the summary section. Therefore, to reduce the volume of the review and avoid repetition of the same information, this section proved brief summary of the submitted studies.

Overall Summary of the Individual PK Studies:

Only the clinical pharmacology studies will be briefly discussed here. The general design for these studies is as follows:

- The screening was conducted at approximately 3 weeks prior to each study.
- Subjects were fasted overnight and until 4 hours after each treatment, except for the food effect study.
- The washout period was at least 10 days, except for study # P01981 (different *in vitro* dissolution rates for PSE SE tablets) in which the washout period was 7 days.
- The PK samples were collected at the following time points: baseline (0 hour), 0.5, 1. 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120 hours postdose. However, for study # P01981 blood was collected until 48 hours.

1. Study # P00439 (single dose BE):

Objectives:

The primary objective of this study is to determine the BE of DL, 3-OH DL, and PSE following a single dose administration of DL D-24, DL- 5mg, and PSE 240 mg.

Design:

Three arms crossover study as follows:

Treatment A: One DL D-24 (5mg DL/240 mg PSE)

Treatment B: One DL 5 mg tablet

Treatment C: One 240 mg PSE tablet (oval extended-release PSE cores from Claritin ® D 24 coated with placebo Claritin® D-24 coat).

Population:

36 healthy subjects (males only)

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Results:

Figure 4.2.1. Mean DL Plasma Profiles (Study # P00439)

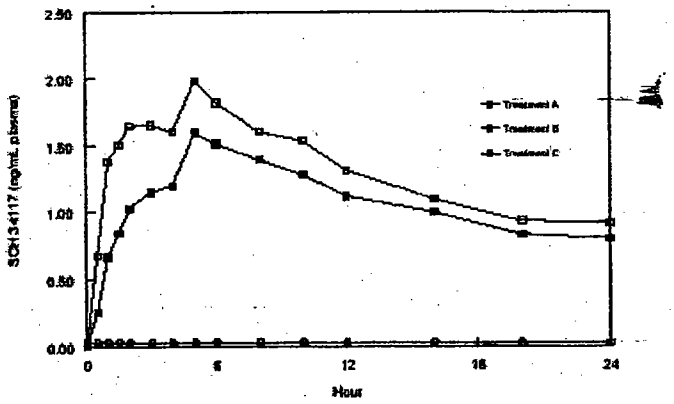

Figure 4.2.2. Mean 3-OH DL Plasma Profiles (Study # P00439)

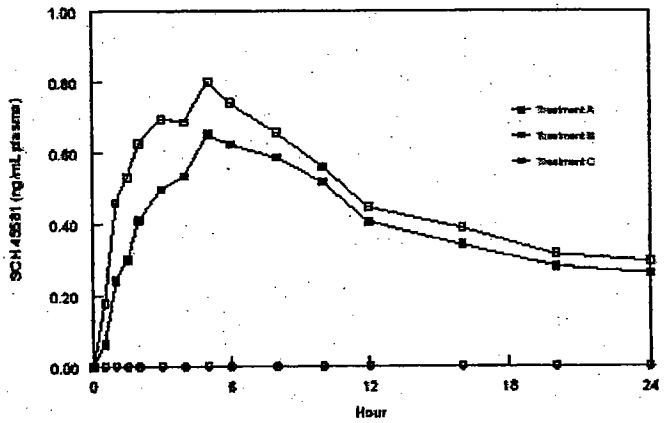

Figure 4.2.3. Mean PSE Plasma Profiles (Study # P00439)

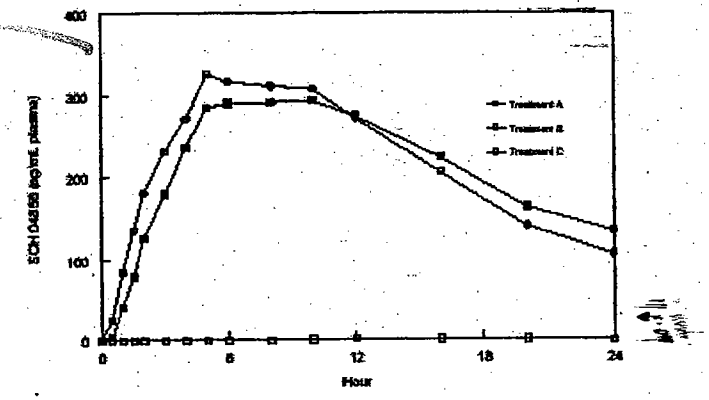

Table 4.2.1. PK of DL and 3-OH DL (Study # P00439)

		DL			
		DL D-24 5-mg/240-mg (Treatment A)		DL 5-mg (Treatment B)	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	1.79	38	2.23	35
Tmax	hr	6.78	57	5.10	53
AUC(tf)	ng·hr/mL	61.1	95	72.5	95
tf	hr	105	19	105	20
AUC(I)	ng·hr/mL	54.8[a]	121	63.3[a]	114
t½	hr	23.7[a]	37	23.5[a]	35
		3-OH DL			
		DL D-24 5-mg/240-mg (Treatment A)		DL 5-mg (Treatment B)	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	0.695	59	0.832	55
Tmax	hr	6.09[b]	33	4.96[b]	31
AUC(tf)	ng·hr/mL	19.6	51	22.6	49
tf	hr	103	30	103	26
AUC(I)	ng·hr/mL	24.4[c]	39	26.0[c]	30
t½	hr	29.6[c]	13	29.5[c]	14

a: n=32.

b: n=35 (all 3-OH DL concentrations for subject 36 were below the LOQ).

c: n=30.

Table 4.2.2. Relative Bioavailability and 90 % Confidence Interval for DL and 3-OH DL (Study # P00439)

Analysis With All Subjects Included			
Treatment Ratio	Parameter	Estimate of Bioavailability	90% Confidence Interval
DL (n=36)			
DL D-24 tablet/ DL 5-mg tablet	AUC(tf)	85.0	78-92
	Cmax	80.2	75-86
3-OH DL (n=36)			
DL D-24 tablet/ DL 5-mg tablet	AUC(tf)	81.2	72-92
	Cmax	80.3	75-86

Table 4.2.3. PK of PSE (Study # P00439)

		Pseudoephedrine			
		DL D-24 5-mg/240-mg		Oval-Extended Release PSE Cores from Claritin D-24	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	328	25	349	18
Tmax	hr	8.42	34	7.36	36
AUC(tf)	ng·hr/mL	6438	42	6225	39
tf	hr	44.0	37	40.0	26
AUC(I)	ng·hr/mL	6780	40	6452	37
t½	hr	10.3	148	7.25	22

Table 4.2.4. Relative Bioavailability and 90 % Confidence Interval for PSE (Study # P00439)

Analysis With All Subjects Included			
Treatment Ratio	Parameter	Estimate of Bioavailability (%)	90% Confidence Interval
Pseudoephedrine (n=36)			
DL D-24 tablet/ 240-mg pseudoephedrine sulphate extended-release core	AUC(tf)	102	94-112
	Cmax	93	89-97

What are the Main Conclusions from Study # P00439?

- The 90% CI for both Cmax and AUC of DL and 3-OH DL were outside the bioequivalence (BE) limits of 80%-125%.
- However, the 90% for the PSE was within 80%-125% for both Cmax and AUC.
- It appears that there is data integrity issue with this study. PSE was detected in relatively high concentrations in two subjects who receive 5 mg DL only containing tablets (Treatment B). The PSE plasma concentration ranged from approximately 14 ng/ml to 63 ng/ml. The sponsor stated that the reason for these measurable concentrations of PSE is unknown.
- The exposure for DL and 3-OH DL as determined by Cmax and AUC following DL D-24 tablet was lower by approximately 15% to 20% than that after DL 5 mg tablet.

Study # P01813 (Single Dose BE-6mg DL/240 mg PSE):

Objectives:

The primary objective of this study was to determine the BE of DL, 3-OH DL, and PSE following a single dose administration of the formulations:

- Clinical DL D-24 (5mg DL/240 mg PSE) formulation
- DL D-24 formulation containing 6 mg of DL (6 mg DL/240 mg PSE)
- DL 5 mg plus concomitantly administered PSE 240 ER formulation.

Design:

Three arms crossover study as follows:

Treatment A: One DL D-24 (5mg DL/240 mg PSE)

Treatment B: One DL D-24 (6 mg DL/240mg PSE) ER tablet

Treatment C: One DL 5 mg tablet plus one PSE 240 mg ER tablet

Population:

42 healthy subjects (male and females)

Results:

Figure 4.2.4. Mean DL Plasma Profiles (Treatments A and C, Study # P01813)

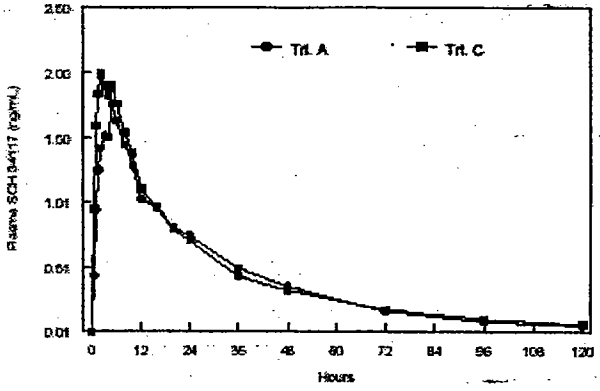

Figure 4.2.5. Mean DL Plasma Profiles (Treatments B and C, Study # P01813)

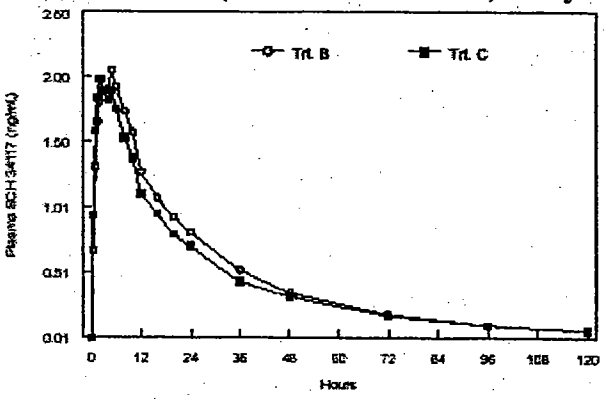

Figure 4.2.6. Mean 3-OH DL Plasma Profiles (Treatments A and C, Study # P01813)

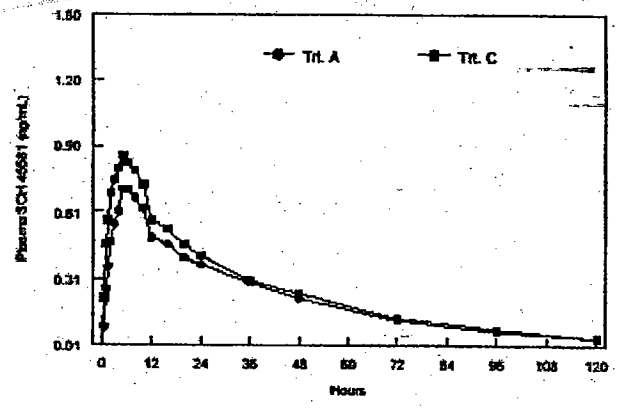

Figure 4.2.7. Mean 3-OH DL Plasma Profiles (Treatments B and C, Study # P01813)

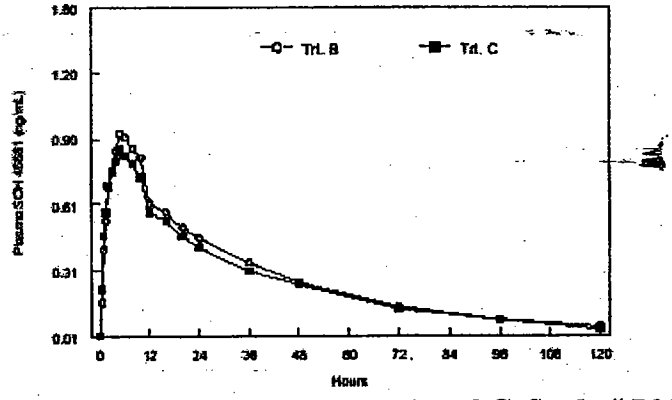

Figure 4.2.8. Mean PSE Plasma Profiles (Treatments A and C, Study # P01813)

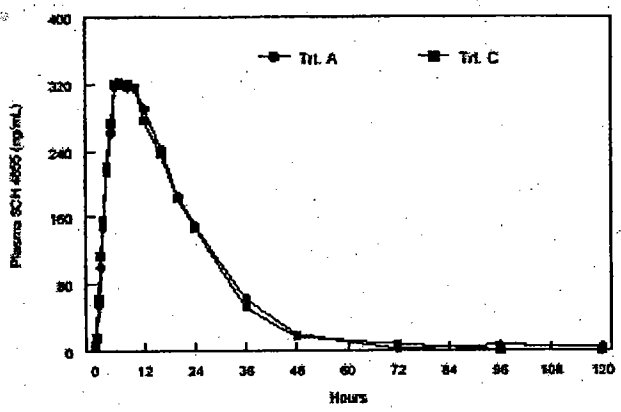

Figure 4.2.9. Mean PSE Plasma Profiles (Treatments B and C, Study # P01813)

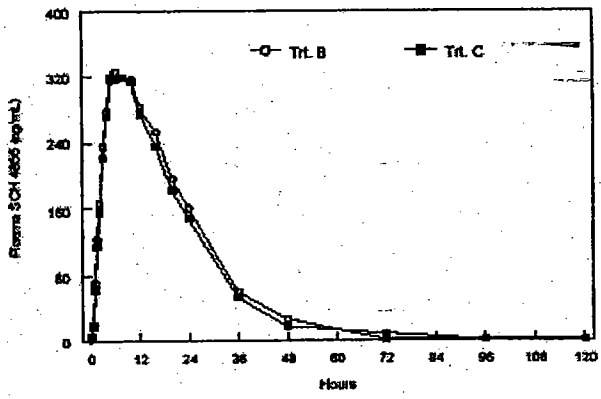

Table 4.2.5. PK of DL (Study # P01813)

		DL (n=42)					
		DL D-24, 5-mg/240-mg (Treatment A)		DL D-24, 6-mg/240-mg (Treatment B)		DL and Pseudoephedrine (Treatment C)	
Parameter	Units	Mean	%CV	Mean	%CV	Mean	%CV
Cmax	ng/mL	1.91	44	2.35	43	2.28	40
Tmax	hr	4.69	52	4.33	50	3.87	67
AUC(tf)	ng·hr/mL	50.7	62	57.8	74	52.7	74
tf	hr	108	16	109	16	111	14
AUC(I)	ng·hr/mL	53.8	94	62.2	95	57.3	101

Table 4.2.6. Relative Bioavailability and 90 % Confidence Interval for DL (Study # P001813)

Treatment Ratio	Parameter	Estimate of Bioavailability (%)	90% Confidence Interval
	DL (n=42)		
DL D-24 (5-mg/240-mg) tablet/ 5-mg DL tablet plus PSE tablet administered concomitantly	AUC(tf) AUC(I) Cmax	92 91 83	83-101 83-100 75-91
DL D-24 (6-mg/240-mg) tablet/ 5-mg DL tablet plus PSE tablet administered concomitantly	AUC(tf) AUC(I) Cmax	106 105 102	96-116 96-116 93-112

Table 4.2.7. Relative Bioavailability and 90 % Confidence Interval for 3-OH DL (Study # P001813)

		3-OH DL (n=42)					
		DL D-24, 5-mg/240-mg (Treatment A)		DL D-24, 6-mg/240-mg (Treatment B)		DL and Pseudoephedrine (Treatment C)	
Parameter	Units	Mean	%CV	Mean	%CV	Mean	%CV
Cmax	ng/mL	0.77	28	1.00	39	0.93	31
Tmax	hr	6.67	52	6.12	48	5.68	58
AUC(tf)	ng·hr/mL	26.5	29	32.8	35	30.1	30
tf	hr	116	8	118	6	118	5
AUC(I)	ng·hr/mL	28.7	31	35.3	35	32.2	29

Table 4.2.8. Relative Bioavailability and 90 % Confidence Interval for 3-OH DL (Study # P001813)

3-OH DL (n=42)			
Treatment Ratio	Parameter	Estimate of Bioavailability (%)	90% Confidence Interval
DL D-24 (5-mg/240-mg) tablet/ 5-mg DL tablet plus PSE tablet administered concomitantly	AUC(tf) AUC(I) Cmax	88 89 83	83-94 83-94 77-90
DL D-24 (6-mg/240-mg) tablet/ 5-mg DL tablet plus PSE tablet administered concomitantly	AUC(tf) AUC(I) Cmax	108 108 105	101-115 101-115 98-114

What are the Main Conclusions from Study # P01813?

- Relative to the DL 5-mg tablet, the 5 mg DL/240 mg PSE tablet met the 80%-125% bioequivalence limits for AUC **but not for Cmax,** whereas the 6/240-mg tablet was bioequivalent to the DL 5-mg tablet based on both Cmax and AUC values
- For 3-OH DL, the 90% CI was within 80%0125%b for AUC, but not for Cmax.
- As the previous study, the 90% CI for the PSE was within 80%-125% for both Cmax and AUC.

- Relative to the PSE 240 mg DL tablet, the 5 mg/240 mg PSE tablet and the DL 6 mg/240 mg PSE tablet met the 80%-125% BE limit for both Cmax and AUC.

Study # PO1981 (single dose BE for different *in vitro* rates for PSE)

Objectives:

The primary objective of this study is to determine the BE and bioavailability of PSE from the standard DL D-24 formulation relative to PSE from the DL D-24 formulations with different *in vitro* dissolution rates: fast, slow, and very fast.

- Clinical DL D-24 (5 mg/240mg DL PSE) formulation
- DL D-24 formulation containing 6 mg of DL (6mg DL/240 mg PSE)
- DL 5 mg plus concomitantly administered PSE 240 ER formulation.

Design:

Four arms crossover study as follows:

Treatment A: Standard formulation: DL D-24 (5mg DL/240 mg PSE) ER tablet

Treatment B: Fast: DL D-24 (6 mg DL/240mg PSE) ER tablet

Treatment C: Slow: DL D-24 (5 mg DL/240mg PSE) ER tablet

Treatment D: very fast DL D-24 (6 mg DL/240mg PSE) ER tablet

Population:

20 healthy subjects (male and females)

Results:

Figure 4.2.10. Mean PSE Plasma Profiles (Treatments A, B, C, and D, Study # P01981)

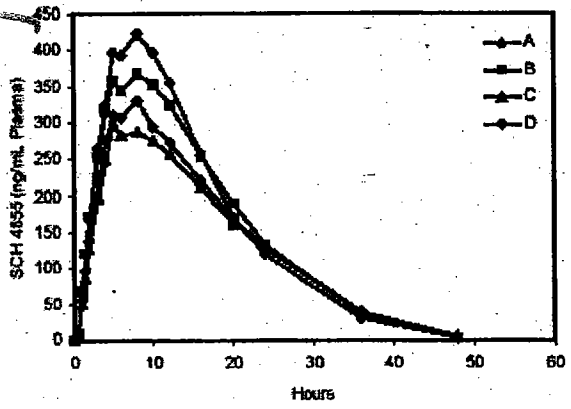

Table 4.2.9. PK of PSE (Study # P01981)

Treatment	Pharmacokinetic Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUC(tf) (ng·hr/mL)	AUC(I) (ng·hr/mL)	tf (hr)
A (Standard)	367[a] (22)	7.53[a] (30)	6701[a] (22)	6941[a] (21)	39.8[a] (14)
B (Fast)	406[a] (19)	7.74[a] (38)	7267[a] (19)	7560[a] (19)	37.9[a] (12)
C (Slow)	329 (13)	7.10 (36)	6190 (27)	6514 (27)	39.0 (20)
D (VeryFast)	443 (23)	7.75 (26)	7451 (25)	7645 (25)	39.0 (14)

a: n=19.

Table 4.2.10. 90% Confidence Interval for PSE (Study # P001981)

Comparison		Relative Bioavailability (%)	Confidence Interval (%)
Fast/Standard	AUC(tf)	109	99-119
	AUC(I)	109	100-120
	Cmax	111	104-120
Slow/Standard	AUC(tf)	89	81-97
	AUC(I)	90	82-99
	Cmax	90	84-96
Very Fast/Standard	AUC(tf)	111	101-121
	AUC(I)	109	100-120
	Cmax	120	112-129

What are the Main Conclusions from Study # P01981?

- Overall, the very fast formulation appeared to exhibits consistently higher PSE levels than other tested formulations.
- Accordingly, the 90% CI for the Cmax for the very fast formulation was outside the 80%-125% limits, whereas the AUC passed.

Study # PO0441 (Effect of Food):

Objectives:

The primary objective of this study is to determine the food effect on the bioavailability of DL, 3-OH DL, and PSE following DL D-24.

Design:

Two arms crossover study as follows:

Treatment A: DL D-24 after overnight fast

Treatment B: DL D-24 after high fat, high-caloric breakfast

Population:

38 healthy subjects (male and females)

Results:

Figure 4.2.11. Mean DL Plasma Profiles (Fed/fasted, Study # P00441)

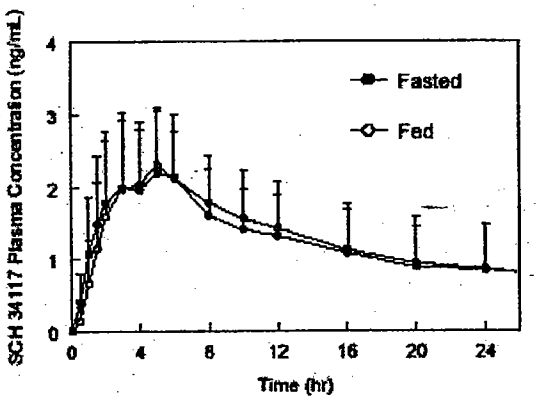

Figure 4.2.12. Mean 3-OH DL Plasma Profiles (Fed/fasted, Study # P00441)

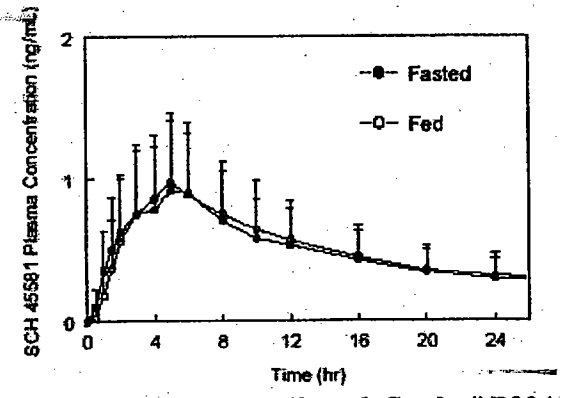

Figure 4.2.13. Mean PSE Plasma Profiles (Fed/fasted, Study # P00441)

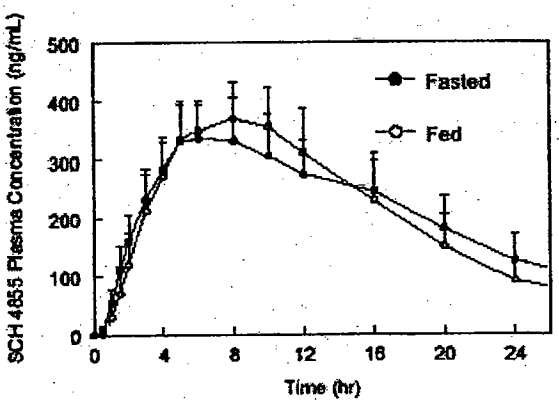

Table 4.2.11. PK of DL, 3-OH, and PSE (Study # P00441)

Treatment	Mean (%CV) Pharmacokinetic Parameters (n=36)				
	Cmax (ng/mL)	Tmax (hr)	AUC(tf) (ng·hr/mL)	AUC(I) (ng·hr/mL)	t½ (hr)
DL					
Fasted	2.50 (39)	5.69 (84)	64.9 (79)	83.8 (118)	29.6 (79)
Fed	2.55 (36)	5.39 (54)	66.6 (82)	83.7 (111)	29.0 (74)
3-OH DL					
Fasted	0.980 (56)	5.53 (26)	24.6 (45)	27.4 (39)	44.3 (123)
Fed	1.01 (50)	5.14 (26)	25.3 (46)	28.8 (36)[a]	40.3 (69)[a]
Pseudoephedrine					
Fasted	358 (19)	7.04 (19)	6842 (24)	7072 (23)	7.04 (19)
Fed	386 (17)	5.92 (15)	6313 (22)	6475 (22)	5.92 (15)

a: n=35.

Table 4.2.12. 90 % Confidence Interval for PSE (Study # P00441)

Comparison		Relative Bioavailability (%)	90% Confidence Interval
DL (n=36)			
Fed/Fasted	AUC(I)	102	97.0-107
Fed/Fasted	Cmax	104	96.0-113
3-OH DL (n=36)			
Fed/Fasted	AUC(I)[a]	102	97.0-107
Fed/Fasted	Cmax	105	99.0-114
Pseudoephedrine (n=36)			
Fed/Fasted	AUC(I)	92.0	87.0-97.0
Fed/Fasted	Cmax	108	104-113

a: n=35.

What are the Main Conclusions from Study # P00441?

- Food did not show any effect on the bioavailability of any of the formulation components: DL, 3-OH, and PSE.
- Accordingly, the 90% CI for both Cmax and AUC for the three components were within 80%-125% limits.
- There was a noticeable variability in the data as the %CV for Cmax and AUC ranged from 15% to 118%.

Study # PO0884 (Multiple Dose):

Objectives:

The primary objective of this study is to determine the PK profile of DL, 3-OH DL, and PSE following daily administration of DL D-24 for 14 days.

Design:

Open label, multiple-dose, and steady-state study.

Population:

18 healthy subjects (male and females)

Results:

Figure 4.2.14. Mean DL (close circles) and 3-OH DL (open circles) Plasma Profiles after Multiple Dose Administration (Study # P00884)

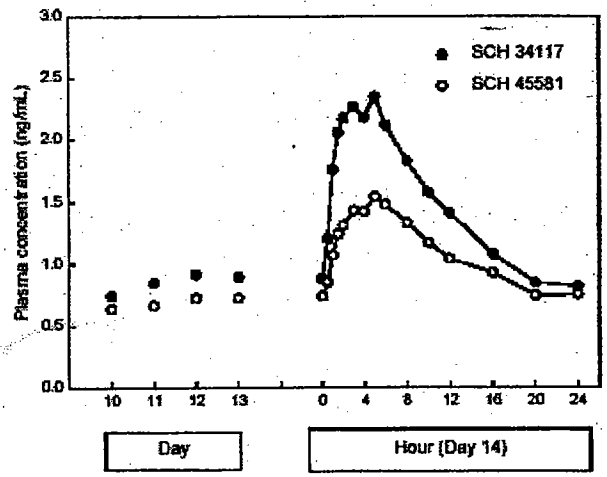

Figure 4.2.15. Mean PSE Plasma Profile after Multiple Dose Administration (Study # P00884)

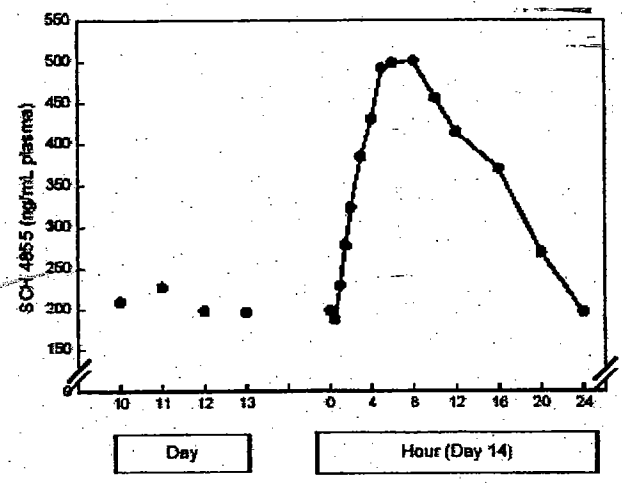

Table 4.2.12. Mean Plasma Cmin of DL and 3-OH DL after Multiple Dose Administration (Study # P00884)

Days[a]	Mean Cmin (ng/mL)	%CV
DL		
10	0.739	39
11	0.847	35
12	0.917	32
13	0.896	37
14	0.880	39
3-OH DL		
10	0.635	32
11	0.664	30
12	0.724	24
13	0.725	28
14	0.739	31

a: Predose.

Table 4.2.13. Mean PK Parameters of DL and 3-OH DL at Steady State (Day 14) (Study # P00884)

Cmax (ng/mL)		Tmax (hr)		Cmin (ng/mL)		Cavg (ng/mL)		AUC(0-24 hr) (ng·hr/mL)		% Fluctuation	
Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
DL											
2.44	35	3.68	39	0.788	39	1.45	34	34.8	34	115	14
3-OH DL											
1.56	20	4.65	26	0.689	27	1.07	21	25.7	21	82.9	18

Table 4.2.14. Mean Plasma Cmin of PSE after Multiple Dose Administration (Study # P00884)

Day[a]	Mean Cmin (ng/mL)	%CV
10	209	44
11	227	37
12	198	36
13	196	37
14	198	46

a: Predose.

Table 4.2.15. Mean PK Parameters of PSE at Steady State (Day 14) (Study # P00884)

Cmax (ng/mL)		Tmax (hr)		Cmin (ng/mL)		Cavg (ng/mL)		AUC(0-24 hr) (ng·hr/mL)		% Fluctuation	
Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
523	27	6.65	21	161	51	366	29	8795	29	102	22

What are the Main Conclusions from Study # P00884?

- Steady state concentration for DL and 3-OH was attained on Day 12
- Steady state concentration for PSE was attained on Day 10

Special Population:

- No special population studies such as hepatic and renal impairment or elderly were conducted for this product.

- It should be noted, however, in the current Clarinex® label, the starting dose of 5 mg every other day is recommended in patients with liver or renal impairment.

4.3 Consult Review (Pharmacometric)

Not applicable.

4.4 Filing Memo

Clinical Pharmacology and Biopharmaceutics Filing Memo

NDAs: 21-605	**Date of Submission:** April 30, 2004 **(Original)**
Generic Name	Desloratadine 5mg/Pseduophedrine sulfate 240 mg
Brand Name:	**CLARINEX-D® 24 HOUR**
Formulations:	Tablet
Route of Administration:	Oral
Indication:	Allergic Rhinitis and Nasal Congestion
Type of Submission:	Original NDA
Sponsor:	Schering Corporation, Kenilworth, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.
Date of Submission:	April 30, 2004
Date Received:	May 10, 2004
Review Date:	May 13 2004
First Draft	May 21, 2004
Second Draft	June 17, 2004
DFS Draft:	June 18, 2004

Background:

This is an original NDA for Clarinex-D® 24 hour extended release "combination" product tablets containing 5 mg desloratadine (DL) and 240 mg Pseuduoephedrine (PSE). The DL component of the tablet is formulated as immediate release coating, whereas the PSE is as extended release tablet core. The proposed indications are for the relief of symptoms of allergic rhinitis and nasal congestion.

What is the Rationale of the Combination Product?

Desloratadine (DL) is a major active metabolite of loratadine. It is currently marketed under the trade name Clarinex for the relief of the nasal and non-nasal symptoms of allergic rhinitis and chronic idiopathic urticaria in patients 12 years of age and older. In terms of formulation, it is currently available as film coated tablets and orally-disintegrating tablets (REDITABS and CLARITIN D-12).

It is believed that DL is considered to be primarily responsible for loratadine activity. Loratadine (Claritin) is currently marketed as tablet and syrup. DL appears to exhibit less first-pass metabolism and a longer plasma elimination half-life than loratadine. On the other hand, PSE is widely used as over-the counter (OTC) oral and nasal decongestant products. Its safety and efficacy profiles are well established.

Claritin® D-24 (loratadine 10 mg/PSE 240 mg) is currently marketed worldwide, including the US, for the treatment of seasonal allergic rhinitis. Based on the favorable PK characteristic and safety profiles of DL over loratadine, the sponsor believe that the proposed combination of DL and PSE (Clarinex-D® 24) would be an ideal combination product for the proposed indication. The safety, efficacy, and PK of DL were submitted in Clarinex NDA # 21-165.

The current NDA further characterizes the PK and safety of DL and PSE following administration of DL D-24 (DL 5mg/PSE 240 mg), DL, and PSE.

What Studies Are Submitted in the Current NDA:

In this NDA five clinical pharmacology studies were submitted which enrolled 154 adult subjects and two Phase III clinical studies (**Tables 1 and 2**). In this memo, the focus will be mainly on the clinical pharmacology studies as will be briefly summarized in the next section. The formulations used in the clinical pharmacology and clinical trials are listed in **Tables 3** and **4**.

The clinical pharmacology studies are grouped as follows:

- One bioequivalency (BE) for the clinical formulation of DL D-24 (Study # P00439).
- One BE study of DL D-24 components and both the clinical DL D-24 formulation and a D-24 formulation containing 6 mg of DL and 240 mg PSE (study # P01813).
- One bioavailability study for DL D-24 formulation containing PSE cores with altered *in vitro* dissolution rate (Study # P01981).
- One effect of food study on DL D-24 (Study # P00441).
- One multiple (repetitive) dose study to characterize the PK of DL D-24 (Study # P00884).

In all PK studies, the plasma levels of DL, 3-OH DL (major metabolite), and PSE were monitored.

According to the sponsor, the following main conclusions were made from these clinical pharmacology studies:

- Food had no effect on the absorption of DL D-24
- Steady state of all 3 analytes (DL, 3-OH DL, and PSE) were reached within 12 days of dosing.
- The percent fluctuation in multiple-dose study was consistent with that of a once-daily formulation.
- The Cmax and AUC of DL and 3-OH DL for the combination product was approximately 15%-20% lower than after DL tablet.
- The combination product was bioequivalent to the monoproduct with respect to PSE.
- No gender differences in PK of DL.
- Different *in vitro* dissolution profiles had no effect on the *in vivo* performance of PSE. However, the formulation with the very fast *in vitro* dissolution rate was not bioequivalent to the standard formulation.
- A phenotypic polymorphism in the DL metabolism was also observed in these studies as was previously observed in the pending NDA for DL Syrup (NDA # 21-300).

None of the above conclusions can be verified at this time until the review is completed.

Table 1: List of Clinical Pharmacology Studies Submitted in the NDA

Study Title/Description	Protocol Number Investigator (Starting Date)	Number of Subjects	Age Range (yr) Sex Distr. (M/F)[a] Ethnic Distr.[b]	Treatment, Dose and Dosing Frequency
A. Bioavailability/Bioequivalence Studies				
SCH 483: Bioequivalence of Desloratadine and Pseudoephedrine Following Single-Dose Administration of DL D-24, Desloratadine 5-mg, and Pseudoephedrine 240-mg **Type of Study:** Single-dose, randomized, open-label, three-way crossover study. **Report Location:** Vol.: 1.14 **Data Listings:** Vol: N/A	P00439 J. Herron, MD (8/4/1999)	36	21-45 36M 24B/12C	• Single dose of DL D-24 (SCH 483) (5-mg/240-mg) extended release tablet. • Single dose of DL (SCH 34117) (5 mg) tablet. • Single dose of pseudoephedrine (SCH 4856) (240 mg) extended release tablet.
SCH 483: Bioequivalency of Desloratadine and Pseudoephedrine Following Single-Dose Administration of DL D-24 (5-mg), DL D-24 (6-mg), and Desloratadine 5-mg and Pseudoephedrine 240-mg Given Concomitantly **Type of Study:** Single-dose, randomized, open-label, three-way crossover. **Report Location:** Vol.: 1.23 **Data Listings:** Vol.: N/A	P01813 J. Herron, MD (3/2/2000)	42	18-45 21M/21F 37C/4B/1H	• Single dose of DL D-24 (SCH 483) (5-mg/240-mg) extended release tablet. • Single dose of DL D-24 (SCH 483) (6-mg/240-mg) extended release tablet. • Single dose of DL (SCH 34117) (5-mg) tablet plus a single dose of pseudoephedrine sulfate (SCH 4855) (240 mg) extended release tablet.
SCH 483: The Bioavailability of Pseudoephedrine From Controlled-Release (24-Hour) Formulations: A single-Dose Four-Way Crossover Study **Type of Study:** Single-dose, randomized, open-label, four-way crossover study. **Report Location:** Vol: 1.28 **Data Listings:** Vol: N/A	P01981 K. Lasseter, MD (8/25/2000)	20	18-45 13M/7F 5C/1B/14H	• Single dose of DL D-24 (SCH 483) (5-mg/240-mg standard dissolution batch) extended release tablet. • Single dose of DL D-24 (SCH 483) (5-mg/240-mg fast dissolution batch) extended release tablet. • Single dose of DL D-24 (SCH 483) (5-mg/240-mg slow dissolution batch) extended release tablet. • Single dose of DL D-24 (SCH 483) (6-mg/240-mg very fast dissolution batch) extended release tablet.

Table 1 (continued): List of Clinical Pharmacology Studies Submitted in the NDA

Study Title/Description	Protocol Number Investigator (Starting Date)	Number of Subjects	Age Range (yr) Sex Distr. (M/F)[a] Ethnic Distr.[b]	Treatment, Dose and Dosing Frequency
B. Bioavailability/Human Pharmacokinetic Studies				
SCH 483: Influence of Food on the Oral Bioavailability of DL D-24 Administered to Healthy Subjects: A Two-Way Crossover Study **Type of Study:** Single-dose, randomized, open-label, two-way crossover study **Report Location:** Vol.: 1.18 **Data Listings:** Vol: N/A	P00441 T. Marbury, MD (8/2/1999)	38	19-44 27M/11 F 24C/11B/3H	• Single-dose of DL D-24 extended release tablet (SCH483) (5-mg/240-mg) under fed or fasted conditions.
SCH 483: The Multiple-Dose Pharmacokinetics of DL D-24 **Type of Study:** Multiple-dose, open-label study **Report Location:** Vol.: 1.21 **Data Listings:** Vol: N/A	P00884 C. Johnson, MD (11/22/1999)	18	21-45 15M/3F 14C/4B	• One DL D-24 (SCH 483) (5-mg/240-mg) extended-release tablet once daily x 14 days.

a: M=Male, F=Female.
b: C=Caucasian, B=Black, H=Hispanic, O=Other.

For detail of the phase III clinical trials, please see the Medical Officer's review. The sponsor conducted two identical Phase III studies as summarized in **Table 2.**

Table 2: Phase III Clinical Trials

Study Number Study Dates Study Centers	Study Design	Numbers of Subjects: (Randomized/Efficacy -Evaluable)[a] Age Range (Years) Sex Distribution
P01875 Aug 2000 to Dec 2000 47 centers in United States	Multicenter, Double-Blind, Double-Dummy, Active-controlled, Parallel-group, Efficacy and Safety Study: DL D-24 QD and DL D-24 AF QD versus DL 5-mg QD and PSE 240-mg QD for 15 days	1495/1410 12-78 527 M, 968 F
P01884 Aug 2000 to Dec 2000 47 centers in United States	Multicenter, Double-Blind, Double-Dummy, Active-controlled, Parallel-group, Efficacy and Safety Study: DL D-24 QD and DL D-24 AF QD versus DL 5-mg QD and PSE 240-mg QD for 15 days	1357/1270 11-78 516 M, 841 F

AF=Alternate Formulation; QD=Once Daily; M=Male; F=Female.
a: All analyses of efficacy included all randomized subjects who received at least one dose of study medication and had both Baseline and some postbaseline data. Confirmatory analyses of primary efficacy included all subjects in the efficacy-evaluable subset.

According to the sponsor, the two formulations, DL D-24 and DL D-24 AF (alternative formulation), used in these studies differed only by a slight modification in the quantity of some of the excipients in the film coat. The details of these differences and for all formulations will be discussed in the review. The main objective of these studies was to evaluate the safety and efficacy of DL D-24 given once daily compared to each component given alone.

Table 3: Formulations Used in Clinical Pharmacology Studies

PROTOCOL NUMBER	DRUG PRODUCT BATCH NUMBER	DATE OF MANUFACTURE	TABLET CORE LOT NUMBER	BATCH SIZE APPROX. TABLET	DRUG SUBSTANCE* LOT NUMBER
P00439	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRO-98-13M1 / DL
P00441	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRO-98-13M1 / DL
P00584	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRO-98-13M1 / DL
P01813	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRO-98-13M1 / DL
P01981	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRO-98-13M1 / DL

Table 4: Formulations Used in Phase III Studies

PROTOCOL NUMBER	DRUG PRODUCT BATCH NUMBER	DATE OF MANUFACTURE	TABLET CORE LOT NUMBER	BATCH SIZE APPROX. TABLET	DRUG SUBSTANCE* LOT NUMBER
P01875	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRO-98-13M1 / DL
P01884	75882-056	27APR1999	9-DCSS-229		C-00180 / PSE C-00181 / PSE IRO-98-13M1 / DL

*Note: PSE = Pseudoephedrine Sulfate USP and DL = Desloratadine

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Summary of the Individual PK Studies:

As stated above, only the clinical pharmacology studies will be briefly discussed in this filing memo. The general design for these studies was follows:

- The screening was conducted at approximately 3 weeks prior to each study.
- Subjects were fasted overnight and until 4 hours after each treatment, except for the food effect study.
- The washout period was at least 10 days, except for study # P01981 (different *in vitro* dissolution rates for PSE SE tablets) in which the washout period was 7 days.
- The PK samples were collected at the following time points: baseline (0 hour), 0.5, 1. 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120 hours postdose. However, for study # P01981 blood was collected until 48 hours.

1. Study # P00439 (single dose BE):

Objectives:

The primary objective of this study is to determine the BE of DL, 3-OH DL, and PSE following a single dose administration of DL D-24, DL- 5mg, and PSE 240 mg.

Design:

Three arms crossover study as follows:

Treatment A: One DL D-24 (5mg DL/240 mg PSE)

Treatment B: One DL 5 mg tablet

Treatment C: One 240 mg PSE tablet (oval extended-release PSE cores from Claritin ® D 24 coated with placebo Claritin® D-24 coat).

Population:

36 healthy subjects (males only)

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Results:

Figure 1. Mean DL Plasma Profiles (Study # P00439)

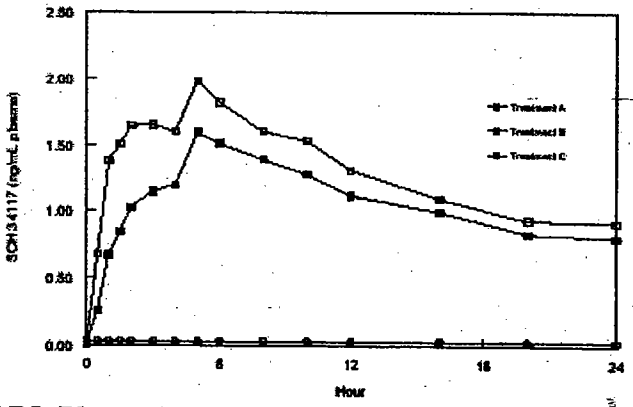

Figure 2. Mean 3-OH DL Plasma Profiles (Study # P00439)

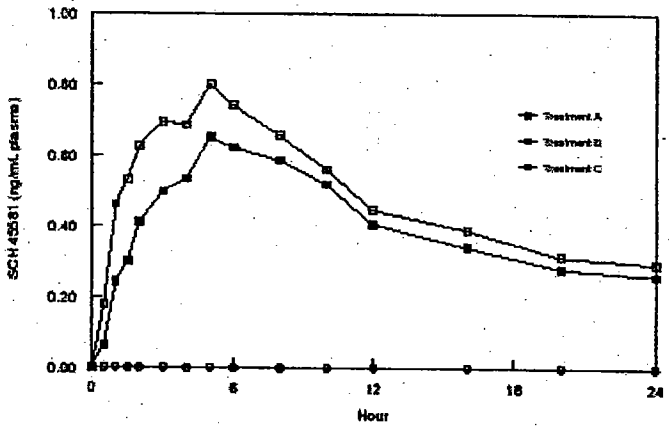

Figure 3. Mean PSE Plasma Profiles (Study # P00439)

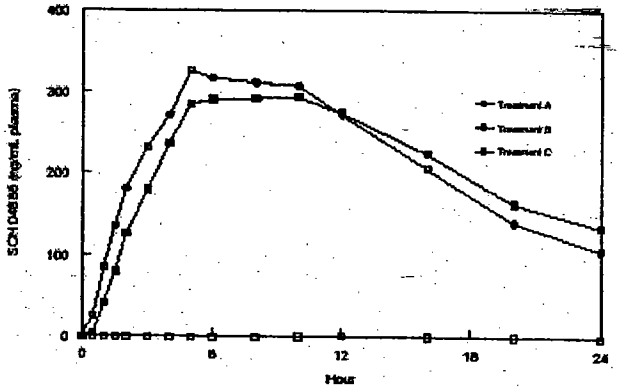

Table 5. PK of DL and 3-OH DL (Study # P00439)

		DL			
		DL D-24 5-mg/240-mg (Treatment A)		DL 5-mg (Treatment B)	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	1.79	36	2.23	35
Tmax	hr	6.78	57	5.10	53
AUC(tf)	ng·hr/mL	61.1	95	72.5	95
tf	hr	105	19	105	26
AUC(I)	ng·hr/mL	54.6[a]	121	63.3[a]	114
t½	hr	23.7[a]	37	23.5[a]	35
		3-OH DL			
		DL D-24 5-mg/240-mg (Treatment A)		DL 5-mg (Treatment B)	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	0.695	59	0.832	55
Tmax	hr	6.09[b]	33	4.96[b]	31
AUC(tf)	ng·hr/mL	19.6	51	22.6	49
tf	hr	103	30	103	26
AUC(I)	ng·hr/mL	24.4[c]	33	28.0[c]	30
t½	hr	29.6[c]	13	29.5[c]	14

a: n=32.
b: n=35 (all 3-OH DL concentrations for subject 36 were below the LOQ).
c: n=30.

Table 6. Relative Bioavailability and 90 % Confidence Interval for DL and 3-OH DL (Study # P00439)

Analysis With All Subjects Included			
Treatment Ratio	Parameter	Estimate of Bioavailability	90% Confidence Interval
DL (n=36)			
DL D-24 tablet/ DL 5-mg tablet	AUC(tf)	85.0	78-92
	Cmax	80.2	75-86
3-OH DL (n=36)			
DL D-24 tablet/ DL 5-mg tablet	AUC(tf)	81.2	72-92
	Cmax	80.3	75-86

Table 7. PK of PSE (Study # P00439)

		Pseudoephedrine			
		DL D-24 5-mg/240-mg		Oval-Extended Release PSE Cores from Claritin D-24	
Parameter	Units	Mean	%CV	Mean	%CV
Cmax	ng/mL	328	25	349	18
Tmax	hr	8.42	34	7.36	36
AUC(tf)	ng·hr/mL	6438	42	6225	39
tf	hr	44.0	37	40.0	26
AUC(I)	ng·hr/mL	6780	40	6452	37
t½	hr	10.3	148	7.25	22

Table 8. Relative Bioavailability and 90 % Confidence Interval for PSE (Study # P00439)

Analysis With All Subjects Included			
Treatment Ratio	Parameter	Estimate of Bioavailability (%)	90% Confidence Interval
Pseudoephedrine (n=36)			
DL D-24 tablet/ 240-mg pseudoephedrine sulphate extended-release core	AUC(tf)	102	94-112
	Cmax	93	89-97

What are the Main Conclusions from Study # P00439?

- The 90% CI for both Cmax and AUC of DL and 3-OH DL were outside the bioequivalence (BE) limits of 80%-125%.
- However, the 90% for the PSE was within 80%-125% for both Cmax and AUC.
- It appears that there is data integrity issue with this study. PSE was detected in relatively high concentrations in two subjects who receive 5 mg DL only containing tablets (Treatment B). The PSE plasma concentration ranged from approximately 14 ng/ml to 63 ng/ml. The sponsor stated that the reason for these measurable concentrations of PSE is unknown.
- The exposure for DL and 3-OH DL as determined by Cmax and AUC following DL D-24 tablet was lower by approximately 15% to 20% than that after DL 5 mg tablet.

Study # P01813 (Single Dose BE-6mg DL/240 mg PSE):

Objectives:

The primary objective of this study is to determine the BE of DL, 3-OH DL, and PSE following a single dose administration of the formulations:

- Clinical DL D-24 (5mg DL/240 mg PSE) formulation
- DL D-24 formulation containing 6 mg of DL (6 mg DL/240 mg PSE)
- DL 5 mg plus concomitantly administered PSE 240 ER formulation.

Design:

Three arms crossover study as follows:

Treatment A: One DL D-24 (5mg DL/240 mg PSE)

Treatment B: One DL D-24 (6 mg DL/240mg PSE) ER tablet

Treatment C: One DL 5 mg tablet plus one PSE 240 mg ER tablet

Population:

42 healthy subjects (male and females)

Results:

Figure 4. Mean DL Plasma Profiles (Treatments A and C, Study # P01813)

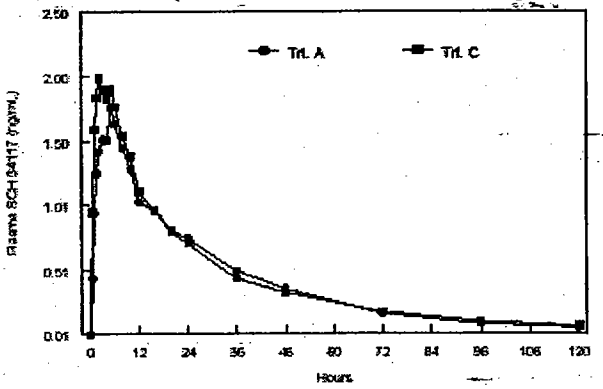

Figure 5. Mean DL Plasma Profiles (Treatments B and C, Study # P01813)

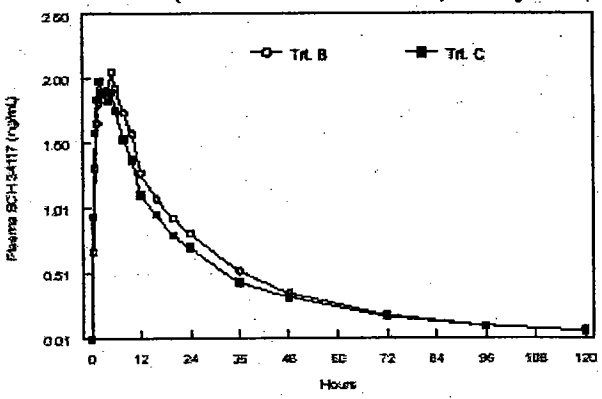

Figure 6. Mean 3-OH DL Plasma Profiles (Treatments A and C, Study # P01813)

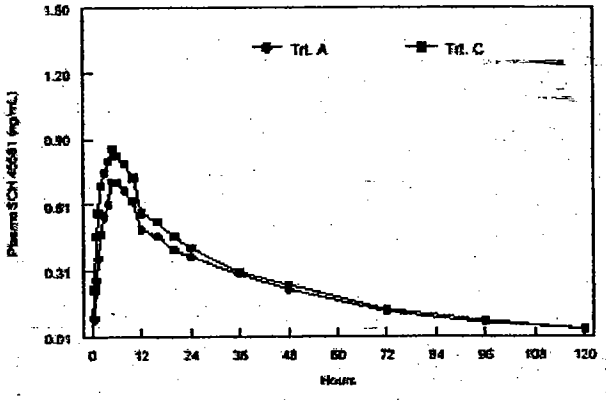

Figure 7. Mean 3-OH DL Plasma Profiles (Treatments B and C, Study # P01813)

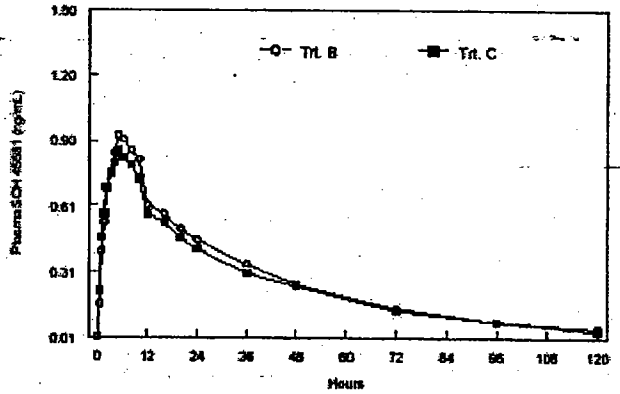

Figure 8. Mean PSE Plasma Profiles (Treatments A and C, Study # P01813)

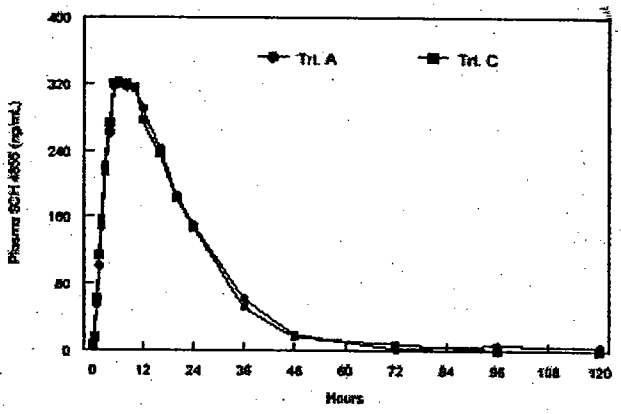

Figure 9. Mean PSE Plasma Profiles (Treatments B and C, Study # P01813)

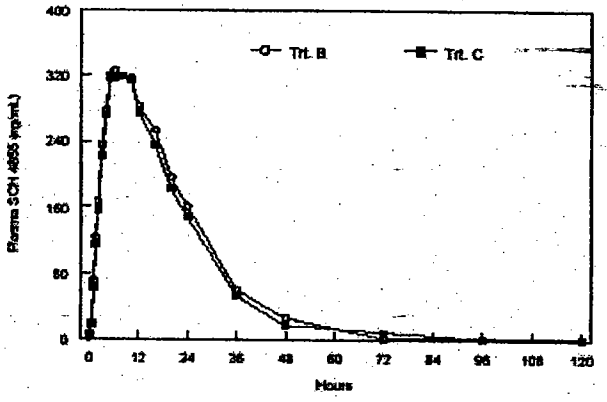

Table 9. PK of DL (Study # P01813)

		DL (n=42)					
		DL D-24, 5-mg/240-mg (Treatment A)		DL D-24, 6-mg/240-mg (Treatment B)		DL and Pseudoephedrine (Treatment C)	
Parameter	Units	Mean	%CV	Mean	%CV	Mean	%CV
Cmax	ng/mL	1.91	44	2.35	43	2.28	40
Tmax	hr	4.69	52	4.33	50	3.87	67
AUC(tf)	ng·hr/mL	50.7	82	57.8	74	52.7	74
tf	hr	108	16	109	16	111	14
AUC(I)	ng·hr/mL	53.8	94	62.2	95	57.3	101

Table 10. Relative Bioavailability and 90 % Confidence Interval for DL (Study # P001813)

Treatment Ratio	Parameter	Estimate of Bioavailability (%)	90% Confidence Interval
	DL (n=42)		
DL D-24 (5-mg/240-mg) tablet/ 5-mg DL tablet plus PSE tablet administered concomitantly	AUC(tf)	92	83-101
	AUC(I)	91	83-100
	Cmax	83	75-91
DL D-24 (6-mg/240-mg) tablet/ 5-mg DL tablet plus PSE tablet administered concomitantly	AUC(tf)	106	96-116
	AUC(I)	105	96-116
	Cmax	102	93-112

Table 11. Relative Bioavailability and 90 % Confidence Interval for 3-OH DL (Study # P001813)

		3-OH DL (n=42)					
		DL D-24, 5-mg/240-mg (Treatment A)		DL D-24, 6-mg/240-mg (Treatment B)		DL and Pseudoephedrine (Treatment C)	
Parameter	Units	Mean	%CV	Mean	%CV	Mean	%CV
Cmax	ng/mL	0.77	28	1.00	39	0.93	31
Tmax	hr	6.87	52	6.12	48	5.68	58
AUC(tf)	ng·hr/mL	26.5	29	32.8	35	30.1	30
tf	hr	116	8	118	6	118	5
AUC(I)	ng·hr/mL	28.7	31	35.3	35	32.2	29

Table 12. Relative Bioavailability and 90 % Confidence Interval for 3-OH DL (Study # P001813)

3-OH DL (n=42)			
Treatment Ratio	Parameter	Estimate of Bioavailability (%)	90% Confidence Interval
DL D-24 (5-mg/240-mg) tablet/ 5-mg DL tablet plus PSE tablet administered concomitantly	AUC(tf)	88	83-94
	AUC(I)	89	83-94
	Cmax	83	77-90
DL D-24 (6-mg/240-mg) tablet/ 5-mg DL tablet plus PSE tablet administered concomitantly	AUC(tf)	108	101-115
	AUC(I)	108	101-115
	Cmax	106	98-114

What are the Main Conclusions from Study # P01813?

- Relative to the DL 5-mg tablet, the 5 mg DL/240 mg PSE tablet met the 80%-125% bioequivalence limits for AUC **but not for Cmax,** whereas the 6/240-mg tablet was bioequivalent to the DL 5-mg tablet based on both Cmax and AUC values.
- For 3-OH-DL, the 90% CI was within 80%0125%b for AUC, but not for Cmax.
- As the previous study, the 90% CI for the PSE was within 80%-125% for both Cmax and AUC.

- Relative to the PSE 240 mg DL tablet, the 5 mg/240 mg PSE tablet and the DL 6 mg/240 mg PSE tablet met the 80%-125% BE limit for both Cmax and AUC.

Study # PO1981 (single dose BE for different *in vitro* rates for PSE)

Objectives:

The primary objective of this study is to determine the BE and bioavailability of PSE from the standard DL D-24 formulation relative to PSE from the DL D-24 formulations with different *in vitro* dissolution rates: fast, slow, and very fast.

- Clinical DL D-24 (5 mg/240mg DL PSE) formulation
- DL D-24 formulation containing 6 mg of DL (6mg DL/240 mg PSE)
- DL 5 mg plus concomitantly administered PSE 240 ER formulation.

Design:

Four arms crossover study as follows:

Treatment A: Standard formulation: DL D-24 (5mg DL/240 mg PSE) ER tablet

Treatment B: Fast: DL D-24 (6 mg DL/240mg PSE) ER tablet

Treatment C: Slow: DL D-24 (5 mg DL/240mg PSE) ER tablet

Treatment D: very fast DL D-24 (6 mg DL/240mg PSE) ER tablet

Population:

20 healthy subjects (male and females)

Results:

Figure 10. Mean PSE Plasma Profiles (Treatments A, B, C, and D, Study # P01981)

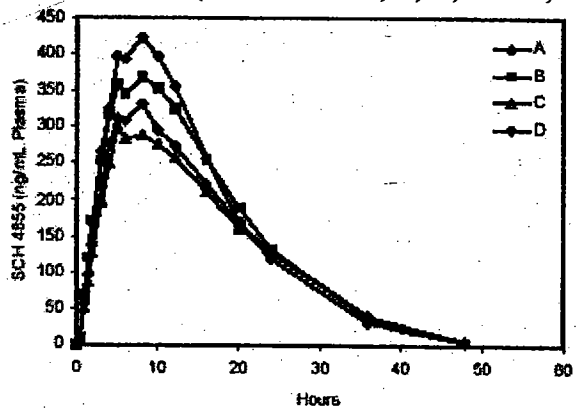

Table 13. PK of PSE (Study # P01981)

Treatment	Pharmacokinetic Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUC(tf) (ng·hr/mL)	AUC(I) (ng·hr/mL)	tf (hr)
A (Standard)	367[a] (22)	7.53[a] (30)	6701[a] (22)	6941[a] (21)	39.8[a] (14)
B (Fast)	406[a] (19)	7.74[a] (38)	7267[a] (19)	7560[a] (19)	37.9[a] (12)
C (Slow)	329 (13)	7.10 (36)	6190 (27)	6514 (27)	39.0 (20)
D (VeryFast)	443 (23)	7.75 (26)	7451 (25)	7645 (25)	39.0 (14)

a: n=19.

Table 14. 90% Confidence Interval for PSE (Study # P001981)

Comparison		Relative Bioavailability (%)	90% Confidence Interval
Fast/Standard	AUC(tf)	109	99-119
	AUC(I)	109	100-120
	Cmax	111	104-120
Slow/Standard	AUC(tf)	89	81-97
	AUC(I)	90	82-99
	Cmax	90	84-96
Very Fast/Standard	AUC(tf)	111	101-121
	AUC(I)	109	100-120
	Cmax	120	112-129

What are the Main Conclusions from Study # P01981?

- Overall, the very fast formulation appeared to exhibits consistently higher PSE levels than other tested formulations.
- Accordingly, the 90% CI for the Cmax for the very fast formulation was outside the 80%-125% limits, whereas the AUC passed.

Study # PO0441 (Effect of Food):

Objectives:

The primary objective of this study is to determine the food effect on the bioavailability of DL, 3-OH DL, and PSE following DL D-24.

Design:

Two arms crossover study as follows:

Treatment A: DL D-24 after overnight fast

Treatment B: DL D-24 after high fat, high-caloric breakfast

Population:

38 healthy subjects (male and females)

Results:

Figure 11. Mean DL Plasma Profiles (Fed/fasted, Study # P00441)

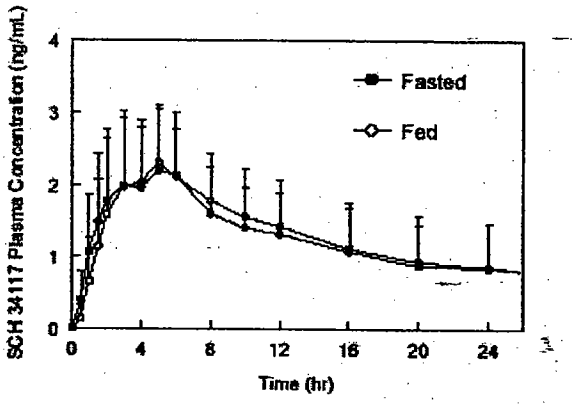

Figure 12. Mean 3-OH DL Plasma Profiles (Fed/fasted, Study # P00441)

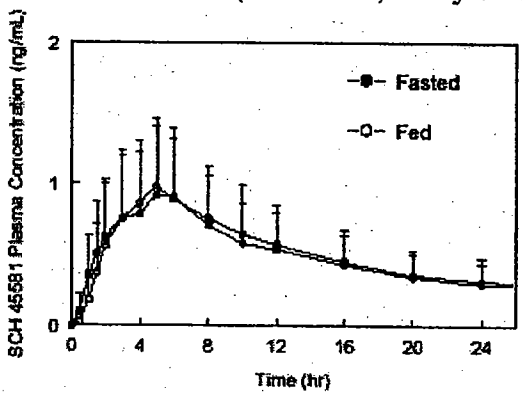

Figure 13. Mean PSE Plasma Profiles (Fed/fasted, Study # P00441)

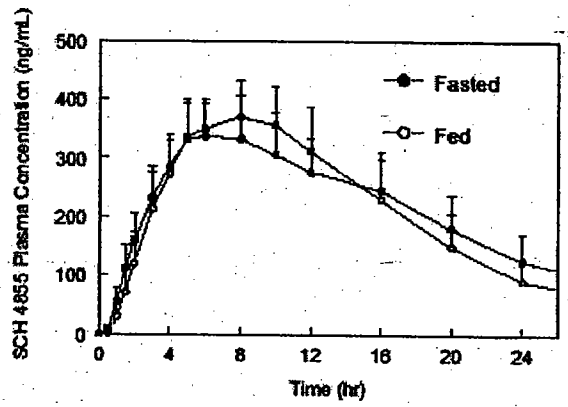

Table 15. PK of DL, 3-OH, and PSE (Study # P00441)

Treatment	Mean (%CV) Pharmacokinetic Parameters (n=36)				
	Cmax (ng/mL)	Tmax (hr)	AUC(tf) (ng·hr/mL)	AUC(i) (ng·hr/mL)	t½ (hr)
DL					
Fasted	2.50 (39)	5.69 (84)	64.9 (79)	83.8 (118)	29.6 (79)
Fed	2.55 (36)	5.39 (54)	66.6 (82)	83.7 (111)	29.0 (74)
3-OH DL					
Fasted	0.980 (56)	5.53 (26)	24.6 (45)	27.4 (39)	44.3 (129)
Fed	1.01 (50)	5.14 (26)	25.3 (46)	28.8 (36)[a]	40.3 (69)
Pseudoephedrine					
Fasted	358 (19)	7.04 (19)	6842 (24)	7072 (23)	7.04 (19)
Fed	386 (17)	5.92 (15)	6313 (22)	6475 (22)	5.92 (15)

a: n=35.

Table 16. 90 % Confidence Interval for PSE (Study # P00441)

Comparison		Relative Bioavailability (%)	90% Confidence Interval
DL (n=36)			
Fed/Fasted	AUC(i)	102	97.0-107
Fed/Fasted	Cmax	104	96.0-113
3-OH DL (n=36)			
Fed/Fasted	AUC(i)[a]	102	97.0-107
Fed/Fasted	Cmax	106	99.0-114
Pseudoephedrine (n=36)			
Fed/Fasted	AUC(i)	92.0	87.0-97.0
Fed/Fasted	Cmax	108	104-113

a: n=35.

What are the Main Conclusions from Study # P00441?

- Food did not show any effect on the bioavailability of any of the formulation components: DL, 3-OH, and PSE.
- Accordingly, the 90% CI for both Cmax and AUC for the three components were within 80%-125% limits.
- There was a noticeable variability in the data as the %CV for Cmax and AUC ranged from 15% to 118%.

Study # PO0884 (Multiple Dose):

Objectives:

The primary objective of this study is to determine the PK profile of DL, 3-OH DL, and PSE following daily administration of DL D-24 for 14 days.

Design:

Open label, multiple-dose, and steady-state study.

Population:

18 healthy subjects (male and females)

Results:

Figure 14. Mean DL (close circles) and 3-OH DL (open circles) Plasma Profiles after Multiple Dose Administration (Study # P00884)

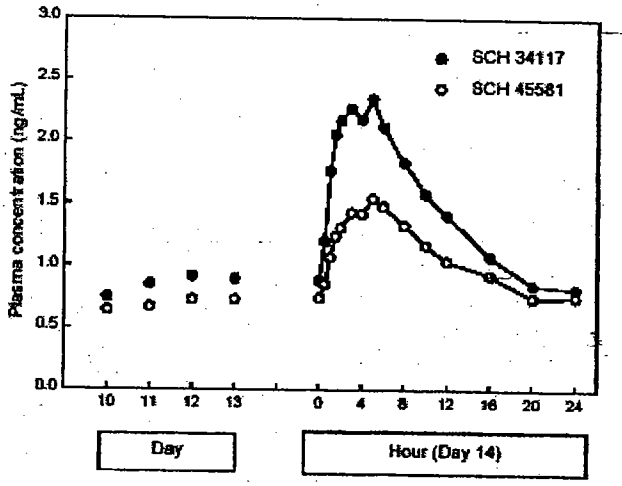

Figure 15. Mean PSE Plasma Profile after Multiple Dose Administration (Study # P00884)

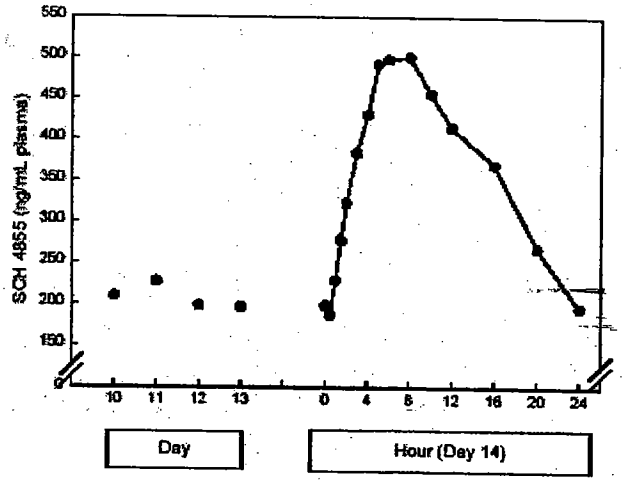

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Table 17. Mean Plasma Cmin of DL and 3-OH DL after Multiple Dose Administration (Study # P00884)

Days[a]	Mean Cmin (ng/mL)	%CV
DL		
10	0.739	39
11	0.847	35
12	0.917	32
13	0.896	37
14	0.880	39
3-OH DL		
10	0.635	32
11	0.664	30
12	0.724	24
13	0.725	28
14	0.739	31

a: Predose.

Table 18. Mean PK Parameters of DL and 3-OH DL at Steady State (Day 14) (Study # P00884)

Cmax (ng/mL)		Tmax (hr)		Cmin (ng/mL)		Cavg (ng/mL)		AUC(0-24 hr) (ng·hr/mL)		% Fluctuation	
Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
DL											
2.44	35	3.68	39	0.788	39	1.45	34	34.8	34	115	14
3-OH DL											
1.56	20	4.65	26	0.689	27	1.07	21	25.7	21	82.9	18

Table 19. Mean Plasma Cmin of PSE after Multiple Dose Administration (Study # P00884)

Day[a]	Mean Cmin (ng/mL)	%CV
10	209	44
11	227	37
12	195	36
13	196	37
14	198	46

a: Predose.

Table 20. Mean PK Parameters of PSE at Steady State (Day 14) (Study # P00884)

Cmax (ng/mL)		Tmax (hr)		Cmin (ng/mL)		Cavg (ng/mL)		AUC(0-24 hr) (ng·hr/mL)		% Fluctuation	
Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
523	27	6.65	21	161	51	366	29	8795	29	102	22

What are the Main Conclusions from Study # P00884?

- Steady state concentration for DL and 3-OH was attained on Day 12
- Steady state concentration for PSE was attained on Day 10

Special Population:

- No special population studies such as hepatic and renal impairment or elderly were conducted for this product.

- It should be noted, however, in the current Clarinex® label, the starting dose of 5 mg every other day is recommended in patients with liver or renal impairment.

General Comments:

- DSI inspection is recommended for this NDA. The reasons for this recommendation are:
    - Data integrity is in question in one of these studies (#P00439) as relatively high concentrations of PSE were observed in two subjects who received DL only tablets.
    - Study # P00439 is a pivotal BE/PK study.

Disclaimer:

None of the observation and data in the above summary review has been verified by the office of Clinical Pharmacology and Biopharmaceutics (OCPB). All conclusions and observations stated in this filing memo were based on the sponsor's statements and/or summary data. Therefore, no comments can be made at this time until all data are thoroughly reviewed. The purpose of this filing memo is only to list the content of the NDA with a synopsis of each study.

RECOMMENDATION:

The NDA is fileable. See also the attached filing form.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaulation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission	Information		Information
NDA Number	21-605	Brand Name	CLARINEX-D® 24 HOUR
OCPB Division I	HFD-870	Generic Name	Desloratadine 5mg/Pseudoephedrine Sulfate 240 mg
Medical Division	HFD-570	Drug Class	Antihistamine
OCPB Reviewer	Sayed (Sam) Al Habet, R.Ph., Ph.D.	Indication(s)	Seasonal Allergic rhinitis (SAR) and nasal congestion
OCPB Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.	Dosage Form	Tablet 5mg/240 mg
		Dosing Regimen	Once daily
Date of Submission	May 20, 2004	Route of Administration	Oral
Estimated Due Date of OCPB Review	February 20, 2005	Sponsor	Schering Corporation
PDUFA Due Date	March 20, 2005	Priority Classification	S
Division Due Date	March 1, 2005		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]		
solution as reference:				
alternate formulation as reference:	x	4		
Bioequivalence studies -				
traditional design; single / multi dose:	x	4		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		
Dissolution:	x	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	x	1?		
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
	5			

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**Yes**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**This is a new NDA for a combination drug product of the approved components: 5 mg Desloratadine (DL) and pseudoephedrine (PSE) sulfate 240 mg. The latter component is formulated as extended release core of the tablet. The sponsor conducted five BE/PK studies as summarized in this filing memo.** **DSI inspection is recommended. Data integrity is in question in one of these studies (#P00439) as relatively high concentrations of PSE were observed in two subjects who received DL only tablets.**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Sayed (Sam) Al Habet, R.Ph., Ph.D.**	
Secondary reviewer Signature and Date	**Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.**	

CC: NDA HFD-570, HFD-870 (Al Habet, Fadiran, Malinowski), CDR (B. Murphy, biopharm file)

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/s/

Sayed Al-Habet
2/3/05 11:41:15 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
2/3/05 11:59:19 AM
BIOPHARMACEUTICS
I concur.