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/s/

Feng Zhou
9/27/01 02:55:41 PM
BIOMETRICS

James Gebert
9/27/01 03:17:54 PM
BIOMETRICS
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-313

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review (FINAL)

NDA: 21-313

Date of Submission: July 29, 2005

Generic Name Desloratadine 2.5mg/Pseudoephedrine sulfate 120 mg

Brand Name: CLARINEX-D® 12 HOUR

Formulations: Tablet

Route of Administration: Oral

Indication: Allergic Rhinitis and Nasal Congestion

Type of Submission: Response to Approvable Letter

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: July 29, 2005

Review Date: December 20, 2005

First Draft January 5, 2006

DFS Version (Final)t: January 10, 2006

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1. Executive Summary:

1.1 Recommendation:

The sponsor's responses to the clinical pharmacology comments in the approvable letter are acceptable.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background:

This is a response to the approvable letter dated October 26, 2001. The following clinical pharmacology and biopharmaceutics comments were sent to the sponsor:

1. (Comment #22). "Submit a more complete analysis of the data to support a claim in the label for a lack of gender effect on the pharmacokinetics (PK) of pseudoephedrine (PSE). You are encouraged to pool all of the PSE pharmacokinetic data before making a statement of lack of gender effect on the PK on PSE. The analysis should be conducted taking into account the weight of the subjects."
2. (Comment # 23) "Provide more references and/or literature information to support the statement in the label regarding the metabolism and elimination of PSE. Also, include supporting evidence for the need for dose adjustment in renally impaired patients."
3. Comment # 24 "From the overall desloratadine pharmacokinetics database, it appears that a substantial subset of patients had significantly higher drug exposure (AUC) than most patients to desloratadine and very low level of 3-hydroxydesloratadine. The exposure to desloratadine resulting from multiple doses in adults who are poor metabolizers is estimated to be six- to nine-fold the median AUC in adults with apparent normal metabolism. Moreover, there are no data to identify the underlying cause of poor metabolism, and so there is no means of prospectively identifying those patients who may have such high levels of exposure to desloratadine. If these patients are inherently poor metabolizers of desloratadine, then the number of patients who experience those high exposure levels may be much greater, particularly if there is a deficient metabolic pathway involved that may be vulnerable to inhibition with concomitant medications.

You are encouraged to determine the mechanism accounting for higher levels of drug exposure observed in some patients, and to assess the potential for drug-drug interactions that might be expected based on the explanatory mechanism. You should also provide data from desloratadine and loratadine to justify the safety of these high levels of desloratadine exposure."

Rational for the Submission:

Based on the above comments the sponsor conducted appropriate studies to answer the above comments. The response to some of these comments was addressed in part in other submissions and in particular comment # 24 of the approvable letter which was extensively investigated in NDA # 21-300 for Clarinex Syrup. Therefore, the issue of drug safety and metabolism in a subset of poor metabolizers has been addressed and found acceptable by OCPB and the Clinical Division.

Due to several CMC related issues and deficiencies, the sponsor re-formulated to improve the stability of the IR layer of the product. As a complete response to the approvable letter and to establish a link between the original formulation that was used in Phase III study and the new formulation, the sponsor conducted four new PK studies including IVIVC analysis. The IVIVC analysis was conducted to set the specification for the extended release PSE component of the product. The focus of this review is on the four new PK studies and the IVIVC analysis.

What is the new Formulation?

According to the sponsor, pseudoephedrine sulfate (PSE) formulation is identical in all aspects to that described in NDA 21-605 for Clarinex D-24 Hour Tablets (See also CMC review). In the original NDA that was submitted in December 8, 2000, the stability data for the IR layer of the original formulation (Formula 3538) was found inadequate. In this NDA, the sponsor submitted a new formulation (Formula # 3775). The composition of the two formulations is shown in **Table 1**. Therefore, the sponsor conducted a study to establish the link between the old and the new formulation (Study P02040 is considered a pivotal study in this NDA).

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- IVIVC analysis using the data from the above study # P02043. This analysis was performed to further support the *in vitro* release specification.

What are the Main Findings?

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

- Following a single dose administration of one original formulation (# 3538) and the final-to-be marketed new formulation (#3775), the PK parameters were comparable for both formulations (Study # P02040, Table 2). In addition, the 90% CI for both Cmax and AUC of DL and 3-OH DL (active metabolite of DL) were within the bioequivalence (BE) limits of 80%-125% (Table 3).

Table 2. Mean (%CV) of PK Parameters Following a Single Dose of the Two Formulations (Study # P02040).

Parameter	Treatment A (original) Mean (%CV)			Treatment B (new) Mean (%CV)		
	DL	3-OH DL	PSE	DL	3-OH DL	PSE
Cmax (ng/mL)	1.03 (31)	0.41 (57)	254 (16)	1.09 (36)	0.43 (56)	263 (13)
Tmax (hr)	5.46 (78)	6.22 ^a (86)	7.28 (36)	4.48 (78)	5.34 ^b (38)	6.73 (41)
t½ (hr)	27.7 ^a (64)	31.9 ^c (32)	7.56 (20)	27.4 ^d (61)	31.3 ^a (25)	7.34 (23)
AUC(tf) (ng-hr/mL)	33.5 (79)	12.2 (54)	4161 (22)	31.6 (88)	12.6 (50)	4588 (25)
AUC(l) (ng-hr/mL)	36.0 ^a (110)	15.4 ^c (33)	4291 (23)	36.9 ^d (114)	15.5 ^a (34)	4745 (25)

Table 3. Relative bioavailability and the 90% CI (Study # P02040)

Protocol No. P02040

Parameter	Treatment B/Treatment A					
	DL		3-OH DL		PSE	
	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
Cmax	99.7	94.2-106	100	94.6-107	103	97.6-109
AUC(tf)	93.7	85.6-102	98.8	92.9-105	107	99.0-115
AUC(l)	98.4	92.7-104	99.1	93.3-105	107	99.3-115

- The steady state for DL, 3-OH DL, and PSE of the new formulation was achieved by Day 10 of BID dosing x 14 days in 18 healthy subjects (Study # P02041, Tables 4 and 5).

Table 4. Mean (%CV) of Cmin (Study # P02041).

Analyte	Day 10	Day 11	Day 12	Day 13	Day 14
DL	1.25 (34)	1.13 (32)	1.10 (36)	1.15 (35)	1.01 (35)
3-OH DL	0.83 (35)	0.77 (39)	0.74 (36)	0.83 (41)	0.67 (45)
PSE	316 (47)	287 (41)	289 ^a (51)	294 (38)	271 (45)

Table 5. Mean (%CV) Steady-State PK Parameters on Day 14 (Study # P02041).

Analyte	Period	Cmax (ng/mL)	Tmax ^a (hr)	Cavg (ng/mL)	AUC (ng-hr/mL)
DL					
	0-12 hr	1.71 (23)	5.0 (1.0-6.0)	1.37 (28)	16.4 (28)
	12-24 hr	1.50 (23)	2.0 (1.0-4.0)	1.24 (25)	14.9 (25)
3-OH DL					
	0-12 hr	1.00 (33)	5.0 (1.5-12)	0.854 (36)	10.2 (36)
	12-24 hr	0.924 (36)	3.0 (0-8)	0.807 (38)	9.69 (38)
PSE					
	0-12 hr	459 (29)	4.0 (1.5-8.0)	388 (33)	4658 (33)
	12-24 hr	447 (33)	4.0 (0-6.0)	361 (34)	4332 (34)

a: Median (minimum-maximum).

- Food had no effect on the PK parameters of DL, 3-OH DL, or PSE (Study # P02042, Tables 6 and 7).

Table 6. Mean (%CV) PK Parameters Under Fed and Fasting Conditions (Study # P02042).

Analyte	Treatment	Pharmacokinetic Parameters				
		Cmax (ng/mL)	Tmax ^a (hr)	AUC(tf) (ng-hr/mL)	AUC(l) (ng-hr/mL)	t _{1/2} (hr)
DL						
	Fasted ^b	1.13 (43)	5.00 (1.50-6.00)	20.9 (48)	21.8 (49)	20.6 (14)
	Fed	1.18 (41)	5.00 (1.50-6.00)	22.1 (46)	23.0 (47)	20.9 (15)
3-OH DL						
	Fasted ^b	0.51 (36)	5.00 (3.00-8.00)	12.7 (32)	14.1 (31)	30.6 (14)
	Fed	0.52 (33)	5.00 (3.00-8.00)	12.6 (27)	14.1 (26)	31.1 (14)
PSE						
	Fasted ^b	297 (26)	5.00 (3.00-10.0)	4274 (29)	4369 (28)	5.90 (18)
	Fed	305 (21)	5.00 (4.00-8.00)	3724 (24)	3840 (23)	5.32 (21)

a: Median (minimum-maximum).

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Table 7. Relative Bioavailability and 90% CI Under Fed and Fasting Conditions (Study # P02042).

Analyte	Comparison	Parameter	Ratio (%)	90% CI
DL				
	Fed/Fasted	AUC(l)	105	98-113
	Fed/Fasted	AUC(tf)	105	98-113
	Fed/Fasted	Cmax	106	97-115
3-OH DL				
	Fed/Fasted	AUC(l)	99.2	95-104
	Fed/Fasted	AUC(tf)	98.6	94-103
	Fed/Fasted	Cmax	102	95-109
PSE				
	Fed/Fasted	AUC(l)	88.2	85-92
	Fed/Fasted	AUC(tf)	87.1	84-91
	Fed/Fasted	Cmax	102	98-107

- Study P02043 was conducted in a four way crossover design with very fast, fast, slow, and standard dissolution rates. Two formulations of Clarinex D-12 (standard and slow batches) and two formulations of DL 5/120 (standard and fast batches) were administered in a random order to 20 healthy subjects. The DL 5/120 standard batch had a modified core with a fast dissolution rate in comparison to the DL D-12 formulation. Full PSE PK plasma concentration-time profiles were measured.

As expected, the Cmax of PSE following the fast batch was higher than other batches and hence the 90% CI limit was outside the 80% to 125% (Tables 8 and 9).

Table 8. Mean (%CV) PK Parameters of PSE (Study # P02043).

Treatment	Pharmacokinetic Parameters				
	Cmax (ng/mL)	Tmax ^a (hr)	AUC(tf) (ng-hr/mL)	AUC(l) (ng-hr/mL)	t½ (hr)
DL D-12 Standard Batch	283 (23)	5.00 (3.00-8.00)	3769 (22)	3848 (22)	5.42 (13)
DL 5/120 Standard Batch	317 (21)	5.00 (3.00-6.00)	3958 (26)	4054 (25)	5.21 (13)
DL 5/120 Fast Batch	358 (23)	4.00 (2.00-5.00)	3802 (25)	3898 (24)	5.13 (15)
DL D-12 Slow Batch	269 (27)	5.00 (3.00-10.00)	3608 (27)	3684 (26)	5.24 (13)

a: Median (minimum-maximum).

Table 9. Relative Bioavailability and 90% CI for PSE (Study # P02043).

Comparison	Parameter	Ratio (%)	90% CI
DL 5/120 Std/DL D-12 Std	AUC(tf)	104.2	99-110
	AUC(l)	104.7	99-110
	Cmax	111.8	107-117
DL D-12 Slow/DL D-12 Std	AUC(tf)	94.9	90-100
	AUC(l)	95.1	90-100
	Cmax	93.9	90-98
DL 5/120 Fast/DL D-12 Std	AUC(tf)	100.3	95-106
	AUC(l)	100.9	96-106
	Cmax	126.1	120-132

- Based on the IVIVC analysis using the PK data from the above Study P02043, there was a good relationship between the *in vitro* dissolution rates and *in vivo* performance for PSE component (Table 10). Therefore, the data support a Level A correlation between the *in vivo* absorption and *in vitro* rate profiles of the PSE.

Table 10. In Vitro in Vivo Regression results (a) (In Vivo Percent Dose Absorbed (Y) Versus In Vitro Percent Drug Release (X))

Formulation	Slope (m)	Intercept (b)	Coefficient of Determination (r ²)	P-value
DL 5/120 Fast Batch	1.029	-13.50	0.9527	0.0002
DL 5/120 Std Batch	1.028	-13.41	0.9558	0.0001
DL D-12 Std Batch	0.976	-10.96	0.9593	0.0001
DL D-12 Slow Batch	1.044	-12.19	0.9573	0.0001

(a): $Y = mX + b$.

The negative intercept is due to the lag time for absorption (i.e., the *in vivo* absorption of PSE is slightly slower than the *in vitro* release). Table 11 shows the IVIVC data following correction for the lag time.

Table 11. Time-Scaled IVIVC Parameters (a) (In Vivo Percent Dose Absorbed (Y) Versus In Vitro Percent Drug Release (X))

Formulation	Slope (m)	Coefficient of Determination (r ²)	P-value
DL 5/120 Fast Batch	1.074	0.9987	<0.0001
DL 5/120 Std Batch	1.083	0.9993	<0.0001
DL D-12 Std Batch	1.059	0.9995	<0.0001
DL D-12 Slow Batch	1.109	0.9984	<0.0001

(a): $Y = mX$.

Overall Conclusions:

The primary conclusion from this NDA is that the new formulation is bioequivalent to the original formulation used in Phase III studies. The steady state was achieved after 10 days of multiple doses. Food had no effect on the PK of DL, 3-OH DL, or PSE. There was good *in vitro* *in vivo* correlation for PSE component of the product.

It should be noted that the data discussed in this NDA are comparable to the data reported for the original formulation used in Phase III study and in particular in relation to the effect of food and steady state (see OCPB review dated October 12, 2001).

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Clinical Pharmacology and Biopharmaceutics 2

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).

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2.0 Summary of the Individual Studies:

2.1 Study # P02040 (Pivotal BE Study):

Objective: To determine the bioequivalence of DL, 3-OH DL, and PSE following single dose administration of the original formulation used in Phase III study and the new final-to-be-marketed formulation.

Subjects: 20 healthy male and females subjects

Design: This is a replicate two-way crossover design. Each subject received the same treatment twice over four-periods as follows:

Treatment A: Phase III original formulation (DL D-12 tablet, 2.5 mg DL/120 mg extended-release PSE (Formulation # 3538).

Treatment B: New Final-to-be-marketed formulation (DL D-12 tablet, 2.5 mg DL/120 mg extended-release PSE (Formualtion # 3775).

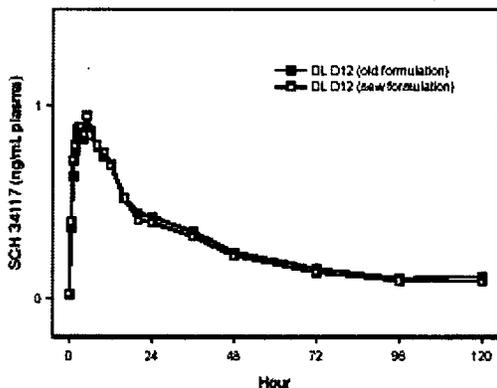
Blood was collected over 120 hours for PK analysis of DL, 3-OH DL, and PSE.

Results:

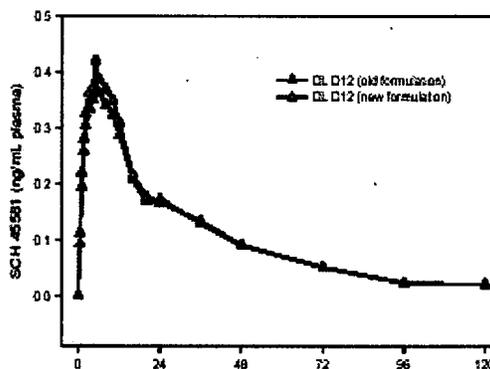
- The plasma concentration-time profiles of DL, 3OH DL, and PSE are superimposed following both formulations (Figures 2.1.1-2.1.3).
- Similarly the PK data for the three analytes are comparable following both formulations (Tables 2.1.1-2.1.3). In addition, the 90% CI limit for all analytes was within 80% to 125% (Tables 2.1.4-2.1.6)

Figures 2.1.2-2.1.3 . Mean Plasma concentration-Time Profiles of DL, 3-OH DL and PSE Following the Original and the New Formulations.

DL



3-OH DL



PSE

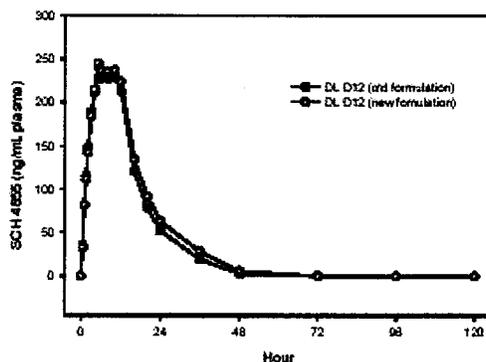


Table 2.1.1. Mean PK Parameters for DL

Parameter	Treatment A (Reference)				Treatment B (Test)			
	Mean	(CV)	Min	Max	Mean	(CV)	Min	Max
C _{max}	1.03	(31)	0.509	1.80	1.09	(36)	0.438	2.19
T _{max} ^c	5.46	(78)	1.00	24.0	4.46	(78)	1.00	16.0
t _{1/2}	27.7 ^a	(84)	11.4	95.7	27.4 ^b	(61)	11.9	61.7
AUC(t _f)	33.5	(79)	10.3	125	31.6	(88)	8.50	128
AUC(t _i)	36.0 ^a	(110)	11.1	185	36.9 ^b	(114)	10.1	187

Units: C_{max} - ng/mL; T_{max}, t_{1/2} - hr; AUC - ng·hr/mL.

Table 2.1.2. Mean PK Parameters for 3-OH DL

Parameter	Treatment A (Reference)				Treatment B (Test)			
	Mean	(CV)	Min	Max	Mean	(CV)	Min	Max
C _{max}	0.406	(57)	0	0.968	0.430	(58)	0	0.969
T _{max} ^d	8.22 ^b	(86)	3	36.0	5.34 ^c	(38)	1.50	10.0
t _{1/2}	31.9 ^a	(32)	17.3	60.6	31.3 ^a	(25)	18.5	53.8
AUC(t _f)	12.2	(54)	0	24.9	12.6	(50)	0	27.4
AUC(t _i)	15.4 ^a	(33)	8.88	26.8	15.5 ^b	(34)	7.72	29.5

Units: C_{max} - ng/mL; T_{max}, t_{1/2} - hr; AUC - ng·hr/mL.

Table 2.1.3. Mean PK Parameters for PSE

Parameter	Treatment A (Reference)				Treatment B (Test)			
	Mean	(CV)	Min	Max	Mean	(CV)	Min	Max
C _{max}	254	(16)	182	341	263	(13)	203	375
T _{max} ^a	7.28	(36)	3.00	12.0	6.73	(41)	3.00	12.0
t _{1/2}	7.56	(20)	4.97	10.6	7.34	(23)	5.31	11.5
AUC(t _f)	4161	(22)	2566	6026	4588	(25)	2827	7352
AUC(t _i)	4291	(23)	2641	6174	4745	(25)	2904	7937

Units: C_{max} - ng/mL; T_{max}, t_{1/2} - hr; AUC - ng·hr/mL.

Tables 2.1.4. 90% CI for DL

Parameter	Treatment B/Treatment A (n=18)					
	Ismean A ^a	σ _{WA} ^b	Ismean B ^a	σ _{WB} ^b	Ratio ^c	90% CI ^c
DL (Subject Nos. 4, 5, 9, and 19 Excluded)						
C _{max}	0.946	0.119	0.943	0.147	99.7	94.2 - 106
AUC(t _f)	21.3	0.269	20.0	0.126	93.7	85.6 - 102
AUC(t _i)	21.5	0.164	21.1	0.104	98.4	92.7 - 104

Tables 2.1.5. 90% CI for 3-OH DL

Parameter	Treatment B/Treatment A (n=16)					
	Ismean A ^a	σ_{WA}^b	Ismean B ^a	σ_{WB}^b	Ratio ^c	90% CI ^c
	3-OH DL (Subject Nos.4, 5, 9, 19 Excluded)					
Cmax	0.429	0.113	0.431	0.161	100	94.6 - 107
AUC(tf)	13.0	0.121	12.9	0.150	98.8	92.9 - 105
AUC(l)	14.4	0.106	14.3	0.124	99.1	93.3 - 105

Tables 2.1.6. 90% CI for PSE

Parameter	Treatment B / Treatment A (n=16)					
	Ismean A ^a	σ_{WA}^b	Ismean B ^a	σ_{WB}^b	Ratio ^c	90% CI ^c
	PSE (Subject Nos.4, 5, 9, 19 Excluded)					
Cmax	253	0.128	262	0.116	103	97.6 - 109
AUC(tf)	4185	0.175	4436	0.109	107	99.0 - 115
AUC(l)	4292	0.178	4593	0.112	107	99.3 - 115

Reviewer's Comments:

- In five subjects, DL was detected in pre-dose blood samples at concentrations ranging from approximately 9% to 18% of the Cmax. According to the sponsor, the detection of DL in pre-dose samples could be attributed to the carryover effect from the previous dosing. The inclusion or exclusion of these subjects in the analysis did not make any difference in the final conclusion in relation to the 90% CI limits (Table 1.1.7).

Table 2.1.7. 90% CI for all Subjects (n=20)

Parameter	Treatment B/Treatment A							
	n_A	Ismean A ^a	σ_{WA}^b	n_B	Ismean B ^a	σ_{WB}^b	Ratio ^c	90% CI ^c
	DL (All Subjects)							
Cmax	20	0.991	0.117	20	1.02	0.175	103	97.5 - 109
AUC(tf)	20	26.5	0.297	20	24.7	0.310	93.2	83.2 - 104
AUC(l)	19	26.0	0.276	19	24.9	0.321	95.9	85.1 - 108
	3-OH DL (All Subjects)							
Cmax	18	0.329	0.113	18	0.326	0.222	99.1	91.0 - 108
AUC(tf)	20	8.46	0.142	20	7.74	0.146	91.8	78.4 - 107
AUC(l)	20	14.8	0.128	20	14.7	0.123	99.0	91.0 - 108
	PSE (All Subjects)							
Cmax	20	251	0.120	20	261	0.115	104	98.9 - 109
AUC(tf)	20	4058	0.173	20	4457	0.137	110	103 - 117
AUC(l)	20	4182	0.174	20	4605	0.138	110	103 - 117

Conclusion:

The two formulations are bioequivalent.

2.2 Study # P02041 (Multiple Dose/Steady-State Study):

Objective: To determine the steady-state pharmacokinetic profile of DL, 3-OH DL and PSE following twice-daily administration of the new formulation for 14 consecutive days.

Subjects: 18 healthy male and females subjects

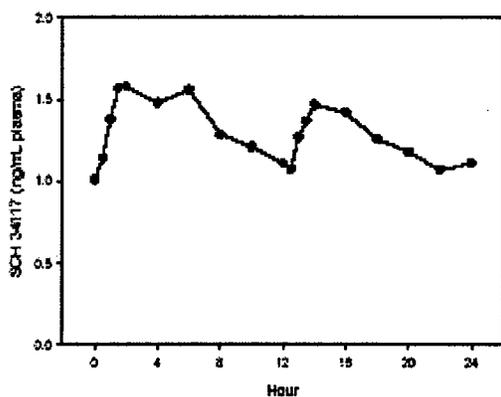
Design: All subjects received the drug twice daily for 14 days. Blood samples were collected on Day 1 and prior to both morning and evening dosing on Days 10, 11, 12, and 13 and then on Day 14 over 24 hours.

Results:

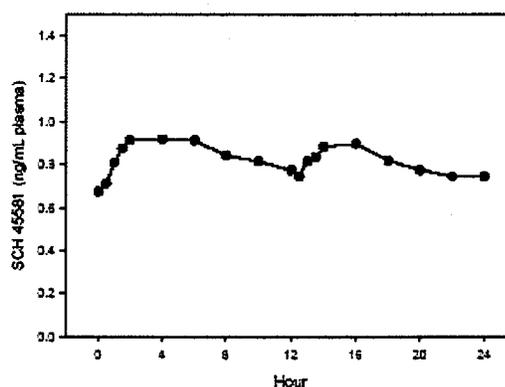
- The plasma concentration-time profiles on Day 14 of DL, 3OH DL, and PSE are shown in **Figures 2.2.1-2.2.3**.
- The PK parameters at each dose interval (0-12 h and 12-24 h) were constant throughout Day 14 for all analytes (**Tables 2.2.1-2.2.3**). Similarly, the individual C_{min} was relatively constant from Day 10 to Day 14 (**Figures 2.2.4-2.2.6**).
- There was no evidence of gender related effect on any of the PK parameters of any the analytes (**Figures 2.2.7-2.2.9**).

Figures 2.2.2-2.2.3. Mean Plasma concentration-Time Profiles of DL, 3-OH DL and PSE on Day 14 for the New Formulation (Note: the drug was administered BID also on Day 14)

DL



3-OH DL



PSE

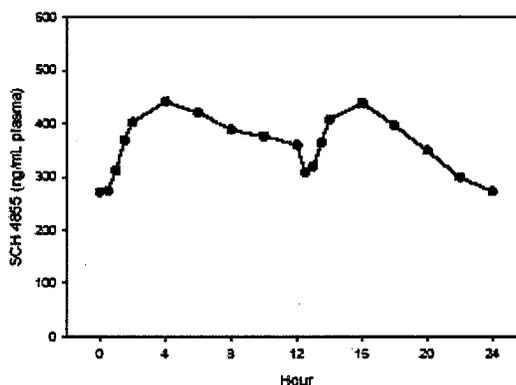


Table 2.2.1. Mean Steady-State PK Parameters of DL on Day 14

Period	C _{max} (ng/mL)	T _{max} ^a (hr)	C _{avg} (ng/mL)	AUC (ng·hr/mL)
0-12 hr	1.71 (23)	5.0 (1.0-8.0)	1.37 (28)	16.4 (28)
12-24 hr	1.50 (23)	2.0 (1.0-4.0)	1.24 (25)	14.9 (25)

a: Median (Range).

Table 2.2.2. Mean Steady-State PK Parameters of 3-OH DL on Day 14

Period	C _{max} (ng/mL)	T _{max} ^a (hr)	C _{avg} (ng/mL)	AUC (ng·hr/mL)
0-12 hr	1.00 (33)	5.0 (1.5-12)	0.854 (36)	10.2 (36)
12-24 hr	0.924 (38)	3.0 (0-8)	0.807 (38)	9.89 (38)

a: Median (Range).

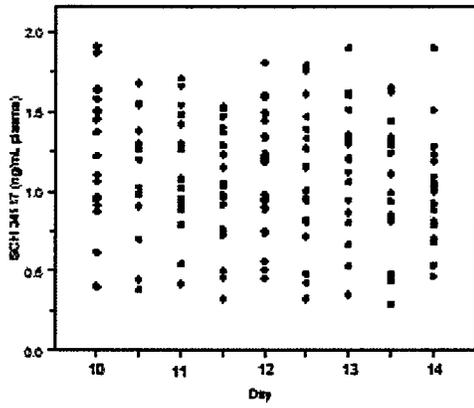
Table 2.2.3. Mean Steady-State PK Parameters of PSE on Day 14

Period	C _{max} (ng/mL)	T _{max} ^a (hr)	C _{avg} (ng/mL)	AUC (ng·hr/mL)
0-12 hr	459 (29)	4.0 (1.5-8.0)	388 (33)	4658 (33)
12-24 hr	447 (33)	4.0 (0-8.0)	361 (34)	4332 (34)

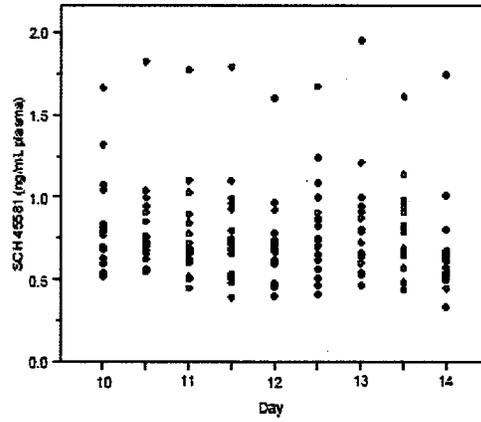
a: Median (Range).

Figures 2.2.4-2.2.6. Individual Cmin From Day 10 to Day 14

DL



3-OH DL



PSE

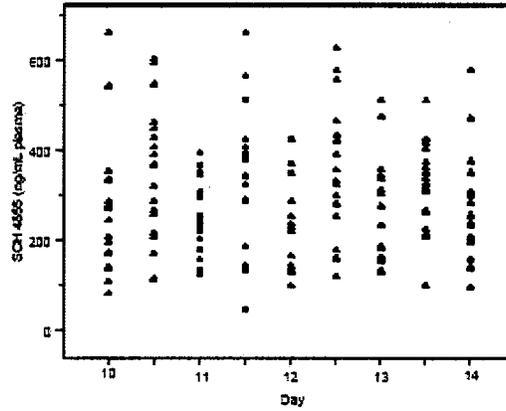


Figure 2.2.7. Box Plot for DL PK Parameters by Gender

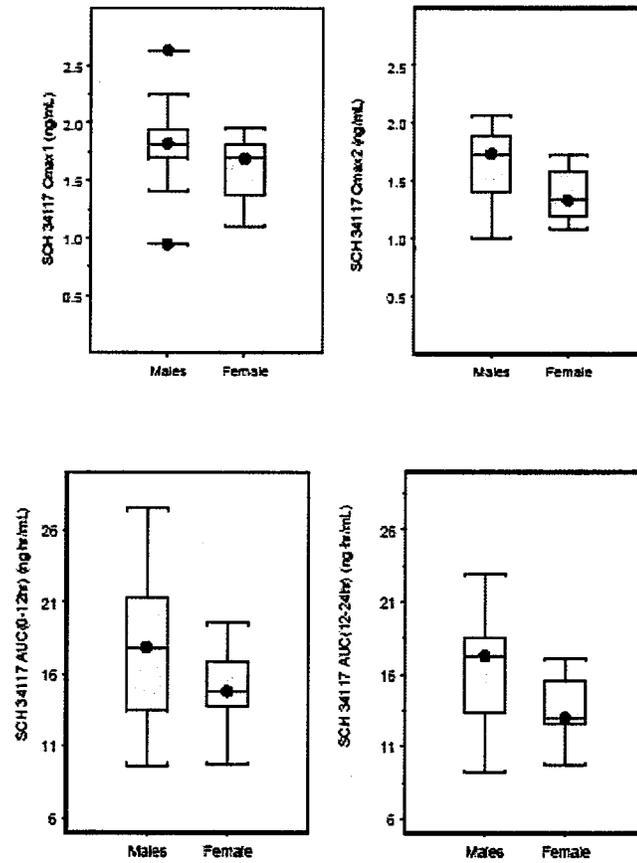


Figure 2.2.8. Box Plot for 3-OH DL PK Parameters by Gender

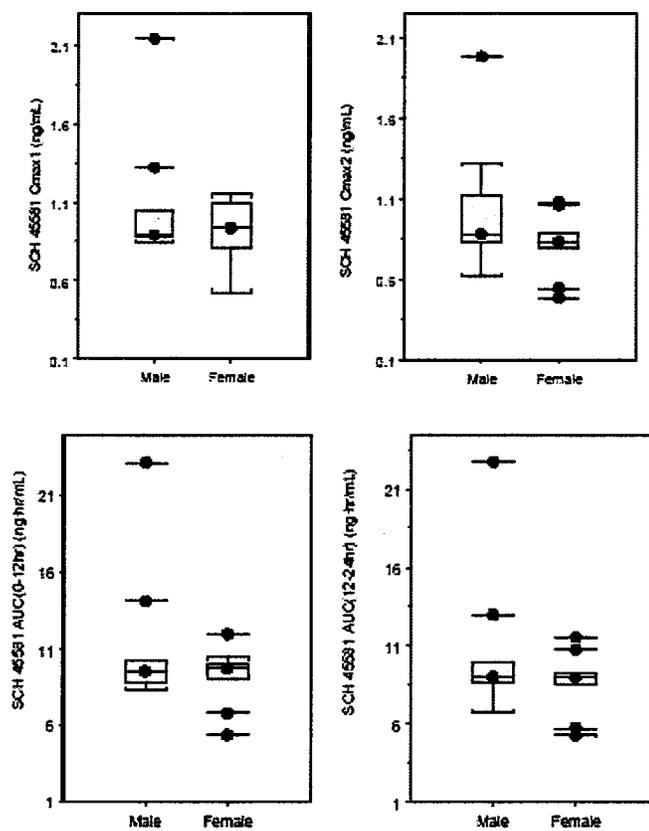
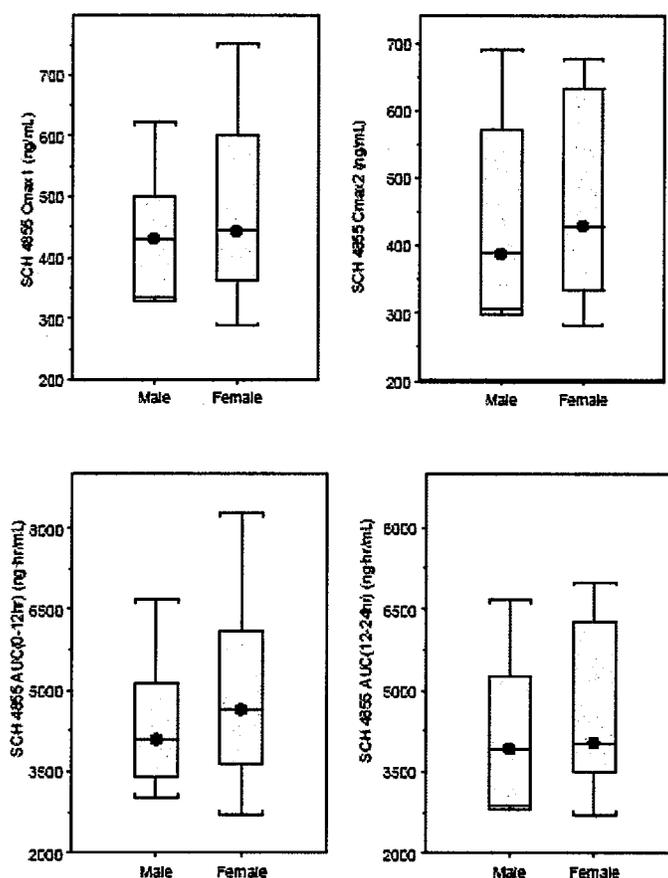


Figure 2.2.9. Box Plot for PSE PK Parameters by Gender



Reviewer's Comments:

- The above data clearly show that the steady state is achieved by Day 10 for all analytes.
- No gender related effect was noted with any of the analytes. Although this is a small sample size, this observation is, in part, satisfies the gender related issue in Comment # 22 in the approvable letter. This issue was also addressed in NDA 21-605 for Clarinex D-24.

Conclusions:

Steady state achieved on Day 10. This is similar to the data obtained for the original formulation in which steady-state was achieved between Day 10 and day 14 (see OCPB review dated Oct 12, 2001).

Gender had no effect on the PK of any of the analytes. Therefore, this satisfies comments # 22 in the approvable letter related to gender effect. Considering this information and the information submitted in NDA 21-605, no additional information is needed at this time in reference to the effect of gender on the PK of any of the analytes.

2.3 Study # P02040 (Effect of Food Study):

Objective: To determine the bioequivalence of DL, 3-OH DL, and PSE following single-dose administration of the new formulation under fed and fasted conditions in healthy adult subjects.

Subjects: 20 healthy male and females subjects

Design: Two-way crossover design as follows:

Treatment A: After over night fasting

Treatment B: After high-fat and high-caloric breakfast

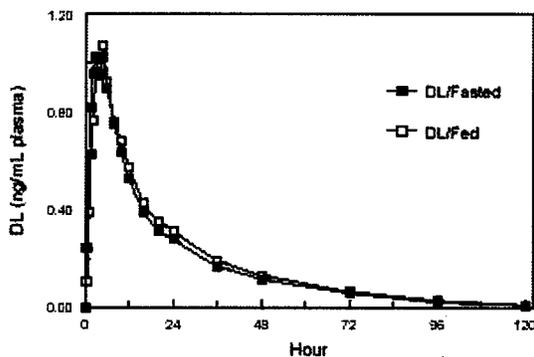
Blood was collected over 120 hours for PK analysis of DL, 3-OH DL, and PSE.

Results:

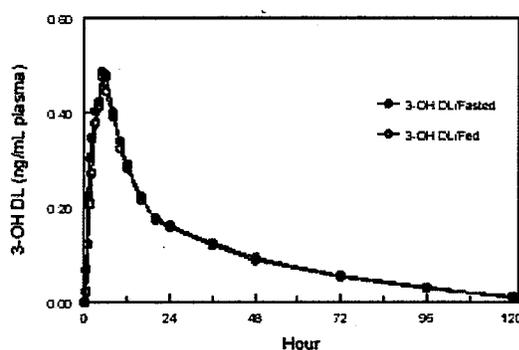
- The plasma concentration-time profiles of DL, 3OH DL, and PSE are superimposed at Fed and Fasting conditions (Figures 2.3.1-2.1.3).
- Similarly the PK data in fed and fasting conditions for the three analytes are comparable (Tables 2.3.1-2.3.3). In addition, the 90% CI limit for all analytes was within 80% to 125% (Tables 2.3.4).

Figures 2.3.1-2.1.3 . Mean Plasma concentration-Time Profiles of DL, 3-OH DL and PSE in Fasting and Fed Conditions.

DL



3-OH DL



PSE

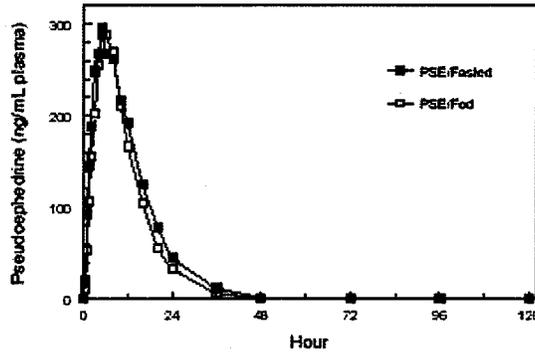


Table 2.3.4. Mean (%CV) PK Parameters for DL, 3-OH DL, and PSE

Treatment (n)	Pharmacokinetic Parameters				
	C _{max} (ng/mL)	T _{max} ^a (hr)	AUC _(f) (ng hr/mL)	AUC _(l) (ng hr/mL)	t _{1/2} (hr)
DL (n=20)					
Fasted ^b	1.13 (43)	5.00 (1.50-8.00)	20.9 (48)	21.8 (49)	20.6 (14)
Fed	1.18 (41)	5.00 (1.50-8.00)	22.1 (46)	23.0 (47)	20.9 (15)
3-OH DL (n=20)					
Fasted ^b	0.51 (38)	5.00 (3.00-8.00)	12.7 (32)	14.1 (31)	30.6 (14)
Fed	0.52 (33)	5.00 (3.00-8.00)	12.6 (27)	14.1 (28)	31.1 (14)
Pseudoephedrine (n=20)					
Fasted ^b	297 (26)	5.00 (3.00-10.0)	4274 (29)	4389 (28)	5.90 (18)
Fed	305 (21)	5.00 (4.00-8.00)	3724 (24)	3840 (23)	5.32 (21)

a: Median (minimum-maximum).
b: n=19.

Table 2.3.5. 90% CI for DL, 3-OH DL, and PSE in Fed and Fasted Conditions

Comparison	Relative Bioavailability (%)	Confidence Interval (%) ^a
DL (n=19)		
Fed/Fasted AUC(l)	105	98-113
Fed/Fasted AUC(f)	105	98-113
Fed/Fasted C _{max}	106	97-115
3-OH DL (n=19)		
Fed/Fasted AUC(l)	99.2	95-104
Fed/Fasted AUC(f)	98.8	94-103
Fed/Fasted C _{max}	102	95-109
Pseudoephedrine (n=19)		
Fed/Fasted AUC(l)	88.2	85-92
Fed/Fasted AUC(f)	87.1	84-91
Fed/Fasted C _{max}	102	98-107

a: Ninety percent confidence interval based on log-transformed parameters.

Conclusion:

Food has no effect on the PK of the new formulation. Similarly, food had no effect on the PK of the original formulation used in Phase III study (see OCPB review dated Oct 12, 2001).

2.4 Study # P02044 (Formulations with Different Release Rates):

Objective: To evaluate the bioequivalence of PSE from DL/PSE formulations with fast and slow dissolution rates relative to each of the standard formulations, as well as the bioequivalence of PSE from the standard formulations. The other objective is to use the data to establish the *in vitro* dissolution specs for PSE via IVIVC (*in vitro/in vivo* correlation).

Subjects: 20 healthy male and females subjects

Design: Four-way crossover design as follows:

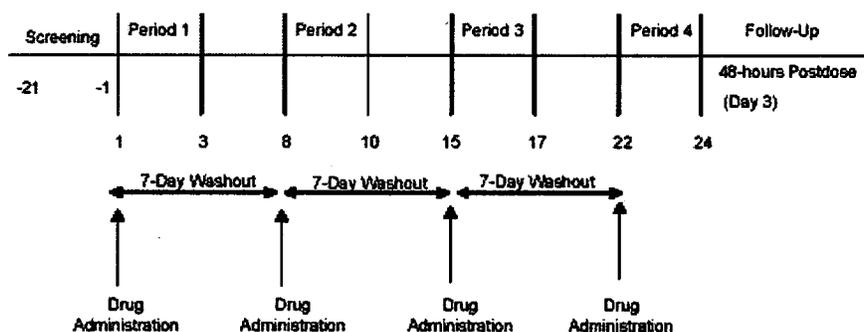
Treatment A (Standard Rate): DL D-12 tablets (2.5 mg DL) 120 mg PSE)

Treatment B (Standard Rate): 5 mg DL/120 mg PSE

Treatment C (Fast rate): 5 mg DL/120 mg PSE

Treatment D (Slow): 2.5 mg DL/120 mg PSE

Scheme of Study Design:



Blood was collected over 48 hours for PK analysis of PSE only.

Results:

- As expected, the C_{max} of PSE following the formulation with fast *in vitro* dissolution rate was approximately 20% higher than the other three formulations (**Figure 2.4.1 and Table 2.4.1**). However, the mean AUC was comparable among the four formulations.
- Also as expected, the 90% CI for C_{max} and AUC following all formulations were within 80%-125%, except for the C_{max} of the fast rate formulations (**Table 2.4.2**).
- As the previous studies, no gender related effects on the PK of PSE was observed in this study (**Table 2.4.3**).

2.5 IVIVC Analysis:

Objective: The objective of this study was to establish an *in vitro/in vivo* correlation (IVIVC) between the *in vivo* absorption rate (percent of dose absorbed) and the *in vitro* release rate (percent of dose released) for four PSE extended release formulations that were discussed in the above (Study # P2043).

Study Design:

The *in vivo* study design is described above (Study # P02043).

The PSE plasma concentration-time profiles for each formulation from study # P02043 were used to determine the percent of dose absorbed *in vivo*.

A point-to-point relationship between *in vitro* release and *in vivo* absorption rate of PSE was established in this analysis. It was necessary to correct for the lag time in the absorption phase in this analysis.

Results:

- There was good correlations between *in vitro* and *in vivo* parameters with a coefficient of determination (r^2) of >0.998 (Table 2.5.1).
- For the fast formulation, the % of dose dissolved *in vitro* and the % of dose absorbed *in vivo* was higher than the other three formulations (Figures 2.5.1 and 2.5.2). This indicates a good correlation. This is further confirmed with the linear regression plots of the % of dose absorbed *in vivo* and the % of dose released *in vitro* for each formulation (Figure 2.5.3 A,B,C,D).

Table 2.5.1. Scaled Time IVIVC Parameters (Y= *in vitro* % absorbed and x= *in vitro* % drug released).

Formulation	Slope (m)	Coefficient of Determination (r^2)	P-value
DL5/120 Fast Batch	1.074	0.9987	<0.0001
DL5/120 Std Batch	1.083	0.9993	<0.0001
DL D12 Std Batch	1.059	0.9995	<0.0001
DL D12 Slow Batch	1.109	0.9984	<0.0001

Y = mX.

Figure 2.4.1. Mean % PSE Absorbed-Time Profiles from Four Formulations (Inset 8 hours).

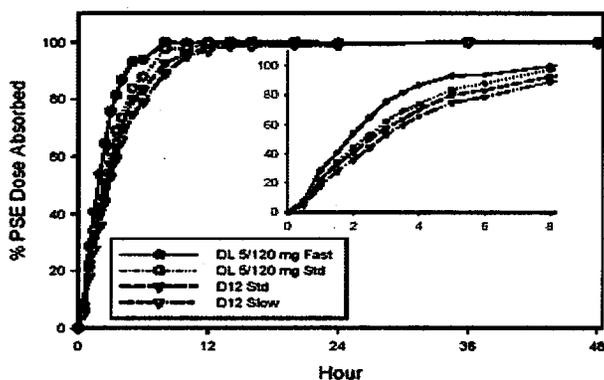
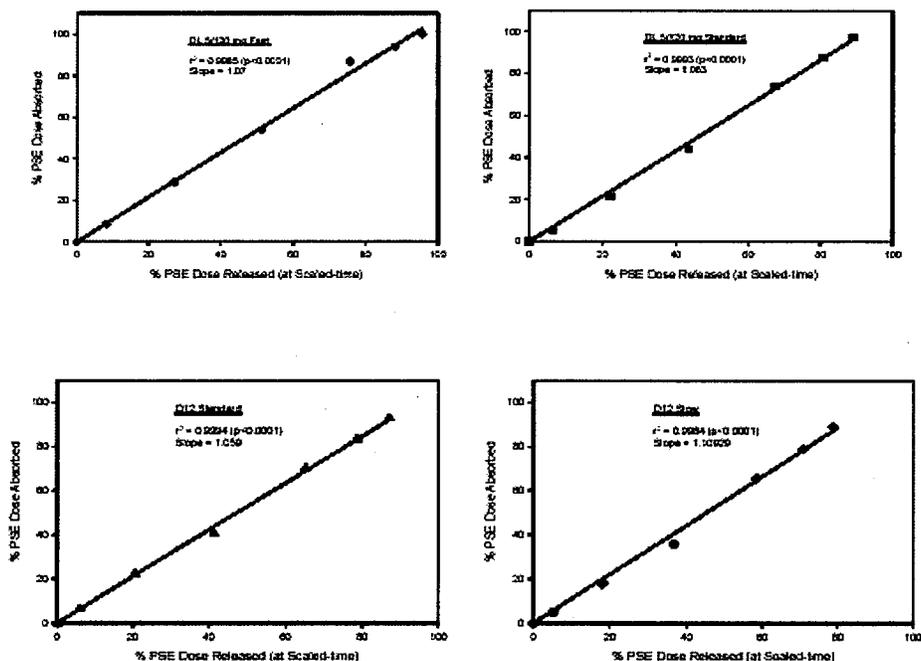


Table 2.5.2. IVIVC Linear Regression Plots



Conclusion:

Level A IVIVC correlation was established in this analysis. Therefore, the *in vitro* release rate can be used as a predictor of *in vivo* performance for PSE in this product. The methodology and *in vitro* release specifications proposed by the sponsor appears to be adequate. For further detail, see CMC review for the final recommended specifications.

2.6. 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.

[Redacted content]

Figure 2.4.1. Mean PSE Plasma Concentration-Time Profiles Following Four Formulations with Different *in vitro* Dissolution rates.

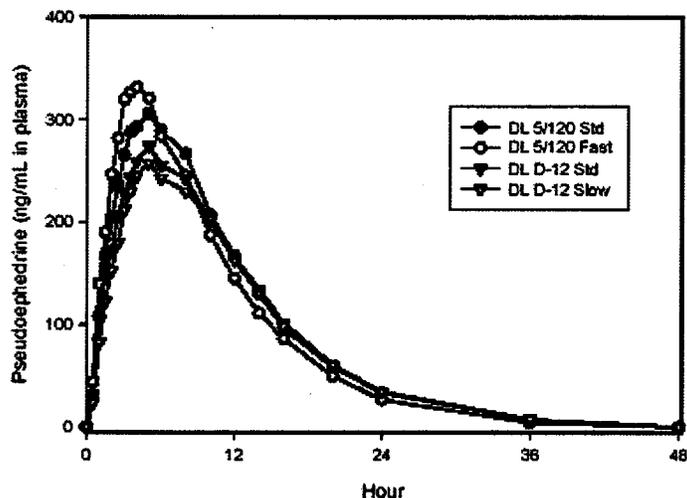


Table 2.4.1. Summary of PSE PK Parameters Following Four Formulations with Different *in vitro* Dissolution rates.

Treatment	Pharmacokinetic Parameters ^a				
	C _{max} (ng/mL)	T _{max} ^b (hr)	AUC(tf) (ng·hr/mL)	AUC(l) (ng·hr/mL)	t _{1/2} (hr)
DL D-12 Standard Batch (A)	283 (23)	5.00 (3.00-8.00)	3769 (22)	3848 (22)	5.42 (13)
DL 5/120 Standard Batch (B)	317 (21)	5.00 (3.00-6.00)	3958 (26)	4054 (25)	5.21 (13)
DL 5/120 Fast Batch (C)	358 (23)	4.00 (2.00-5.00)	3802 (25)	3898 (24)	5.13 (15)
DL D-12 Slow Batch (D)	269 (27)	5.00 (3.00-10.00)	3608 (27)	3684 (26)	5.24 (13)

Table 2.4.1. 90% CI of PSE Following Four Formulations with Different *in vitro* Dissolution rates.

Comparison		Relative Bioavailability (%)	Confidence Interval (%)
DL 5/120 Std / DL D-12 Std (B/A)	AUC(tf)	104.2	99-110
	AUC(l)	104.7	99-110
	C _{max}	111.8	107-117
DL D-12 Slow / DL D-12 Std (D/A)	AUC(tf)	94.9	90-100
	AUC(l)	95.1	90-100
	C _{max}	93.9	90-98
DL 5/120 Fast / DL D-12 Std (C/A)	AUC(tf)	100.3	95-108
	AUC(l)	100.9	96-108
	C _{max}	126.1	120-132
DL D-12 Slow / DL 5/120 Std (D/B)	AUC(tf)	91.1	88-96
	AUC(l)	90.8	86-96
	C _{max}	84.0	80-88
DL 5/120 Fast / DL 5/120 Std (C/B)	AUC(tf)	96.3	91-102
	AUC(l)	96.3	91-102
	C _{max}	112.8	108-118

Table 2.4.4. Summary of PK Parameters of PSE by Gender

Comparison	% Estimate (90% Confidence Interval)					
	Male (n=10)			Female (n=10)		
	AUC(tf)	AUC(l)	Cmax	AUC(tf)	AUC(l)	Cmax
DL 5/120 Std / DL D-12 Std (B/A)	101.5 (93-110)	102.1 (94-111)	110.3 (102-119)	107 (98-116)	107.4 (99-116)	113.3 (106-121)
DL D-12 Slow / DL D-12 Std (D/A)	93.5 (86-102)	93.8 (87-102)	91.9 (85-99)	96.4 (89-105)	96.4 (89-105)	96.0 (90-102)
DL 5/120 Fast / DL D-12 Std (C/A)	99.7 (92-108)	100.2 (92-109)	125.2 (116-135)	101 (93-110)	101.6 (94-110)	127 (119-135)
DL D-12 Slow / DL 5/120 Std (D/B)	92.2 (85-100)	91.9 (85-100)	83.3 (77-90)	90.0 (83-98)	89.7 (83-97)	84.7 (79-90)
DL 5/120 Fast / DL 5/120 Std (C/B)	98.3 (90-107)	98.2 (91-106)	113.5 (105-122)	94.3 (87-103)	94.6 (87-103)	112.1 (105-120)

Conclusion:

The formulation with fast dissolution rate had higher Cmax than other formulations and was not bioequivalent to other formulations.

18 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sayed Al-Habet
1/10/2006 03:33:17 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
1/10/2006 03:54:42 PM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-313
Proprietary Drug Name:	Clarinet-D12 2.5/120mg E-R Tablets
Generic Name:	Desloratadine/Pseudoephedrine
Indication:	Treatment of Seasonal Allergic Rhinitis (SAR)
Dosage Form:	Tablet
Strength:	2.5mg DL/120mg PSE
Route of Administration:	Oral
Dosage and administration:	Adults and children (age 12 years and older): One tablet twice daily
Applicant:	Schering Corporation
Clinical Division:	DPADP (HFD-570)
Submission Date:	December 8, 2000
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader :	Emmanuel Fadiran, Ph. D.

TABLE OF CONTENTS

ITEM	PAGE NUMBER
Title page	1
Table of Contents	2
1. Executive Summary	3
1.1. Comments to Sponsor	3
1.2. Comments to the Medical Officer	4
1.3. Comments to the Chemistry Reviewer	4
1.4. Labeling Comments	5
1.5. Recommendation	6
2. Question-Based Review	7
3. Background and Rationale	19
3.1 Introduction	21
3.1.1 Pharmacokinetics	21
3.1.2 Chemistry Overview	21
3.1.3 Formulation	21
3.1.4. Indication	22
3.1.5. Dosage and Administration	23
4. Safety	23
5. Attachment 1: Study P0240	24
• Pharmacokinetics Results	26
• Comments	29
• Conclusion	30
• Dissolution	30
6 Attachment 2: Study P00440	33
• Pharmacokinetics Results	45
• Comments	39
• Conclusion	39
• Dissolution	40
7. Attachment 3: Study P00883	42
• Pharmacokinetics Results	45
• Comments	49
• Conclusion	49
• Dissolution	50
8. Attachment 4: Study P00446	52
• Pharmacokinetics Results	54
• Comments	59
• Conclusion	59
• Dissolution	59
9. Attachment 5: Study P01352	62
• Pharmacokinetics Results	65
• Comments	69
• Conclusion	69
• Dissolution	70
10. Attachment 6: Filing/Review Form	76

1. EXECUTIVE SUMMARY

Clarinox D-12 ER tablet is a bilayer combination of immediate-release desloratadine 2.5 mg and pseudoephedrine sulfate 120 mg in a sustained release matrix formulation designed for twice daily dosing. It is indicated for the relief of symptoms of seasonal allergic rhinitis in adults and children 12 years of age and older.

In support of this application, the sponsor has submitted the results of two clinical safety and efficacy studies as well as the results of five pharmacokinetic studies.

The PK studies evaluated 126 healthy adult volunteers. These studies included a formulation selection study (P00230), a food effect study (P00440), a component interaction study (P00446), a multiple dose study (P00883) and a study to evaluate the bioequivalence of pseudoephedrine from several extended release formulations (P01352).

The results of the clinical pharmacology studies determined the appropriate formulation to be selected for the PSE core and showed no component interaction between DL and PSE within the D-12 formulation. In addition the bioavailability of DL D-12 was not effected by a high-fat, high-caloric meal. Steady-state concentrations of the DL, 3-OH DL, and pseudoephedrine were obtained following twice daily dosing of DL D-12 for 14 days. In a pseudoephedrine bioequivalence study it was demonstrated that DL D-12 formulations with pseudoephedrine dissolution rate profiles that were faster and slower than the standard formulation (to-be-marketed formulation) were bioequivalent in vivo. This indicates that the specifications for the PSE component may be widened to those specifications of the fast and slow formulations while maintaining bioequivalence to the to-be-marketed formulation.

1.1 COMMENTS TO SPONSOR

1. Please submit the components (including batch numbers) of the Drixoral and solution formulations used in studies P00230 and P00446).
2. This reviewer recommends, based on the BE data submitted, the following dissolution specifications for Clarinox D-12:

Table 1. Proposed dissolution specifications for Clarinox D-12

Time (hours)	Percent PSE sulfate release (sponsor's)	Percent PSE sulfate release (this reviewer's)
1		29-44
2		50-66
6		NLT 80%
0.5		

3. If the sponsor chooses to claim in the label a lack of gender effect on the pharmacokinetics of PSE, it is necessary to carry out a more complete analysis of the data. The sponsor is encouraged to pool all the PSE pharmacokinetic data generated in this submission before making a statement of lack of gender effect on the PK on PSE. This analysis should be conducted taking into account the weigh of the subjects.
4. Please provide more references/literature information to support the statement in the label regarding the metabolism and elimination of PSE. Also, include supporting evidence for the need in dose adjustment in renally impaired patients.

5. The sponsor is encouraged to identify the enzyme (s) responsible for the presence of slow metabolism observed in some subjects.

1.2. COMMENTS TO THE MEDICAL OFFICER

1. In order to show bioequivalency of the immediate release layer containing DL, the sponsor used a DL bilayer tablet that contained placebo for the PSE layer as a reference for DL. The use of this formulation (not approved formulation) as a reference for the DL portion of Clarinex D-12 was proposed by the sponsor in a pre-NDA meeting with the agency. The OCPB team accepted this formulation as a reference most likely based on the following bases:
 - The sponsor has previously shown that DL follows linear pharmacokinetics in the range of 2.5 to 20 mg.
 - The sponsor proposed and conducted 2 clinical trials to determine the safety and efficacy of this formulation.
 - The lack of an approved reference for DL Clarinex D-12.
 - Clarinex 5mg tablet and the DL portion on Clarinex D-12 have similar formulations (quantitatively and qualitatively) with similar dissolution profiles and dissolution specifications.
2. Females tend to have statistically significant higher PSE C_{max} values than males (see Table 2.1 below, from study P01352). This 24% increase in the C_{max} may not be clinically relevant. A graphical representation between weight and C_{max} showed that the females used in this study had lower weight (mean= 51.35 kg) than males (mean=80.35 kg) which may explain the variability in C_{max}. However, since these findings are based on a single study, which included 8 females and 8 males, the sponsor has been requested to perform some additional analysis of the data generated with regard to the PK of PSE. See comment 4 to sponsor regarding this matter.

Table 2.1. PK parameters of PSE in male and female volunteers following single-dose oral administration of controlled-release (12-hr) Clarinex tablet formulations (refer to study P01352).

Parameter	Female (n=8)	Male (n=8)	Ratio (F/M)	90%CI
AUC _{inf} (ng*hr/mL)	4199	3977	106	101-111
AUC _t (ng*hr/mL)	4028	3778	107	102-113
C _{max} (ng/mL)	332	268	124	119-129

3. Two slow metabolizers were identified in these PK studies (one in study P00440 and one in P00446). The DL AUC_{inf} values in these subjects were 8 to 10-fold higher than the mean AUC_{inf} (27 ng*hr/mL). The 3-OH DL AUC_{inf} values were 3-fold lower (to undetectable values) than the mean value (~15 ng*hr/mL). Low ratios for AUC 3-OH DL/AUC DL have been identified in previous Clarinex NDAs (21-312, 21-300 and 21-297) suggesting the existence of DL slow metabolizers. The clinical relevance of these observations on the safety of Clarinex should be evaluated by the medical reviewer.

[REDACTED]

Reviewer's remarks:

The red underlined text represents new additions to the label made by the sponsor. The sponsor will be requested to provide more references/literature information to support the statements regarding the metabolism and elimination of PSE as well as information to support the need in dose adjustment in renally impaired subjects (see comments to sponsor). The sponsor provided only one reference on the renal excretion of PSE.

[REDACTED]

Reviewer's remarks:

The sponsor is encouraged to pool all the PSE pharmacokinetic data generated in this submission before making a statement of lack of gender effect on the PK on PSE (see comments to sponsor).

1.5 RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-313 submitted on December 8, 2000. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB. However, the clinical relevance of the existence of desloratadine

slow metabolizers on the safety of Clarinex should be evaluated by the medical reviewer.
Please forward the above comments to the sponsor.

Reviewer

Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader

cc

NDA 21-313/N-000: Division File

HFD-870: Malinowski, Hunt

HFD-570: Fadiran, Sullivan, Trout, Suarez-Sharp

**APPEARS THIS WAY
ON ORIGINAL**

The present review has been focused on the following issues.

2. QUESTION BASED REVIEW

Q1. Was the to-be-marketed formulation used in the pharmacokinetic studies?

The following formulation of Clarinex D-12 ER tablets was used in all the PK studies and is the same as the to-be-marketed formulation except for a change in the

Table 1.1a. Components for formula number 3538 (standard batch)

<u>Ingredients</u>	<u>mg/tablet</u>
<u>Immediate Release Layer</u>	
<u>Sustained Released Layer</u>	

The sponsor increased _____ during _____ Since this change corresponds to a Level II change on the manufacturing process, according to SUPAC guidance, no BE bridging studies are needed. The sponsor provided dissolution data for tablets generated with this new _____ specification. This change in _____ has shifted the _____ : the different times point (especially at _____) to the edge of the _____ without being out of specifications (tablets under stability evaluation).

Study P00230 was conducted to select the formulation of DL D-12, that is bioequivalent to currently marketed formulations of PSE (Drixoral nasal decongestant, and a solution formulation of PSE). In this study, two formulations were tested: formulation 3526 and 3525. Formulation 3525 was bioequivalent to both Drixoral and a solution formulation, but not formulation 3536 (see Table 1.1). Based on these findings, formulation 3525 was used in all the subsequent PK and clinical studies and is the same as the to-be-marketed formulation.

Table 1.1. Point estimates and 90% confidence intervals for the log-transformed C_{max} and AUC_{inf} values of PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
TrtA/trtC	AUC _t	98.2	92-105
	C _{max}	88.5	81-96
TrtA/trtD	AUC _t	109	102-116
	C _{max}	105	97-115
TrtB/trtC	AUC _t	96.8	91-103
	C _{max}	81	74-88
TrtB/trtD	AUC _t	107	100-114
	C _{max}	96.2	88-105

A:3526; B:3525, C:Drixoral nasal decongestant tablet, and D:PSE solution (n=16).

Table 1.2. Dissolution data for Clarinex D-12 tablets/PSE

3526 formulation														
	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												26	1.4
1	✓												38	1.6
2													65	2.4
4													86	2.2
6													96	2.4
8												✓	99	2.2

3525 formulation														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												27	2.4
1	✓												37	1.5
2													60	4.0
4													79	2.2
6													90	1.8
8												✓	97	1.4

Q2. Are the proposed dissolution method and specifications supported by the data provided by the sponsor?

The Clarinex (12-hr) dissolution method and specifications proposed by the sponsor are listed below.

Table 2.1. Proposed dissolution method for Clarinex D-12 tablets

Method	
Apparatus:	USP apparatus II (paddle)
Detection:	UV at —
Speed:	50 rpm
Temperature:	37 °C ± 0.5 °C
Medium:	0-1 hours: 0.1N HCL 1-8 hours: 0.1M PO ₄ buffer pH 7.5
Volume:	1000 mL

Table 2.2. Sponsor's proposed dissolution specifications for Clarinex D-12

Time (hours)	Percent PSE sulfate released
1	
2	
6	NLT %
	DL dissolved
0.5	Q= %

The sponsor conducted study P01352 to determine the bioequivalency of 4 formulations of DL-D-12: standard formulation (formula # 3538), slow formulation (#3636), fast formulation (#3637) and very fast formulation (#3638). Study P01352 was considered pivotal by this reviewer for setting the Clarinex D-12 dissolution specifications. These formulations differ in the amount of inactive ingredients of the extended release layer (PSE layer). The data provided by the sponsor showed that Treatments B (fast batch) and C (slow batch) were bioequivalent to Treatment A (standard batch). However, Treatment D (very fast batch) was not bioequivalent to treatment A (see Table 2.3). The individual dissolution data for Clarinex D-12 tablets from the four different formulations is provided in Table 2.5. Figure 2.1 shows the dissolution profiles (average data) for the four formulations.

Table 2.3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
TrtB/trtA	AUCt	105		97-113	
	AUCinf	104	103.9	97-111	96.8-11.5
	Cmax	117	117.8	110-124	110.9-125.1
TrtC/trtA	AUCt	104		96-112	
	AUCinf	104	103.2	97-111	96.8-11.5
	Cmax	97	97.1	92-103	91.5-103.2
TrtD/trtA	AUCt	103		95-111	
	AUCinf	102	103.1	95-110	96.08-110.7
	Cmax	126	126.2	119-134	118.8-134

*A: standard batch; B: fast batch; C: slow batch; D: very fast batch

The sponsor has increased

Table 2.4. Proposed dissolution specifications for Clarinex D-12

Time (hours)	Percent PSE sulfate release (sponsor's)	Percent PSE sulfate release (this reviewer's)
1		29-44
2		50-66
6	NLT 80%	NLT 80%
	DL dissolved	
0.5	Q= 20%	

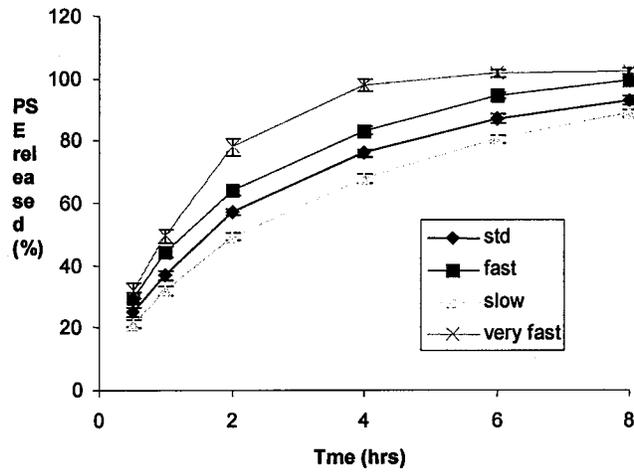


Figure 2.1. Mean in vitro PSE sulfate released profiles for very fast, fast, standard and slow extended release formulations of Clarinex D-12 tablets.

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Table 2.5. Dissolution data for PSE from Clarinex D-12 tablets

Standard formulation (3538)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												25	1.6
1													37	1.6
2													57	1.2
4													76	1.2
6													87	1.4
8												└	93	1.4
Very fast formulation (3638)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												32	2.4
1													50	2.3
2													78	2.7
4													98	1.9
6													102	1.2
8												└	102	0.9
Fast formulation (3637)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												30	1.6
1													44	1.8
2													54	1.3
4													33	1.2
6													14	0.9
8												└	90	1.1
Slow formulation (3636)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												21	1.2
1													32	1.3
2													49	1.2
4													68	1.4
6													80	1.2
8												└	89	1.2

Q3. Were DL and PSE from the DL D-12 tablet equivalent to the reference product? Did PSE affect the BA of DL (and viseversa) from the DL D-12 formulation?

The sponsor conducted study P00446 to evaluate the bioequivalence of single-dose oral administration of desloratadine/pseudoephedrine combination product (DL D-12, 2.5 mg DL/120 mg pseudoephedrine) in 36 female/male healthy volunteers. Desloratadine 2.5 mg/PSE placebo layer was used as a reference product for DL and Drixoral® (nasal decongestant, 120 mg) as a reference for PSE.

Individual DL and 3-OH DL Cmax and AUC(inf) values following the administration of the Clarinex D-12 and DL tablets are shown in Figures 3.1 and 3.2, respectively. Likewise, individual Cmax and AUCinf for PSE following administration of Clarinex D-12 and Drixoral tablets are represented in Figures 3.3 and 3.4, respectively. Figure 3.2 shows that one subject presented high DL AUCinf values. This subject showed

a % ratio of 3-OH DL AUC/ DL AUC less than 10, suggesting slow metabolism. The presence of slow metabolism for DL has been observed in previous Clarinex NDAs (NDA 20-300 and 21-313). The clinical relevance of these observations on the safety of Clarinex should be evaluated by the medical reviewer.

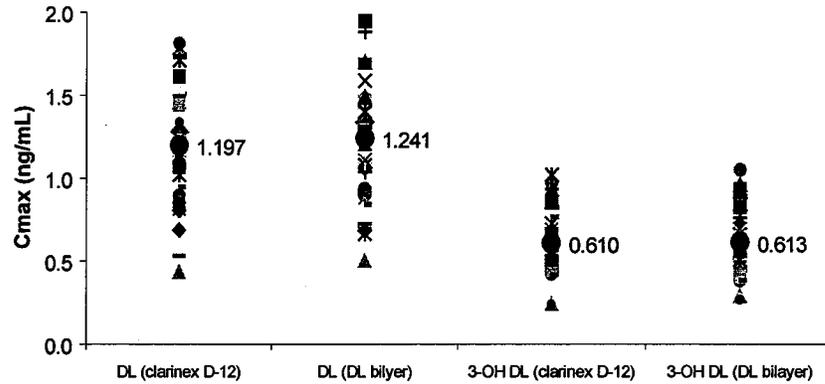


Figure 3.1. Individual DL and 3-OH DL Cmax values following single administration of Clarinex D-12 tablets and DL bilayer tablets.

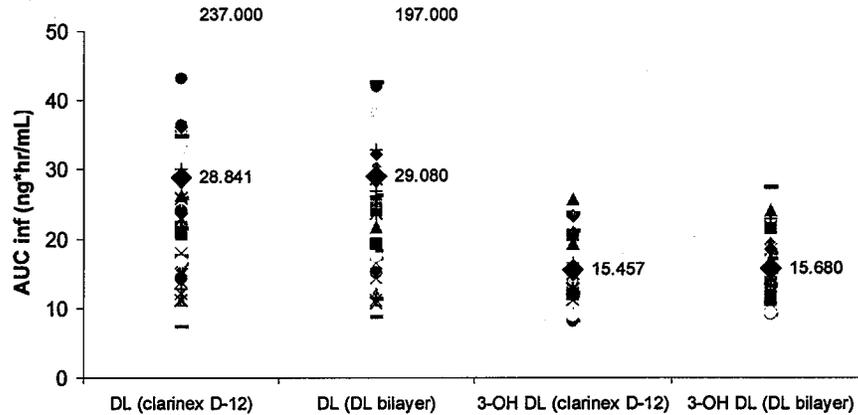


Figure 3.2 Individual DL and 3-OH DL AUC inf values following single administration of Clarinex D-12 tablets and DL bilayer tablets. The values 237 and 197 represent high values for subject 19, a slow DL metabolizer who had no detectable levels of the metabolite.

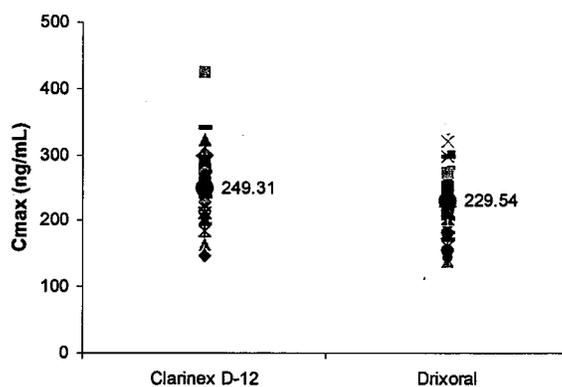


Figure 3.3. Individual PSE Cmax values following single administration of Clarinex D-12 tablets and Drixoral® tablets.

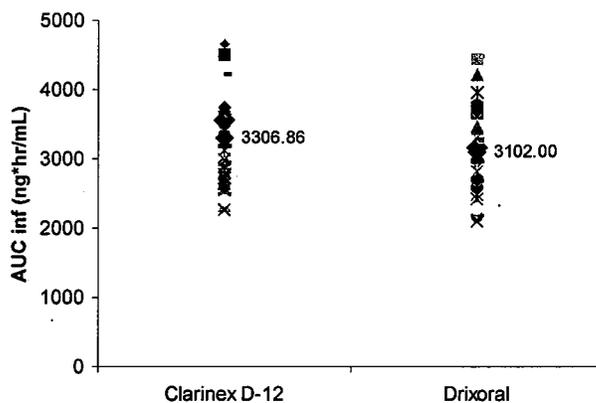


Figure 3.4. Individual PSE AUCinf values following single administration of Clarinex D-12 tablets and Drixoral® tablets.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL, its metabolite and PSE are presented in Table 3.1. The CIs of AUC(I) and Cmax for DL and its metabolite after Clarinex D-12 relative to DL bilayer tablets met the 80-125% bioequivalence guideline. The CIs of AUC(I) and Cmax for DL D-12 relative to Drixoral also met the 80-125% bioequivalence guideline.

The results indicated that the Clarinex D-12 and DL tablets were bioequivalent with regard to DL and its metabolite and the DL D-12 and Drixoral® tablets were bioequivalent with regard to PSE.

Table 3.1. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL and PSE following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
<i>Desloratadine</i>					
Clarinex D-12/ DL bilayer	AUCinf	95.8	96.3	90-102	84.7-109.4
	Cmax	95.9	98.9	91-101	91.9-106.4
<i>3-OH DL</i>					
Clarinex D-12/ DL bilayer	AUCinf	97.3	97.5	94-101	88.3-105.1
	Cmax	98.8	99.5	96-102	92.4-107.2
<i>Pseudoephedrine</i>					
Clarinex D-12/ Drixoral	AUCinf	105	105.7	101-110	92.9-120.2
	Cmax	109	108.5	102-116	99.9-117.8

In order to show bioequivalency of the immediate release layer containing DL, the sponsor used as a bilayer tablet that contains placebo for PSE as a reference for DL. The use of this formulation (not approved formulation) as a reference for the DL portion of Clarinex D-12 was discussed by the sponsor in a Pre-NDA meeting with the agency. The OCPB team accepted this formulation as a reference most likely based on the following:

1. The sponsor has previously shown that DL follows linear pharmacokinetics in the range of 2.5 to 20 mg.
2. The sponsor's proposal on conducting two clinical trials to determine the safety and efficacy of this formulation.
3. The lack of an approved reference for this product.

Because the sponsor has provided data on the safety and efficacy of DL-D-12 and given the nature of the reference used, this reviewer is of the opinion that the data generated in this bioequivalence study with respect to DL be disregarded. The agency should rely on the clinical trials to generate any conclusions about the safety and efficacy of the drug.

It can be concluded from these findings that:

- The Clarinex D-12 and DL-bilayer tablets (not approved reference) were bioequivalent with regard to DL and 3-OH DL. However, given the nature of the reference used, this reviewer is of the opinion that the data generated in this bioequivalence study for DL be disregarded. This agency should rely on the clinical trials to generate any conclusions about the safety and efficacy of the drug.
- The Clarinex D-12 and Drixoral® tablets were bioequivalent with regard to PSE.

Q4. Was the bioavailability of DL and PSE from the DL D-12 tablet affected by the presence of food?

Study P00440 was conducted to assess the influence of food on the oral bioavailability of DCL D-12 components by determining the bioequivalence of a single-dose oral administration of DL D-12 (2.5 mg DCL/120 mg pseudoephedrine) under either a fed or fasted conditions in healthy adult subjects. Subjects received DL D-12 either after a 10-hr fast or following the consumption of a standardized high-fat, high-caloric breakfast (total calories: 841; protein 31.6g; fat: 53.8g; carbohydrates: 57.4g).

The mean plasma concentration-time profiles for DL and its metabolite and for PSE following administration of Clarinex tablets under fed and fasted conditions are shown in Figures 4.1 and 4.2, respectively. In this study one subject presented high DL AUC_{inf} values. This subject showed a % ratio of 3-OH DL AUC/ DL AUC less than 10, suggesting slow metabolism. The presence of slow metabolism for DL has been observed in previous Clarinex NDAs (NDA 20-300 and 21-313). The clinical relevance of these observations on the safety of Clarinex should be evaluated by the medical reviewer.

The point estimates and the 90% CIs for the log-transformed C_{max} and AUC(I) for DL, its metabolite and PSE are presented in Table 4.1. The CIs of AUC(I) and C_{max} for DL, its metabolite and PSE under fed condition relative to fasted conditions met the 80-125% bioequivalence guideline.

This indicates that the Clarinex D-12 tablet administered under fasted and fed conditions were bioequivalent, and that a high-fat and high-caloric meal had no effect on the bioavailability of DL, its metabolite and PSE from the DL D-12 tablet.

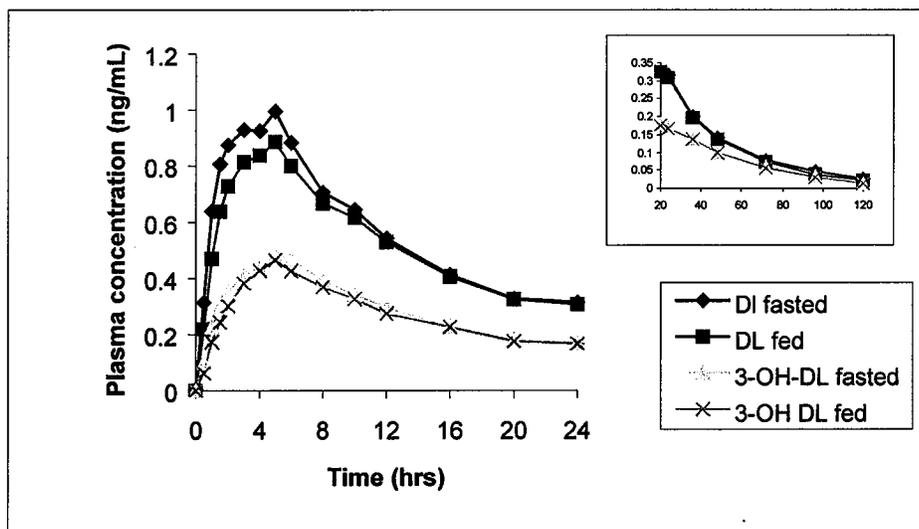


Figure 4.1. Mean DL and 3-OH DL plasma concentration-time profiles following single administration of controlled-released (12-hr) Clarinex tablets under fed and fasted conditions. The insert reflects the terminal phase for both drugs.

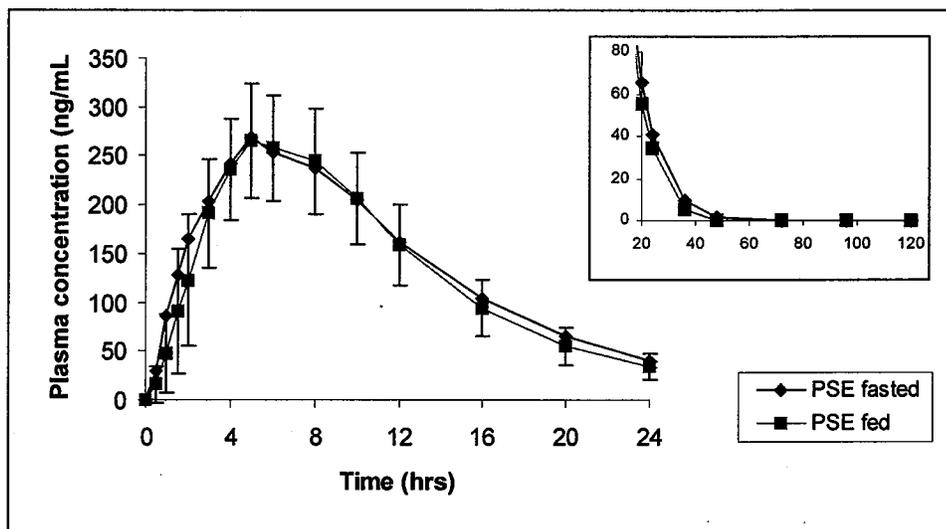


Figure 4.2. Mean PSE plasma concentration-time profiles following single administration of controlled-released (12-hr) Clarinex tablets under fed and fasted conditions. The insert reflects the terminal phase for PSE.

Table 4.1. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL, and PSE following single administration of the treatments

Treatment	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
<i>Desloratadine</i>					
Fed/fasted	AUCinf	95.1	98.2	92-98	95.1-101.4
	Cmax	92.7	94.1	87-99	88.4-100.3
<i>3-OH DL</i>					
Fed/Fasted	AUCinf	94.9	99.9	92-98	97.15-102.7
	Cmax	97.9	100.9	95-101	89.6-113.65
<i>Pseudoephedrine</i>					
Fed/fasted	AUCinf	92.9	100.44	89-97	95.75-105.36
	Cmax	102	97.8	97-108	92.9-103.14

Q5. What were the PK parameters of DL, its metabolite and PSE following multiple administration of DL D-12 tablet?

The sponsor conducted study P00883 to determine the pharmacokinetic profile of desloratadine, 3-OH desloratadine and pseudoephedrine following twice daily administration of DL D-12 (2.5 mg DL/120 mg pseudoephedrine) for 14 consecutive days in 16 healthy subjects.

The mean plasma concentration-time profiles for DL, 3-OH DL and PSE following Clarinex-D-12 tablets twice daily administration are shown in Figures 5.1 and 5.2, respectively. The mean pharmacokinetic parameters for PSE, DL and its metabolite

are summarized in Table 5.1. Figures 5.3 and 5.4 represent the individual Cmin values for DL and PSE, respectively.

Figures 5.1 and 5.3 show that steady-state conditions for DL and 3-OH DL were attained on Days 10-12 following repeated administration of DL D-12, as indicated by a lack of difference in the mean trough plasma concentrations between these days. The lack of statistical difference ($p=0.421$) in the mean trough plasma concentrations (200 to 216 ng/mL) of pseudoephedrine indicates that steady-state conditions for pseudoephedrine had been attained by Day 10 of multiple dose administration of DL D-12 tablets (Figures 5.2 and 5.4).

After twice daily dosing of DL D-12 tablets, mean and individual DL AUC(0-24 hr) values (mean, 40.4 ng·hr/mL; range, 28.0 to 63.0 ng·hr/mL, (Figure 5.5) were within the range of those (mean, 51.1 ng·hr/mL; range, 26 to 147 ng·hr/mL) reported previously in healthy volunteers receiving once daily dosing for 14 days of a 5-mg DL tablet (NDA 21-947). Likewise, After twice daily dosing of a DL D-12, mean and individual 3-OH DL AUC(0-24 hr) values (mean, 32.2 ng·hr/mL; range, 23.0 to 49.0 ng·hr/mL, (see Table 5.1) were within the range of those (mean, 33.2 ng·hr/mL; range, 16.5 to 59.0 ng·hr/mL) reported previously in healthy normal metabolizers receiving once daily dosing of a 5-mg DL tablet. This suggests that daily exposure to DL and 3-OH DL after multiple oral BID dosing of DL D-12 tablets was comparable to that after multiple QD dosing of DL 5 mg tablets.

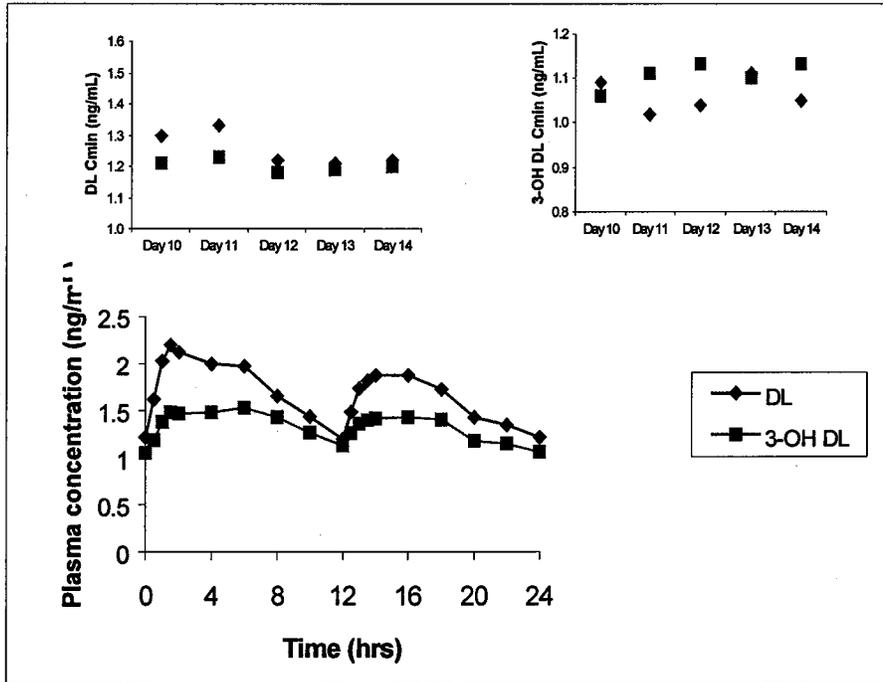


Figure 5.1. Mean DL and 3-OH DL plasma concentration-time profiles (on Day 14) following twice-daily administration of Clarinex D-12 for 14 days. The insert correspond to the average Cmin for DL and 3-OH DL on Days 10, 11, 12, 13 and 14 at time 0 (triangles) and 12 hrs (squares).

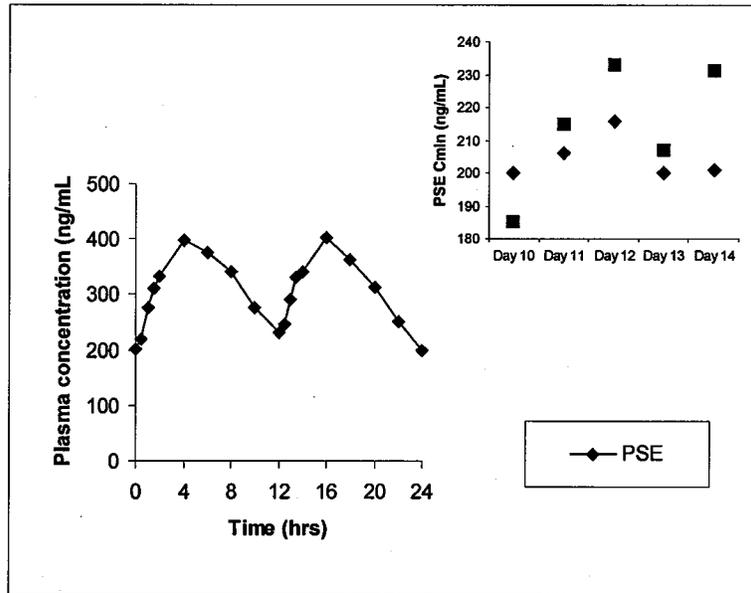


Figure 5.2. Mean PSE plasma concentration-time profiles (on Day 14) following twice-daily administration of Clarinex D-12 for 14 days. The insert correspond to the average Cmin for DL and 3-OH DL on Days 10, 11, 12, 13 and 14 at time 0 (triangles) and 12 hrs (squares).

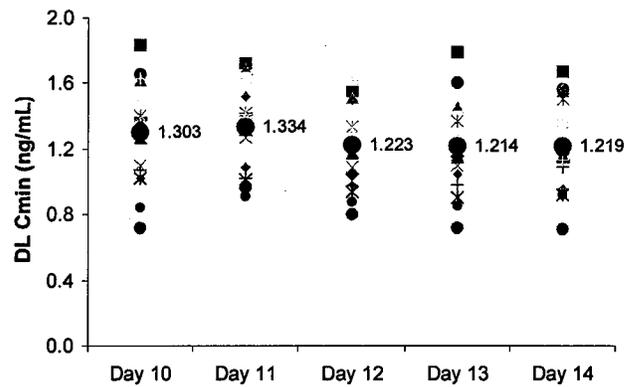


Figure 5.3. Individual DL Cmin values following twice daily administration of Clarinex D-12 tablets for 14 days.

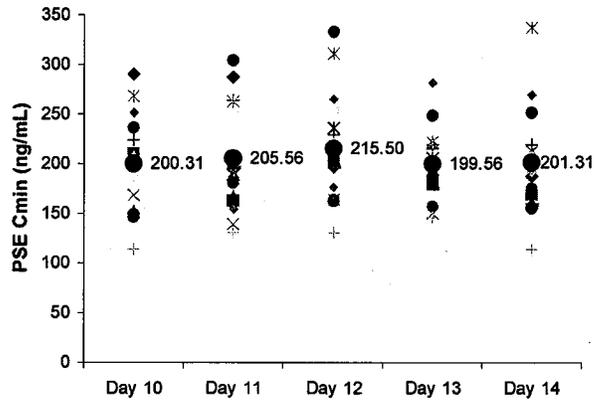


Figure 5.4 Individual PSE Cmin values following twice daily administration of Clarinex D-12 tablets for 14 days .

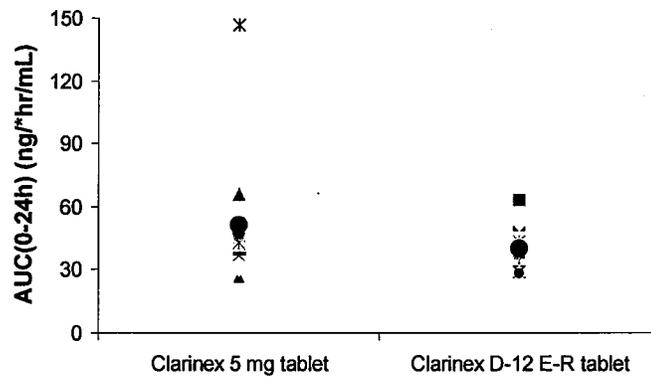


Figure 5.5. Individual DL AUC(0-24h) following multiple administration (14 days) of Clarinex tablets 5mg QD (NDA 21-297) and Clarinex D-12 BID (current NDA).

Table 5.1. Mean (%CV) pharmacokinetic parameters of DL, 3-OH DL and PSE following twice daily administration of Clarinex (12-hr) tablets for 14 days

PK parameter	DL	3-OH DL	PSE
Cmax1 (ng/mL)	2.31 (20)	1.51 (26)	408 (19)
Cmax2 (ng/mL)	2 (26)	1.52 (21)	409 (17)
Tmax1 (hr)	2.31 (80)	4.09 (55)	4.88 (26)
Tmax2 (hr)	2.94 (50)	3.44 (59)	3.94 (35)
Cavg1 (ng/mL)	1.77 (22)	1.39 (42)	324 (17)
Cavg2 (ng/mL)	1.6 (24)	1.29 (23)	315 (13)
C12 (ng/mL)	1.2 (25)	1.13 (22)	231 (23)
C24 (ng/mL)	1.22 (28)	1.06 (25)	198 (16)
AUC(0-12hr) (ng*hr/mL)	21.2 (22)	16.7 (23)	3886 (17)
AUC(12-24hr) (ng*hr/mL)	19.2 (24)	15.5 (23)	3781 (13)
AUC(τ) avg (ng*hr/mL)	20.2 (23)	16.1 (23)	3834 (15)
AUC (0-24hr) (ng*hr/mL)	40.4 (23)	32.2 (23)	7667 (15)
%Fluctuation1	64 (33)	34 (27)	55
%Fluctuation2	49 (25)	36 (24)	66
%Fluctuation, avg	57 (25)	35 (20)	61

*Number 1 refers to 0 to 12 hrs period and number 2 refers to 12 to 24 hrs period.

From these observations one can conclude the following:

- Steady-state concentrations for DL, its metabolite and PSE were attained by day 10-12.
- The average steady-state and individual AUC(0-24hr) values for DL and its metabolite following twice daily administration of Clarinex D-12 tablets were within those observed for Clarinex 5 mg tablet administered once daily for 14 days.
- The degree of fluctuation (%) for DL, its metabolite and PSE was 57, 35 and 61, respectively.

3. BACKGROUND AND RATIONALE

Desloratadine (DL, SCH 34117; formerly known as descarboethoxyloratadine, DCL) is an active metabolite of loratadine (SCH 29851, Claritin) which possesses qualitatively similar pharmacodynamic activity with a relative oral potency 2 to 4 times that of loratadine. Like loratadine, DL is a selective, oral, peripheral H₁-receptor antagonist. Pharmacokinetic studies have shown that administration of the proposed therapeutic dose of 5.0-mg DL gives the same systemic exposure (plasma AUC) of DL as administration of the marketed dose of 10-mg loratadine (NDA 21-165). Loratadine is also marketed in the United States and internationally as loratadine D-12 and loratadine D-24 tablets containing loratadine plus sustained-release pseudoephedrine (PSE) for the treatment of SAR.

The safety and efficacy data obtained for desloratadine in adolescents and adults during clinical trials revealed that it is effective in the treatment of SAR or CIU, well tolerated, and characterized by an adverse event profile similar to that previously observed with loratadine.

Pseudoephedrine sulfate is a widely used over-the-counter oral nasal decongestant. At effective recommended oral dosages, pseudoephedrine sulfate produces minimal other sympathomimetic effects, such as presser activity and CNS stimulation.

After oral administration, the effects of the drug may be noted in 15-30 minutes, with peak activity at 30-60 minutes.

DL D-12 is a bilayer combination of immediate-release desloratadine 2.5 mg and pseudoephedrine sulfate 120-mg in a sustained release matrix formulation designed for twice daily dosing. Based on its antihistaminic activity, the DL component can be expected to reduce mainly sneezing, nasal discharge, nasal itching, and non-nasal symptoms. PSE component is an established oral sympathomimetic nasal decongestant. Based on its activity, PSE can be expected to reduce nasal congestion and stuffiness. According to the sponsor, the combination of an antihistamine with a sympathomimetic amine has generally produced an additive effect, providing a greater therapeutic benefit than either component alone.

In support of this application, the sponsor has submitted the results of two clinical safety and efficacy studies as well as the results of five pharmacokinetic studies.

The clinical program for DL D-12 comprised 2 Phase-III, randomized, multicenter, double blind, active-controlled, parallel-group studies (P00355 and P00362) conducted under identical protocols. Both studies were designed to evaluate whether DL D-12 BID provided greater symptomatic relief than either of its components alone, and to establish the safety profile of DL D-12 relative to its components in subjects with SAR.

Clinical Safety and Efficacy Studies

Study P00355. This was a Phase-III, multicenter, randomized, active-controlled, double-blind, parallel-group efficacy and safety study in subjects with SAR. The number of patients randomized was 598 with ages ranging between 12-76 years.

Study P00362. This was a Phase-III, multicenter, randomized, active-controlled, double-blind, parallel-group efficacy and safety study in subjects with SAR. The number of patients randomized was 650 with ages ranging between 12-78 years.

- Both studies had active comparators (5.0 mg DL and 120 mg PSE).
- Both studies had a treatment period of 15 consecutive days. The primary efficacy time point was the average over the 15 days of treatment. Efficacy variables were also analyzed for each of the first 4 days of treatment and the average over each of Week 1 and Week 2.
- The efficacy and safety assessments were typical of those used in allergy studies, based on historical precedent.

Pharmacokinetic Studies

Five studies were conducted in the clinical pharmacology program, which evaluated 126 healthy adult volunteers. These studies include a formulation selection study (P00230), a food effect study (P00440), a component interaction study (P00446), a multiple dose study (P00883) and a study to evaluate the bioequivalence of pseudoephedrine (P01352). The safety of DL was evaluated on reported adverse events, clinical laboratory tests, vital signs, and ECGs. Pharmacokinetic evaluation was based on measurement of plasma DL, 3-OH DL, and pseudoephedrine using a validated HPLC-MS/MS method.

3.1 INTRODUCTION

3.1.1 PHARMACOKINETICS

The pharmacokinetics of DL and its metabolite have been presented in detail in a previous NDA for Clarinex (NDA 21165).

Pharmacokinetic/Pharmacodynamic Correlation. No studies have been conducted.

3.1.2 CHEMISTRY OVERVIEW

DL Chemical name: The chemical name is 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6] cyclohepta [1,2-b]pyridine and has the following structural formula:

Structural formula:

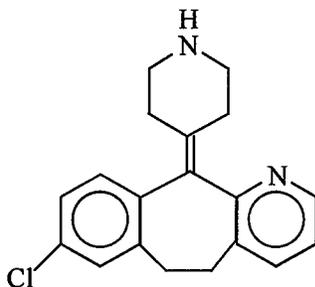


Figure 1. Structural formula of DL.

Molecular formula: C₁₉H₁₉ClN₂

Molecular weight: 310.8

Solubility: DL is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol.

PSE Chemical name: Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is (C₁₀H₁₅NO)₂ · H₂SO₄; the chemical name is a-[1-(methylamino) ethyl]-[S-(R*,R*)]- is a-[1-(methylamino) ethyl]-[S-(R*,R*)]- benzenemethanol sulfate (2:1) (salt).

The molecular weight of pseudoephedrine sulfate is — It is a white powder, freely soluble in water and methanol and sparingly soluble in chloroform.

3.1.3 FORMULATION

CLARINEX-D 12 HOUR Extended Release Tablets are oval-shaped blue and white bilayer tablets containing 2.5 mg desloratadine in the blue immediate-release layer and 120 mg of pseudoephedrine sulfate in the white extended-release layer which is released slowly allowing for twice-daily administration.

The following formulation of Clarinex D-12 ER tablets was used in all the PK studies and is the same as the to-be-marketed formulation except for a change in the

Table 7.1. Components for formula number 3538 (standard batch)

Ingredients	mg/tablet
--------------------	------------------

Immediate Release Layer

Sustained Released Layer

The sponsor increased

Since this change correspond to a Level II change on the manufacturing process, according to SUPAC-MR guidance, no BE bridging studies are needed. The sponsor provided dissolution data for tablets generated with this new specification. This change in as shifted the different times points (especially at to the edge of the ; without being out of specifications (tablets under stability evaluation).

3.1.4 INDICATION (as per proposed label)

CLARINEX-D 12 HOUR Extended Release Tablets is indicated for the relief of symptoms of seasonal allergic rhinitis in adults and children 12 years of age and older. CLARINEX-D 12-HOUR Extended Release Tablets can be administered when the antihistaminic properties of desloratadine and the nasal decongestant activity of pseudoephedrine are desired

3.1.5 DOSAGE AND ADMINISTRATION (as per proposed label)

Adults and children 12 years of age and over: The recommended dose of CLARINEX-D 12 HOUR Extended Release Tablets is one tablet twice a day and can be administered with or without a meal.

4 SAFETY AND EFFICACY

According to the medical officer, the data submitted with this application demonstrate that desloratadine, at the proposed dose (2.5mg BID), is effective in the relief of the symptoms of SAR, excluding nasal congestion. The treatment effect size is small, but statistically significant. The data also demonstrated efficacy of the pseudoephedrine component in the treatment of nasal congestion associated with SAR. The safety of DL D-12, including the adverse event profile, is comparable to that of its components.

Despite the demonstration of acceptable safety and efficacy, the Application is not recommended for approval from a clinical perspective. An "Approvable" action is recommended. The application is not deemed adequate for approval from a clinical standpoint because the Applicant has not sufficiently addressed the important issue of the poor metabolizer phenotype. The safety of this product has not been established in the subset of the population who metabolize desloratadine poorly.

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**"THE BIOAVAILABILITY OF PSEUDOEPHEDRINE FROM CONTROLLED-
RELEASE (12-HOUR) FORMULATIONS: A FOUR-WAY CROSSOVER
STUDY"**

Name of Sponsor: Schering-Plough Corporation
Included Protocols: P00230
Development Phase of Study: I
Study Initiation Date: 8 February 1999
Study Completion Date: 31 March 1999
Sponsor's Project Physician: Paul Glue, M.D., Ph.D.
Sponsor's Project Director: Christopher Banfield, Ph.D.
Date of the Report: March 10, 2000
Report Number: 00048052

OBJECTIVE

- to determine the bioavailability of pseudoephedrine from 2 extended-release formulations and the bioequivalence relative to a pseudoephedrine sulfate solution and pseudoephedrine from a Repetab formulation (Drixoral, Nasal Decongestant).

SUBJECTS

Seventeen healthy male volunteers between the ages of 20 and 39 years inclusive (mean=28 years) weighing between 61 and 83 kg (mean=74.2 kg) were enrolled into the study. Sixteen subjects were Caucasian and 1 was Black.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a Phase I, open-label, single-dose, randomized, 4-way crossover study with at least a 7-day washout period between each treatment. Sixteen healthy male and female subjects received each of the following treatments in the order assigned by a computer-generated random code:

Treatment A: One 120-mg bilayer extended-release pseudoephedrine sulfate tablet (Formula No. 3526; Batch No. 52875-135).
Treatment B: One 120-mg bilayer extended-release pseudoephedrine sulfate tablet (Formula No. 3525; Batch No. 52875-134).
Treatment C: One Drixoral, Nasal Decongestant tablet containing 120-mg pseudoephedrine.
Treatment D: 30 mg pseudoephedrine sulfate administered orally as a solution at approximately 8 am, 11 am, 2 pm and 5 pm.

For Treatments A, B, and C, following an overnight fast (approximately 10 hr), the appropriate tablet(s) was administered with 120 mL of room-temperature non-carbonated water in the morning at approximately 8 am. For Treatment D, pseudoephedrine sulfate as a powder was reconstituted with 20 mL of room-temperature non-carbonated water and consumed by the subjects.

FORMULATION

The DL D-12 tablet(s) were manufactured, y SPRI, Kenilworth, NJ, USA. The following formulations (Table 1) were used:

Table 1. Formulations for DL D-12 Pseudoephedrine Tablets, 120 mg

Strength	120 mg	120mg
Formula. No.	3525	3526
Batch No.	52875-134	52875-135
FMR No.	99521D09	99522D09
Manf. Date	1/19/99	1/19/99
Manf. Site	Kenilworth, NJ	Kenilworth, NJ
Batch Size (tablets)		

Formula 3526 is the same as the to-be marketed formulation. See the end of this study review for information regarding tablet formulation, dissolution method and dissolution data. The sponsor did not provide the components for Drixoral and the solution formulations used in this study.

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Blood samples for PSE determinations were drawn immediately prior to drug administration (0 hour) and then at, 0.5, 1, 2, 3, 3.5, 4, 5, 6, 6.5, 7, 8, 9, 9.5, 10, 11, 12, 16, 24, 36 and 48 hr post-dose.

Analytical Method

Plasma samples were analyzed for pseudoephedrine concentrations using a method with a lower limit of quantitation (LOQ) of 10 ng/mL and a linear range of 10 to 400 ng/mL in human plasma.

SAFETY MEASUREMENTS

Safety was assessed by monitoring adverse events, laboratory safety tests (CBC, blood chemistries and urinalysis), pre and poststudy physical examinations, vital signs and electrocardiograms.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The mean and %CV were calculated for plasma concentrations of SCH 04855 at each time point for each treatment. Concentration values less than the assay LOQ (10.0 ng/mL) were reported as and set to zero in the calculations. Individual plasma concentration-time data were used to calculate the pharmacokinetic parameters using model-independent methods.

Statistical Analysis

Summary statistics were calculated for the concentration data and the derived pharmacokinetic parameters for each pseudoephedrine treatment. The derived pharmacokinetic parameters [C_{max}, T_{max}, AUC(tf), AUC(I)] were analyzed using a

crossover analysis of variance model. The effects due to subject, period and treatment were extracted. The Cmax and AUC values were log-transformed and the following were calculated using the pooled residual error and associated degrees of freedom from the ANOVA:

- 90% Confidence Intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean. CIs were also constructed for original-scale of Cmax and AUC values.
- Power to detect a 20% difference in treatment means for an alpha level of 0.05 (two-tailed).

Reviewer’s remarks

The sponsor used 16 different sequences in this study (different sequence for each of the 16 subjects). For this reason, this reviewer could not user WinNonlin program to calculate 90% CI. This reviewer consulted the department of statistics for an advice on the suitability of the design of this study. Dr. Machado considered this an unusual design and that it is recommend as few sequences as possible. Dr. Shurmann stated that in this design, "subject" and "sequence" are just two different labels for the same thing and that instead of our usual SAS PROC GLM model with factors SEQ SUBJ(SEQ) PER TRT, we should use a model with the factors SUBJ PER TRT.

Since this is not a pivotal BE study, this reviewer is of the opinion that the sequence design used this study is irrelevant for its purpose.

RESULTS

Analytical Method

Pre-Study Validation: The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

In study Validation Results

Table 2. In-study validation information for Pseudoephedrine

Human Plasma heparin	
Linearity	Satisfactory: Standard curve range from 10 to 399.4 ng/mL; $r^2 \geq 0.998$
Accuracy	Satisfactory: -1.6 (% bias) at 30.1 ng/mL; -5.7 at 150 ng/mL; -1.8 at 280 ng/mL..
Precision	Satisfactory: 10 (% bias) at 30.1 ng/mL; 5.8 at 150 ng/mL; 6.1 at 280 ng/mL
Specificity	Satisfactory: Chromatograms submitted

Pharmacokinetic Results

A total of 17 subjects entered the study, and 16 completed all four-treatment periods. The mean plasma concentration-time profiles for PSE following administration of the four formulations are presented in Figure 1. The mean pharmacokinetic parameters for PSE are summarized in Table 3 and the individual Cmax and AUC(inf) values

following the administration of the four formulations are shown in Figures 2 and 3, respectively.

The volume of 3 blood samples (Subject 12: 0 hr Treatment A and 0.5 hr Treatment C; and Subject 13: 0.5 hr Treatment C) were not sufficient for analysis. One blood sample for Subject 17 (3.5 hr Treatment B) was missing. As a result, plasma concentration data at these time points for these subjects were missing. According to the sponsor, these missing data were considered to have no impact on the interpretation of the pharmacokinetic parameters for these subjects. This reviewer agrees with this statement.

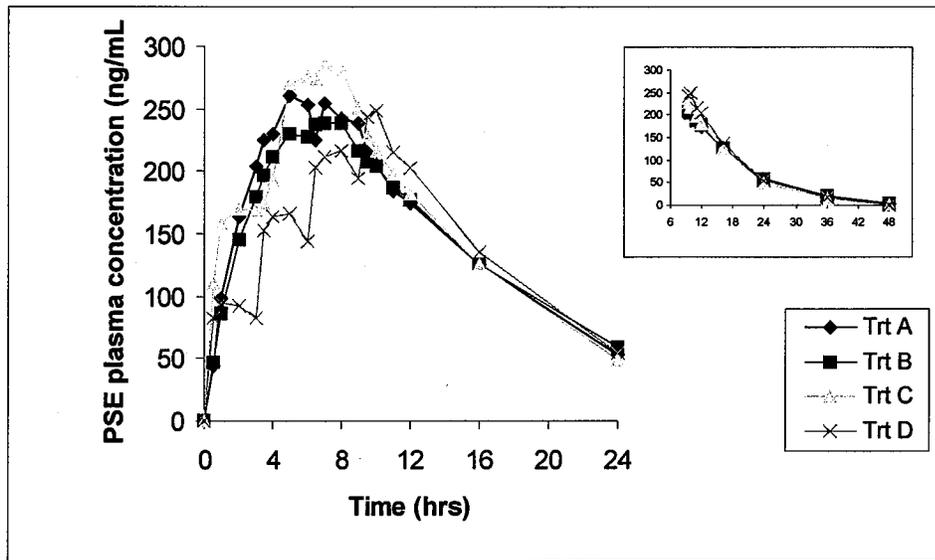


Figure 1. Mean PSE plasma concentration-time profiles following single administration of controlled-released (12-hr) Clarinex tablet formulations: A: formula 3526; B: formula 3525; C: Drixoral nasal decongestant containing 120 mg of PSE; D: 30 mg PSE sulfate administered as a solution at approx. 8 am, 11 am, 2 pm and 5 pm. The insert refers to the end of PSE profile.

Table 3. Mean (%CV) pharmacokinetic parameters of PSE following single administration of two extended-released (12-hr) PSE tablet formulations, Drixoral nasal decongestant tablet and PSE solution (n=16).

Treatment	Mean (%CV) PK Parameters		
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)
A (formula 3526)	279 (19)	6.19 (24)	4202 (27)
B (Formula 32525)	254 (16)	6.16 (27)	4105 (24)
C (Drixoral)	317 (23)	6.47 (20)	4228 (22)
D (PSE solution)	265 (19)	9.16 (17)	3820 (23)

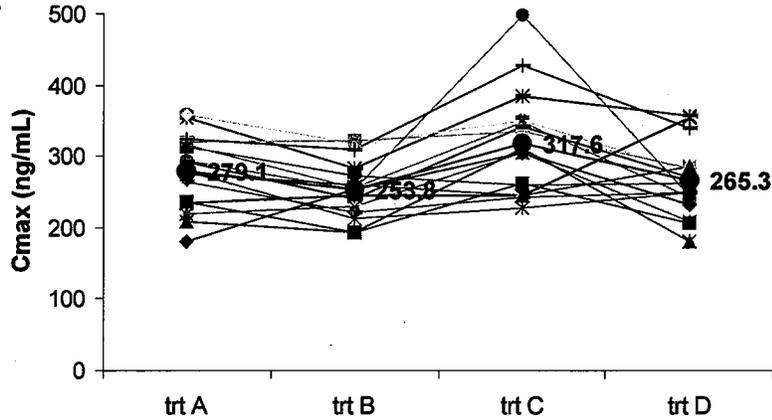


Figure 2. Individual PSE Cmax values following single administration of two extended-released (12-hr) PSE tablet formulations (A:3526; B:3525), Drixoral nasal decongestant tablet (trt C) and PSE solution (trt D) (n=16).

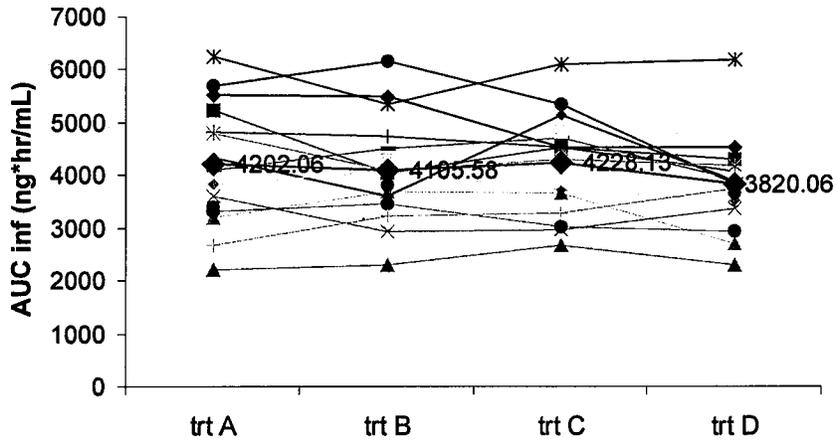


Figure 3. Individual PSE AUC inf values following single administration of two extended-released (12-hr) PSE tablet formulations (A:3526; B:3525), Drixoral nasal decongestant tablet (trt C) and PSE solution (trt D) (n=16).

The estimates of bioequivalence and the 90% confidence intervals for the log-transformed Cmax and AUC values for Treatments B and B relative to C and D are included in Table 4. For Treatment A, the CI of AUC(tf) and Cmax, relative to Treatments C and D, met the 80-125% bioequivalence guideline, indicating that the 120-mg bilayer extended-release pseudoephedrine sulfate tablet, Formula No. 3526, was bioequivalent with Drixoral, Nasal Decongestant tablet and the solution. For Treatment B, the confidence intervals of AUC(tf) and Cmax, relative to Treatment D, met the 80-125% bioequivalence guideline. Relative to Treatment C, the confidence interval of AUC(tf) for Treatment B

met the 80-125% bioequivalence guideline; however, the confidence interval for Cmax did not meet the 80-125% bioequivalence guideline. *The results indicated that the 120-mg bilayer extended-release pseudoephedrine sulfate tablet, Formula No. 3525, was bioequivalent with a solution, but was not bioequivalent with Drixoral, Nasal Decongestant tablet.*

Table 4. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
		Sponsor's findings	Sponsor's findings
TrtA/trtC	AUCt	98.2	92-105
	Cmax	88.5	81-96
TrtA/trtD	AUCt	109	102-116
	Cmax	105	97-115
TrtB/trtC	AUCt	96.8	91-103
	Cmax	81	74-88
Trt B/ trt D	AUCt	107	100-114
	Cmax	96.2	88-105

A:3526; B:3525, C:Drixoral nasal decongestant tablet, and D:PSE solution (n=16).

GENERAL COMMENTS

The objective of this study was to select the PSE formulation that is equivalent to current PSE formulation for further development of the Clarinex D-12 tablet. For this purpose the sponsor evaluated two different formulations of PSE in a study design which involved 16 subjects and 16 different sequence combinations. The statistician's opinion is that this design is unusual. It is generally recommended to use the least number of sequences as possible.

COMMENTS TO SPONSOR

1. Please submit the components (including batch numbers) of the Drixoral and Solution formulations used in this study.

CONCLUSION

- The 120-mg bilayer extended-release pseudoephedrine sulfate tablet, Formula No. 3526, was bioequivalent with Drixoral, Nasal Decongestant tablet and a solution.
- The 120-mg bilayer extended-release pseudoephedrine sulfate tablet, Formula No. 3525, was bioequivalent with a solution, but was not bioequivalent with Drixoral, Nasal Decongestant tablet.

Dissolution

The Clarinex (12-hr) tablet formulations used in this study, proposed dissolution method and specifications are listed below.

Table D1. Proposed dissolution method for Clarinex D-12 tables

Method

Sustained Released Layer

Approximate total weight

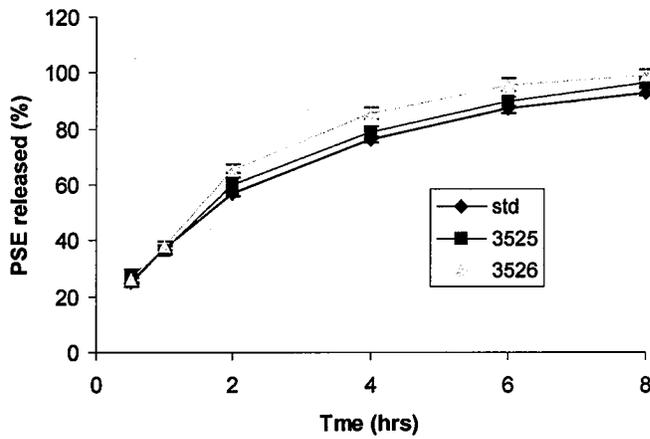


Figure 1D. Mean in vitro PSE sulfate released profiles for standard formula (from study 01352), 3525, and 3526 extended release formulations of Clarinex D-12/PSE tablets.

Table D5. Dissolution data for Clarinex D-12 tablets/PSE

Standard formulation (from study 01352)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5													25	1.6
1													37	1.6
2													57	1.2
4													76	1.2
6													87	1.4
8													93	1.4
3526 formulation														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev

0.5	┌												26	1.4
1													38	1.6
2													65	2.4
4													86	2.2
6													96	2.4
8												└	99	2.2

3525 formulation															
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev	
0.5	┌												27	2.4	
1													37	1.5	
2													60	4.0	
4													79	2.2	
6													90	1.8	
8												└	97	1.4	

"INFLUENCE OF FOOD ON THE ORAL BIOAVAILABILITY OF DL D-12 ADMINISTERED TO HEALTHY SUBJECTS: A TWO-WAY CROSSOVER STUDY"

Name of Sponsor: Schering-Plough Corporation
Included Protocols: P00440
Development Phase of Study: I
Study Initiation Date: 26 July 1999
Study Completion Date: 8 September 1999
Sponsor's Project Physician: Mark Marino, M.D.
Sponsor's Project Director: Christopher Banfield, Ph.D.
Date of the Report: 18 April 2000
Report Number: 00070053

OBJECTIVE

- to assess the influence of food on the oral bioavailability of DCL D-12 components by determining the bioequivalence of desloratadine (SCH 34117, DCL), 3-OH desloratadine (SCH 45581), and pseudoephedrine (SCH 4855) following single-dose oral administration of DCL D-12 (2.5 mg DCL/120 mg pseudoephedrine) under either a fed or fasted conditions in healthy adult subjects.

SUBJECTS

Thirty-six healthy volunteers (24 males and 12 females) between the ages of 18 and 44 years inclusive (mean=29.4 years) with a BMI between 19 and 28 kg/m² (mean=23.7 kg/m²) were enrolled into the study. Twenty-five subjects were Caucasian, 10 were Black and 1 was classified as other.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a Phase I, randomized, open-label, 2-way crossover study in 36 healthy subjects with at least a 14-day washout period between each treatment.

Subject 7 did not complete the study. Therefore, the total number of subjects in the study was 35 rather than 36. Each subject received the following treatments in the order assigned by a computer-generated random code:

Treatment A: One DCL D-12 (2.5 mg DCL/120 mg pseudoephedrine) tablet administered after a 10-hr fast.

Treatment B: One DCL D-12 (2.5 mg DCL/120 mg pseudoephedrine) tablet administered immediately following a standardized high-fat, high-caloric breakfast.

Each DCL D-12 tablet was administered with 180 mL of non-carbonated room temperature water. For Treatment A, subjects received DCL D-12 after a 10-hr fast. For Treatment B, subjects consumed the standardized high-fat, high-caloric breakfast over a 20-min period, and then received DCL D-12 within 5 min after breakfast (total calories: 841; protein 31.6g; fat: 53.8g; carbohydrates: 57.4g)

FORMULATION

The Clarinex D-12 tablet(s) were manufactured by SPRI, Kenilworth, NJ, USA. The following formulation (Table 1) was used:

Table 1. Formulation for Clarinex D-12 Tablets

Strength	120 mg PSE; 2.5 mg DL
Formula. No.	3538
Batch No.	75882-053
FMR No.	99627D02
Manf. Date	5/12/99
Manf. Site	Kenilworth, NJ
Batch Size (tablets)	

Formula 3538 is the same as the to-be marketed formulation. See the end of this study review for information regarding tablet formulation, dissolution method and dissolution data.

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Blood samples for PSE, DL and 3-OH DL determinations were drawn immediately prior to drug administration (0 hour) and then at, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96 and 120 hr post-dose.

Analytical Method

Plasma concentrations of DL, 3-OH DL, and PSE were determined using validated liquid chromatography with () methods with lower limit of quantifications (LOQ) of 0.025 ng/mL, 0.025 ng/mL, and 10.0 ng/mL, respectively.

SAFETY MEASUREMENTS

Safety was assessed by monitoring adverse events, laboratory safety tests (CBC, blood chemistries and urinalysis), pre and poststudy physical examinations, vital signs and electrocardiograms.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The mean and %CV were calculated for plasma concentrations of DL, 3-OH DL and PSE at each time point. Concentration values less than the assay LOQ were reported as and set to zero in the tables and calculations. The plasma concentration-time data for DL, 3-OH DL and PSE were subjected to pharmacokinetic analysis by non-compartmental methods using the WinNonlin™ Professional computer program.

Statistical Analysis

Summary statistics (mean and %CV) were calculated for the concentration data at each sampling time and for the derived pharmacokinetic parameters. The pharmacokinetic parameters were then subjected to statistical analysis by using a cross-over analysis of variance (ANOVA) model. The effects due to sequence, subject within sequence, period, and treatment were extracted. Cmax and AUC values were log-transformed, and 90% confidence intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean were calculated.

Reviewer's remarks

This reviewer used WinNonlin program to calculate 90% confidence intervals for the ratio of the means (Cmax and AUCinf) between treatments (A vs. B; see Table 4).

RESULTS

Analytical Method

Pre-Study Validation: The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

In-Study Validation

Table 2. In-study validation information for DL, 3-OH DL and PSE

	DL	3-OH DL	PSE
Linearity	Satisfactory: Standard curve range from 0.025 to 10.0 ng/mL; $r^2 \geq 0.996$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.99$	Data not submitted
Accuracy	Satisfactory: 6.3% (% Bias) at 0.075 ng/mL; 7.9% at 0.998 ng/mL; 8.8% at 7.48 ng/mL.	Satisfactory: -10.3% (% Bias) at 0.075 ng/mL; -6.4% at 1.0 ng/mL; -4.1% at 7.5 ng/mL.	Data not submitted
Precision	Satisfactory: (%CV) 10.7 at 0.075 ng/mL; 4.6 at 0.998 ng/mL; 7.3 at 7.48 ng/mL.	Satisfactory: 8.3% at 0.075 ng/mL; 3.7% at 1.0 ng/mL; 6.7% at 7.5 ng/mL.	Data not submitted
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted	Data not submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite and for PSE following administration of Clarinex tablets under fed and fasted conditions are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for PSE, DL and its metabolite are summarized in Table 3. Individual DL and 3-OH DL C_{max} and AUC(inf) values following the administration of the tablet under fed and fasted conditions are shown in Figures 3 and 4, respectively. Likewise, individual C_{max} and AUC_{inf} for PSE are represented in Figures 5 and 6, respectively. For 3-OH DL, the plasma concentrations for Subject 33 were very low, and AUC(I) for this subject could not be calculated accurately. According to the sponsor, this subject was considered to be a slow metabolizer. As a result, Subject 33 was excluded from all calculations for 3-OH DL. Two slow metabolizer were identified in these studies (one in study P00440 and one in P00446). The DL AUC_{inf} values in these subjects were 8 to 10-fold higher than the mean AUC_{inf} (27 ng*hr/mL) and 3-OH DL values of 5.11 ng*hr/mL, which were 3-fold lower (to undetectable values of the metabolite) than the mean values (15 ng*hr/mL). Low ratios of AUC DL/AUC 3-OH DL have been identified in previous Clarinex NDAs (21-312 and 21-300) suggesting the existence of DL slow metabolizers. The clinical relevance of these observations on the safety of Clarinex should be evaluated by the medical reviewer.

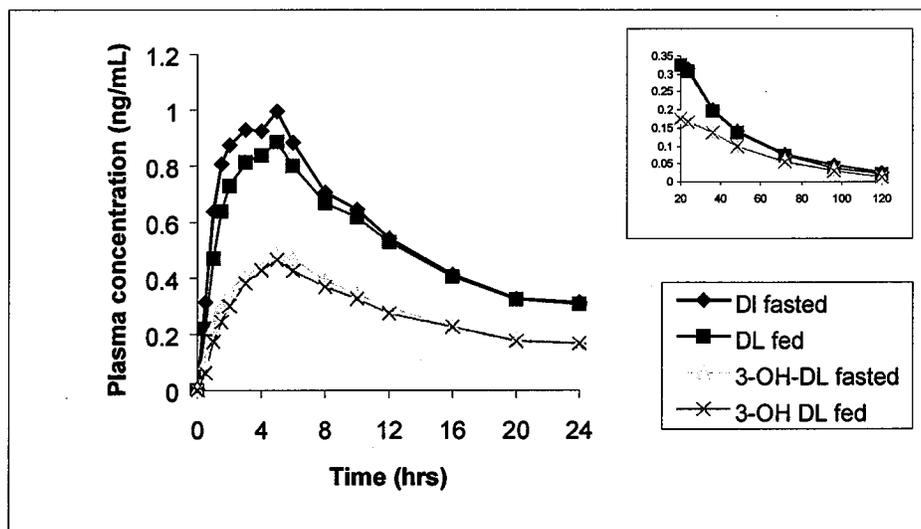
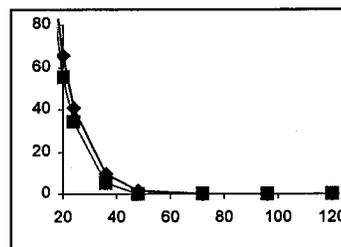


Figure 1. Mean DL and 3-OH DL plasma concentration-time profiles following single administration of controlled-released (12-hr) Clarinex tablets under fed and fasted conditions. The insert reflects the terminal phase for both drugs.



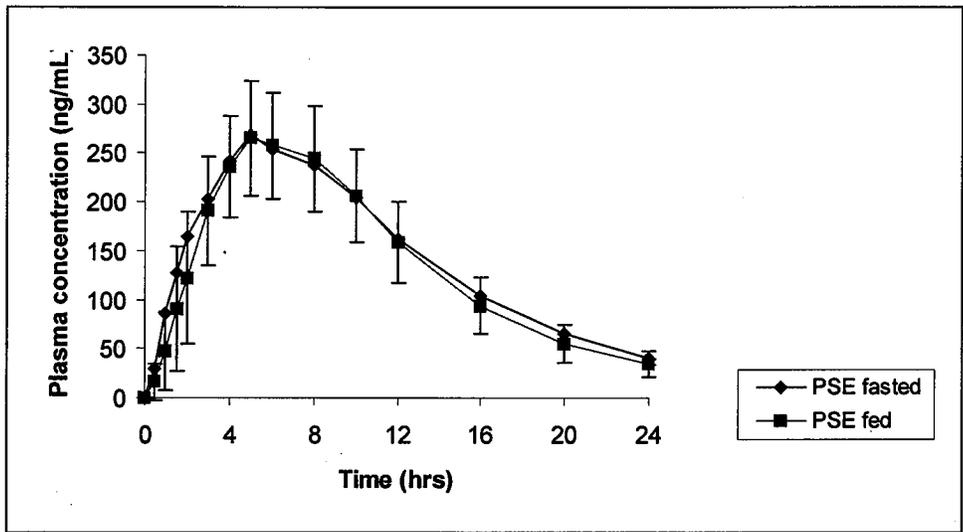


Figure 2. Mean PSE plasma concentration-time profiles following single administration of controlled-released (12-hr) Clarinex tablets under fed and fasted conditions. The insert reflects the terminal phase for PSE.

APPEARS THIS WAY
ON ORIGINAL

Table 3. Mean (%CV) pharmacokinetic parameters of DL, 3-OH DL and PSE following single administration of Clarinex (12-hr) tablets (2.5mgDL/120mgPSE)

Treatment	Mean (%CV) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
Desloratadine					
Fasted	1.09 (19)	4.16 (38)	23.5 (77)	27.3 (123)	23.5 (63)
Fed	1.01 (26)	4.21 (59)	21.7 (69)	25.1 (109)	22.9 (59)
3-OH Desloratadine					
Fasted	0.504 (23)	5.26 (20)	13.6 (24)	15.3 (22)	34.5 (16)
Fed	0.496 (25)	5.13 (47)	13 (24)	14.5 (22)	32.3 (20)
Pseudoephedrine					
Fasted	273 (24)	5.03 (23)	3725 (26)	3890 (24)	6.29 (19)
Fed	277 (20)	5.6 (25)	3429 (22)	3587 (21)	5.52 (21)

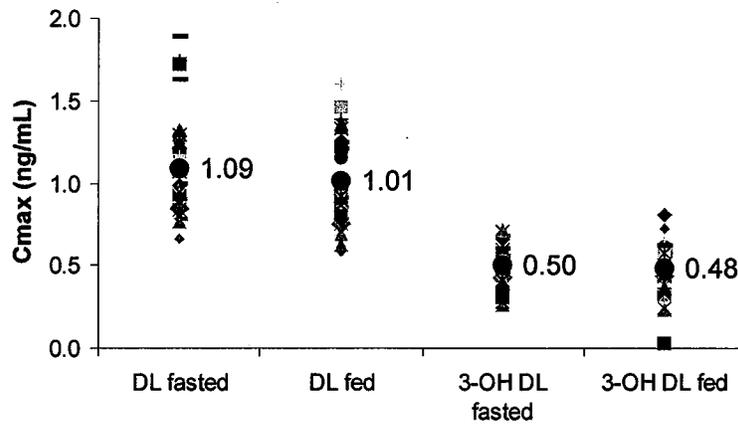


Figure 3. Individual DL and 3-OH DL Cmax values following single administration of Clarinex D-12 tablets under fed and fasted conditions.

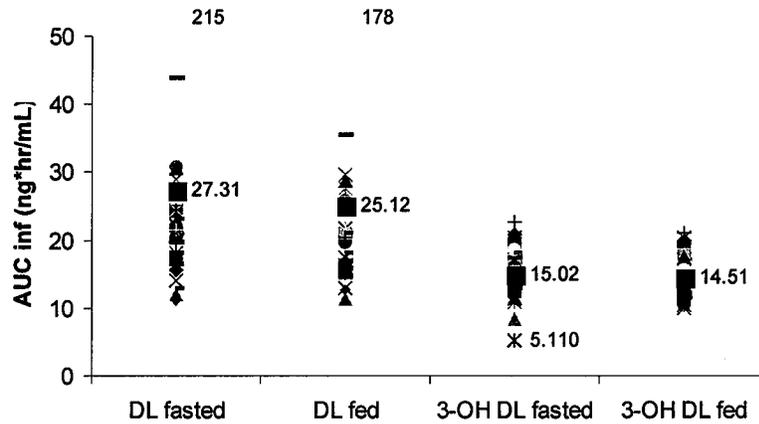


Figure 4. Individual DL and 3-OH DL AUC inf values following single administration of Clarinex D-12 tablets under fed and fasted conditions. Data labels (high values) correspond to a potential slow metabolizer.

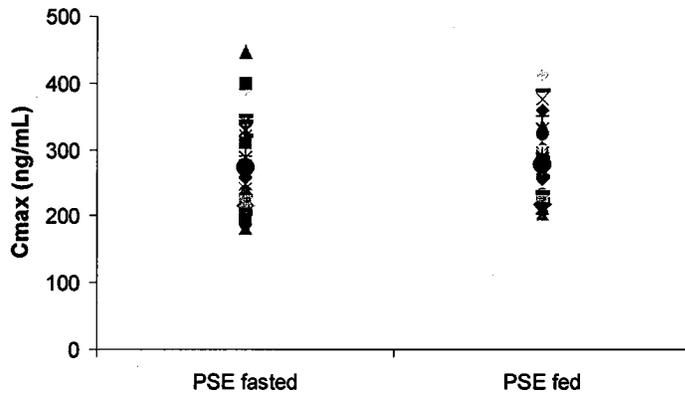


Figure 5. Individual PSE Cmax values following single administration of Clarinex D-12 tablets under fed and fasted conditions.

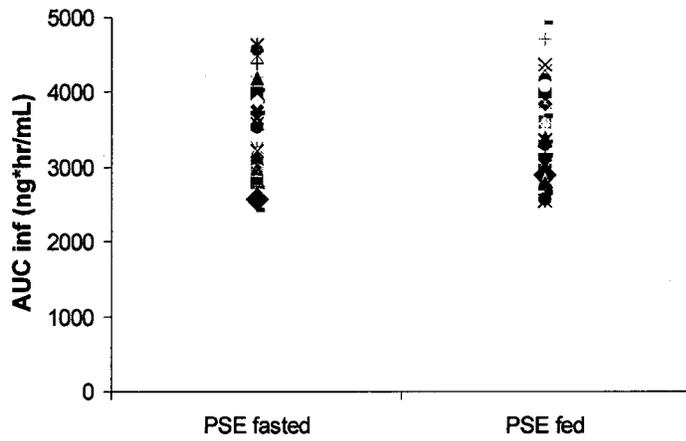


Figure 6. Individual PSE AUCinf values following single administration of Clarinex D-12 tablets under fed and fasted conditions.

Preliminary statistical analysis was performed to examine the extreme pharmacokinetic values and the impact of outliers on the overall results. It was found that exclusion of outliers did not change the overall bioequivalence conclusion of the study. Therefore, all subjects (except Subject 33 for 3-OH DL) were included in the final statistical analysis.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL, its metabolite and PSE are presented in Table 4. The CIs of AUC(I) and Cmax for DL, its metabolite and PSE under fed condition relative to fasted conditions met the 80-125% bioequivalence guideline.

This indicates that the Clarinex D-12 tablet administered under fasted and fed conditions were bioequivalent, and that a high-fat and high-caloric meal had no effect on the bioavailability of DL, its metabolite and PSE from the DL D-12 tablet.

Table 4. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL and PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
Desloratadine					
Fed/fasted	AUCinf	95.1	98.2	92-98	95.1-101.4
	Cmax	92.7	94.1	87-99	88.4-100.3
3-OH DL					
Fed/Fasted	AUCinf	94.9	99.9	92-98	97.15-102.7
	Cmax	97.9	100.9	95-101	89.6-113.65
Pseudoephedrine					
Fed/fasted	AUCinf	92.9	100.44	89-97	95.75-105.36
	Cmax	102	97.8	97-108	92.9-103.14

CONCLUSION

- High-fat and high-caloric meal had no effect on the bioavailability OF DL, its metabolite and PSE from the Clarinex D-12 tablets.

**APPEARS THIS WAY
ON ORIGINAL**

Batch number 75882-053 (formula 3538)

Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
3 Percent PSE sulfate dissolved/dosage form														
0.5													25	1.6
1													37	1.6
2													57	1.2
4													76	1.2
6													87	1.4
8													93	1.4
4 Percent DL dissolved/dosage form														
0.5													88	11.5
1													96	7.38

COMMENTS

This batch of Clarinex tablets is within the specifications proposed by the sponsor and by this reviewer. Refer to study P01352 for details on the rationale for selecting these specifications.

**APPEARS THIS WAY
ON ORIGINAL**

"THE MULTIPLE DOSE PHARMACOKINETICS OF CLARINEX D-12"

Name of Sponsor: Schering-Plough Corporation
Included Protocols: P00883
Development Phase of Study: I
Study Initiation Date: 23 DEC 1999
Study Completion Date: 14 FEB 2000
Sponsor's Project Physician: Paul Glue, M.D., Ph.D.
Sponsor's Project Director: Christopher Banfield, Ph.D.
Date of the Report: 27 JUN 2000
Report Number: 1515783

OBJECTIVE

- to determine the pharmacokinetic profile of desloratadine (SCH 34117, DL), 3-OH desloratadine (SCH 45581, 3-OH DL) and pseudoephedrine (SCH 4855) following twice daily administration of DL D-12 (2.5 mg DL/120 mg pseudoephedrine) for 14 consecutive days in healthy subjects.

SUBJECTS

Eighteen healthy volunteers, 9 males and 9 females, between the ages of 21 and 43 years, inclusive (mean=36 years) with a BMI between 21 and 28 kg/m² (mean=25 kg/m²) and weighing between 56 and 98 kg (mean=69 kg) were enrolled into this study. Fourteen subjects were Hispanic (78%), 2 were Caucasian (11%) and 2 were Black (11%).

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a Phase I, single-site, open-label, multiple-dose steady state study. Sixteen subjects completed the study. Two subjects (Subjects 2 and 14) dropped out because of personal reasons and were not replaced. Each subject received one DL D-12 (2.5 mg DL/120 mg pseudoephedrine) tablet in the morning (8 am) and in the evening (8 pm) of Days 1 through 14. Each dose was administered with 180 mL of non-carbonated room temperature water. Each subject was fasted overnight at approximately 10 hr prior to and until 4 hr after the morning dosing on Day 14.

Each subject received the following treatment twice a day for 14 days:

Treatment A: Desloratadine 2.5-mg (2.5 mg DCL/0 mg pseudoephedrine) bilayer tablet.

FORMULATION

The Clarinex D-12 tablets were manufactured by SPRI, Kenilworth, NJ, USA. The following formulation (Table 1) was used:

Table 1. Formulations for Clarinex D-12 Tablets

Strength	120 mg PSE; 2.5 mg DL
Formula. No.	3538
Batch No.	75882-053
FMR No.	99627D02
Manf. Date	5/12/99
Manf. Site	Kenilworth, NJ
Batch Size (tablets)	

Formula 3538 is the same as the to-be marketed formulation. The batch size was _____ tablets. See page 19 for information regarding tablet formulation, dissolution method and dissolution data.

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Blood samples for PSE, DL and 3-OH DL determinations were collected into heparin-containing tubes immediately prior to dosing on Day 1 and prior to both morning and evening dosing on Days 10, 11, 12 and 13 and then on Day 14 at the following times: 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 16, 18, 20, 22 and 24 hr after the morning dosing.

Analytical Method

Plasma concentrations of DL, 3-OH DL and pseudoephedrine were determined using _____ methods. The lower limits of quantitation (LOQ) were 0.025 ng/mL, 0.025 ng/mL and 10.0 ng/mL, respectively. The methods were validated over the concentration range of 0.025 to 10.1 ng/mL for DL, 0.025 to 10.0 ng/mL for 3-OH DL and 10 to 401 ng/mL for pseudoephedrine. Plasma concentrations below the assay LOQ were reported as zero. The analyses were performed at _____

SAFETY MEASUREMENTS

Safety was assessed by monitoring adverse events, laboratory safety tests (CBC, blood chemistries and urinalysis), pre and poststudy physical examinations, vital signs and electrocardiograms.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The mean and %CV were calculated for plasma concentrations of DL, 3-OH DL and pseudoephedrine at each time point. The trough plasma concentrations (C_{min}) on Days 10 through 14 were the observed values.

Individual plasma DL, 3-OH DL and pseudoephedrine concentration-time data obtained on Day 14 were used to determine the following pharmacokinetic parameters using non-compartmental methods: the maximum plasma concentration during a dosing interval (C_{max1}, between 0 and 12 hr; and C_{max2}, between 12 and 24 hr), time to reach

the maximum plasma concentration after the morning (Tmax1) and the evening (Tmax2) doses, and plasma concentration at 12 hr (C12) and at 24 hr (C24) were observed values. The areas under the plasma concentration-time curve from time zero to 12 hr [AUC(0-12 hr)], from time 12 to 24 hr [AUC(12-24 hr)] and from time zero to 24 hr [AUC(0-24 hr)] were calculated using the trapezoidal method. The average plasma concentration and percent fluctuation over the period of 0 to 12 hr (Cavg1 and %Fluctuation1, respectively) and from 12 to 24 hr (Cavg2 and %Fluctuation2, respectively) were calculated as follows:

$$\begin{aligned} \text{Cavg1} &= \text{AUC (0-12hr)}/12\text{hr} \\ \text{Cavg2} &= \text{AUC (12-24hr)}/12\text{hr} \\ \% \text{fluctuation1} &= (\text{Cmax1}-\text{C12})/\text{Cavg1} *100 \\ \% \text{fluctuation2} &= (\text{Cmax2}-\text{C24})/\text{Cavg2} *100 \end{aligned}$$

The average values of steady-state Cmax, Tmax, Cavg, AUC and %Fluctuation over a dosing interval were calculated as the average of the respective parameter values over 0 to 12 hr period and over 12 to 24 hr period for each individual.

Statistical Analysis

Summary statistics (mean, standard deviation and %CV) were calculated for the concentration data at each sampling time and for the derived pharmacokinetic parameters. To determine if steady-state had been attained, plasma concentrations at 0 hr on Days 10-14 were analyzed extracting the effects due to subject and day as per the study protocol.

RESULTS

Analytical Method

Pre-Study Validation: The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

In study Validation Results

Table 2. In-study validation information for DL, 3-OH DL and PSE

	DL	3-OH DL	PSE
Linearity	Satisfactory: Standard curve range from 0.025 to 10.1 ng/mL; $r^2 \geq 0.998$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.999$	Data not submitted
Accuracy	Satisfactory: 4.4% (% Bias) at 0.076 ng/mL; 1.1% at 1.01 ng/mL; -2.7 % at 7.58 ng/mL.	Satisfactory: 2.3% (% Bias) at 0.075 ng/mL; -4.9% at 1.0 ng/mL; -9.8% at 7.53 ng/mL.	Data not submitted
Precision	Satisfactory: (%CV) 6 at 0.076 ng/mL; 2.6 at 1.01 ng/mL; 2.3 at 7.58 ng/mL.	Satisfactory: 4.7% at 0.075 ng/mL; 2.8% at 1.0 ng/mL; 1.9% at 7.53 ng/mL.	Data not submitted
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted	Data not submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for DL, 3-OH DL and PSE

following Clarinex-D-12 tablets twice daily administration for 14 days of are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for PSE, DL and its metabolite are summarized in Table 3. Individual DL and 3-OH DL C_{max} and AUC(0-12) and AUC (12-24hr) values following the administration of the Clarinex D-12 tablet are shown in Figures 3 and 4, respectively. Likewise, individual C_{max} and AUC (0-12hr) and AUC(12-24 hr) for PSE following administration of Clarinex D-12 tablets are represented in Figures 5 and 6, respectively. Individual C_{min} values for DL and PSE at steady-state (days 10, 11, 12, 13, and 14) are presented in Figures 7 and 8, respectively.

Pharmacokinetics of DL

Figure 1 (insert for DL) shows that steady-state conditions for DL were attained on Day 12 following repeated administration of DL D-12, as indicated by a lack of statistically significant difference ($P>0.05$) in the mean trough plasma concentrations between Day 12 and Day 14. After twice daily dosing of a DL D-12 tablet, mean and individual DL AUC(0-24 hr) values (mean, 40.4 ng·hr/mL; range, 28.0 to 63.0 ng·hr/mL, (Figure 9) were within the range of those (mean, 51.1 ng·hr/mL; range, 26 to 147 ng·hr/mL) reported previously in healthy volunteers receiving once daily dosing for 14 days of a 5-mg DL tablet (NDA 21-947). This suggests that daily exposure to DL after multiple oral dosing of DL D-12 tablets was comparable to that after DL tablets.

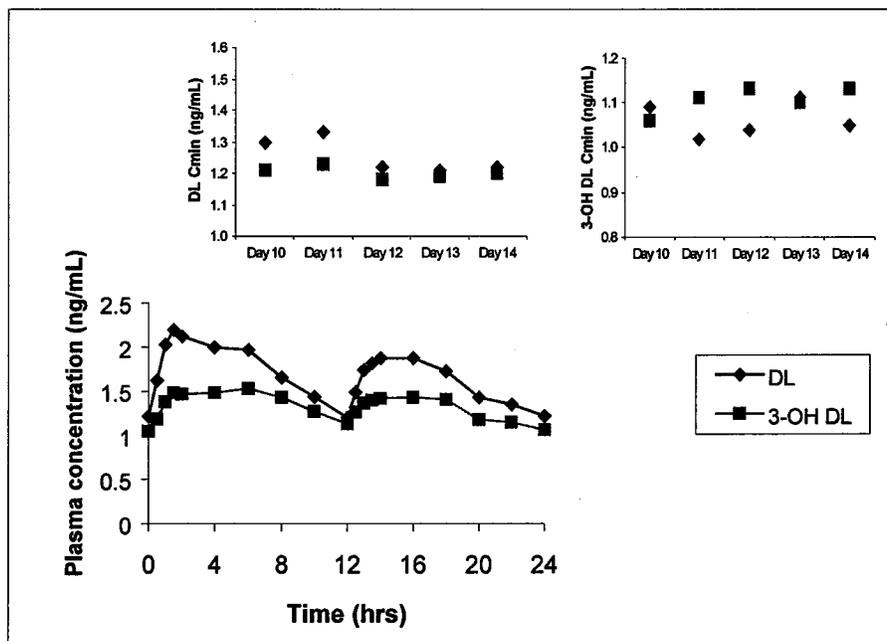


Figure 1. Mean DL and 3-OH DL and plasma concentration-time profiles (on Day 14) following twice-daily administration of Clarinex D-12 for 14 days. The insert correspond to the average C_{min} for DL and 3-OH DL on Days 10, 11, 12, 13 and 14 at time 0 (triangles) and 12 hrs (squares).

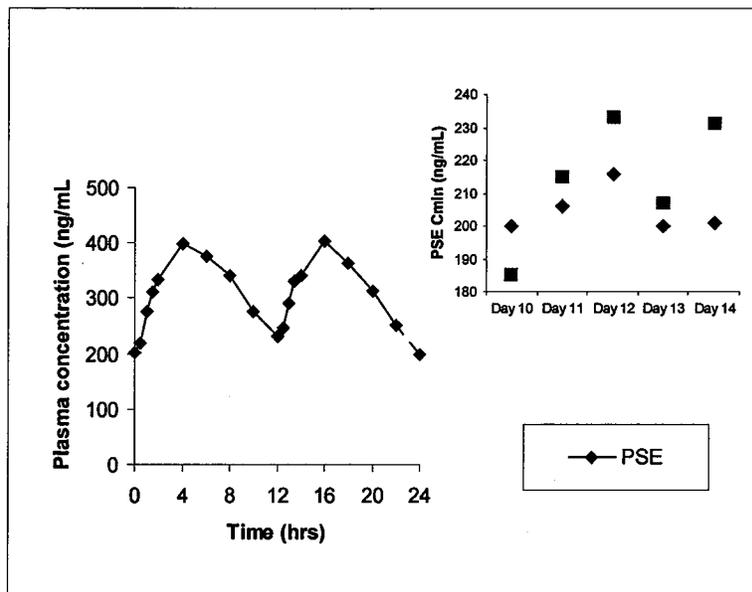


Figure 2. Mean PSE plasma concentration-time profiles (on Day 14) following twice-daily administration of Clarinex D-12 for 14 days. The insert correspond to the average Cmin for DL and 3-OH DL on Days 10, 11, 12, 13 and 14 at time 0 (triangles) and 12 hrs (squares).

Table 3. Mean (%CV) pharmacokinetic parameters of DL, 3-OH DL and PSE following twice daily administration of Clarinex (12-hr) tablets for 14 days

PK parameter	DL	3-OH DL	PSE
Cmax1 (ng/mL)	2.31 (20)	1.51 (26)	408 (19)
Cmax2 (ng/mL)	2 (26)	1.52 (21)	409 (17)
Tmax1 (hr)	2.31 (80)	4.09 (55)	4.88 (26)
Tmax2 (hr)	2.94 (50)	3.44 (59)	3.94 (35)
Cavg1 (ng/mL)	1.77 (22)	1.39 (42)	324 (17)
Cavg2 (ng/mL)	1.6 (24)	1.29 (23)	315 (13)
C12 (ng/mL)	1.2 (25)	1.13 (22)	231 (23)
C24 (ng/mL)	1.22 (28)	1.06 (25)	198 (16)
AUC(0-12hr) (ng*hr/mL)	21.2 (22)	16.7 (23)	3886 (17)
AUC(12-24hr) (ng*hr/mL)	19.2 (24)	15.5 (23)	3781 (13)
AUC(τ) avg (ng*hr/mL)	20.2 (23)	16.1 (23)	3834 (15)
AUC (0-24hr) (ng*hr/mL)	40.4 (23)	32.2 (23)	7667 (15)
%Fluctuation1	64 (33)	34 (27)	55
%Fluctuation2	49 (25)	36 (24)	66
%Fluctuation, avg	57 (25)	35 (20)	61

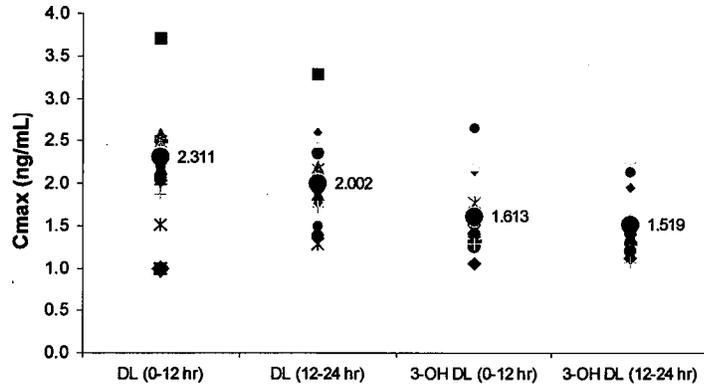


Figure 3. Individual DL and 3-OH DL Cmax values (day 14) following twice daily administration of Clarinex D-12 tablets for 14 days.

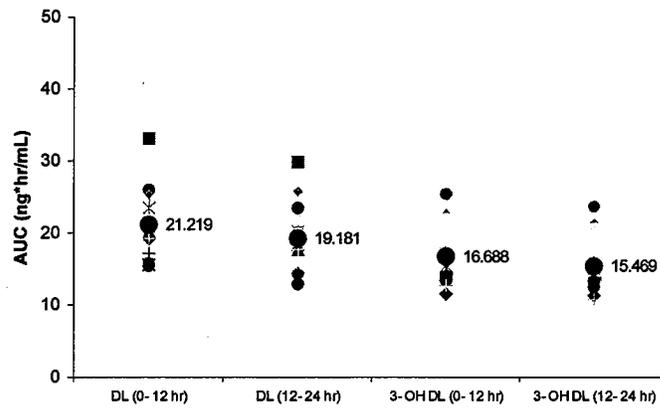


Figure 4. Individual DL and 3-OH DL AUC inf values (day 14) following twice daily administration of Clarinex D-12 tablets for 14 days.

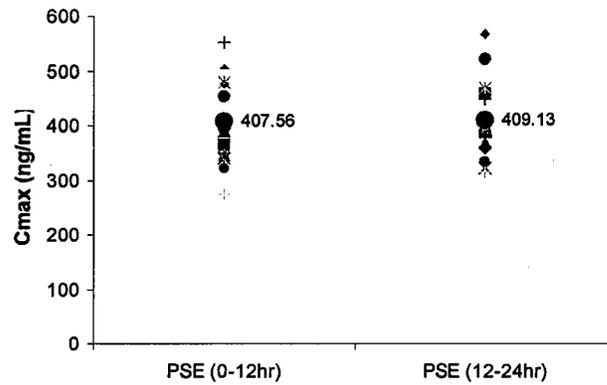


Figure 5. Individual PSE Cmax values (day 14) following twice daily administration of Clarinex D-12 tablets for 14 days.

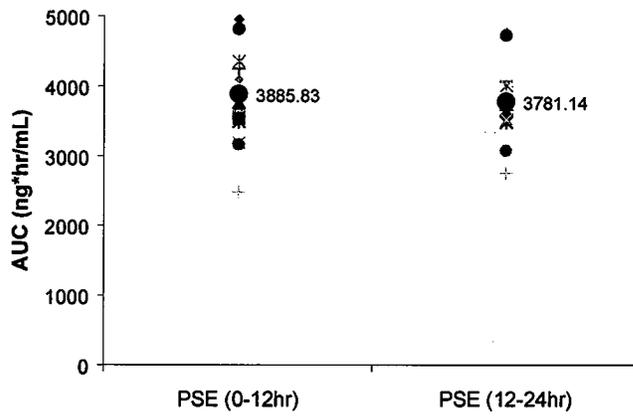


Figure 6. Individual PSE AUCinf values (day 14) following twice daily administration of Clarinex D-12 tablets for 14 days.

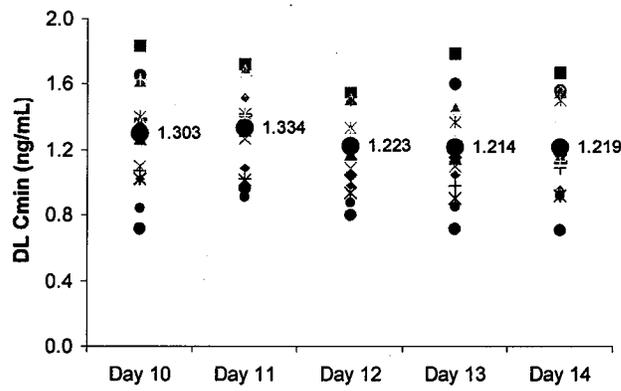


Figure 7. Individual DL Cmin values following twice daily administration of Clarinex D-12 tablets for 14 days.

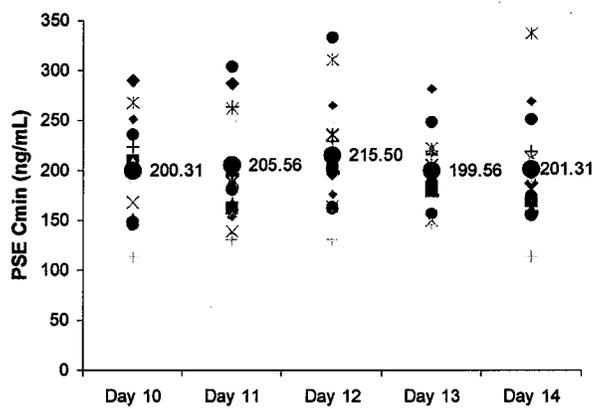


Figure 8. Individual PSE Cmin values following twice daily administration of Clarinex D-12 tablets for 14 days.

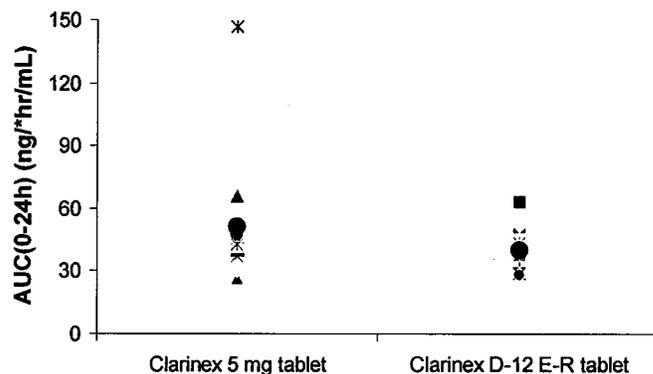


Figure 9. Individual DL AUC(0-24h) following multiple administration (14 days) of Clarinex tablets 5mg QD (NDA 21-297) and Clarinex D-12 BID (current NDA).

Pharmacokinetics of 3-OH DL

Results of the ANOVA analysis indicate that there was a significant difference in the mean Cmin values over the period of Days 10 to 14 ($p < 0.001$). However, according to the sponsor, there was no consistent trend in the fluctuations of the mean trough plasma concentrations (see the insert for 3-OH DL on Figure 1). This may suggest that 3-OH DL plasma concentrations have reached steady state on Day 14.

After twice daily dosing of a DL D-12, mean and individual 3-OH DL AUC(0-24 hr) values (mean, 32.2 ng·hr/mL; range, 23.0 to 49.0 ng·hr/mL, (see Table 3) were within the range of those (mean, 33.2 ng·hr/mL; range, 16.5 to 59.0 ng·hr/mL) reported previously in healthy normal metabolizers receiving once daily dosing of a 5-mg DL tablet. This suggests that daily exposure to 3-OH DL after multiple oral dosing of DL D-12 tablets was comparable to that after DL tablets.

Pharmacokinetics of PSE

The lack of statistical difference ($p = 0.421$) in the mean trough plasma concentrations (200 to 216 ng/mL) of pseudoephedrine indicates that steady-state conditions for pseudoephedrine had been attained by Day 10 of multiple dose administration of DL D-12 tablets (refer to insert in Figure 2).

CONCLUSION

- Steady-state concentrations for DL, its metabolite and PSE were attained by day 10-12.
- The average steady-state and individual AUC(0-24hr) values for DL and its metabolite following twice daily administration of Clarinex D-12 tablets were within those observed for Clarinex 5 mg tablet administered once daily for 14 days.
- The degree of fluctuation (%) for DL, its metabolite and PSE was 57, 35 and 61, respectively.

Table D4. Dissolution data for Clarinex D-12 tablets/PSE

Batch number 75882-053 (formula 3538)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
5 Percent PSE sulfate dissolved/dosage form														
0.5													25	1.6
1													37	1.6
2													57	1.2
4													76	1.2
6													87	1.4
8													93	1.4
6 Percent DL dissolved/dosage form														
0.5													88	11.5
1													96	7.38

COMMENTS

This batch 758802-053 of Clarinex tablets is within the specifications proposed by the sponsor and by this reviewer. Refer to study P01352 for details on the rationale for selecting these specifications.

**APPEARS THIS WAY
ON ORIGINAL**

**"BIOEQUIVALENCE OF DESLORATADINE AND PSEUDOEPHEDRINE
FOLLOWING SINGLE-DOSE ADMINISTRATION OF DL D-12
DESLORATADINE 2.5 mg AND PSEUDOEPHEDRINE 120 mg TABLET"**

Name of Sponsor: Schering-Plough Corporation
Included Protocols: P00446
Development Phase of Study: I
Study Initiation Date: 12 July 1999
Study Completion Date: 5 September 1999
Sponsor's Project Physician: Mark Marino, M.D.
Sponsor's Project Director: Christopher Banfield, Ph.D.
Date of the Report: 19 April 2000
Report Number: 00070052

OBJECTIVE

- to evaluate the bioequivalence of desloratadine (SCH 34117, DL), 3-OH desloratadine (SCH 45581) and pseudoephedrine (SCH 4855) following single-dose oral administration of desloratadine/pseudoephedrine combination product (DL D-12, 2.5 mg DL/120 mg pseudoephedrine), desloratadine 2.5 mg reference product, and pseudoephedrine (Drixoral® nasal decongestant, 120 mg) in healthy subjects.

SUBJECTS

Thirty-six healthy male and female (19 males and 17 females) volunteers between the ages of 19 and 45 years inclusive (mean=33.7 years) with a BMI between 21 and 28 kg/m² (mean=25.5 kg/m²) were enrolled into the study. Thirty-one subjects were Hispanic, four were Black and one was classified as other.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a Phase I, randomized, open-label, 3-way crossover study in 36 healthy subjects with at least a 14-day washout period between each treatment. Subject 27 did not complete the study. Therefore, the total number of subjects in the analysis was 35 rather than 36.

Each subject received the following treatments in the order assigned by a computer-generated random code:

Treatment A: DL D-12 (2.5 mg DL/120 mg pseudoephedrine) bilayer tablet.
Treatment B: Desloratadine 2.5-mg (2.5 mg DL/0 mg pseudoephedrine) bilayer tablet (desloratadine reference)
Treatment C: Drixoral ® nasal decongestant tablet (120 mg Pseudoephedrine) (PSE reference).

Following a 10-hr fast, subjects received each treatment with 180 mL of non-carbonated room temperature water. No food was allowed for 4 hr after dosing.

FORMULATION

The Clarinex D-12 tablets and DL bilayer tablets were manufactured by SPRI, Kenilworth, NJ, USA. The following formulations (Table 1) were used:

Table 1. Formulations for Clarinex D-12 Tablets

Strength	120 mg PSE; 2.5 mg DL
Formula. No.	3538
Batch No.	75882-053
FMR No.	99627D02
Manf. Date	5/12/99
Manf. Site	Kenilworth, NJ
Batch Size (tablets)	

Table 2. Formulations for DL bilayer Tablets

Strength	2.5 mg DL
Formula. No.	3567
Batch No.	53664-011
FMR No.	99643D02
Manf. Date	5/11/99
Manf. Site	Kenilworth, NJ
Batch Size (tablets)	

Formula 3538 is the same as the to-be marketed formulation. Refer to the end of this study review for information regarding tablet formulation, dissolution method and dissolution data. The sponsor did not provide the components or batch number for the Drixoral formulation used in this study.

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Blood samples for PSE, DL and 3-OH DL determinations were drawn immediately prior to drug administration (0 hour) and then at, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96 and 120 hr post-dose.

Analytical Method

Plasma concentrations of DL, 3-OH DL, and PSE were determined using _____ methods with lower limit of quantifications (LOQ) of 0.025 ng/mL, 0.025 ng/mL, and 10.0 ng/mL, respectively.

SAFETY MEASUREMENTS

Safety was assessed by monitoring adverse events, laboratory safety tests (CBC, blood chemistries and urinalysis), pre and poststudy physical examinations, vital signs and electrocardiograms.

DATA ANALYSIS

Pharmacokinetic Data Analysis

The mean and %CV were calculated for plasma concentrations of DL, its metabolite and PSE at each time point. Concentration values less than the assay LOQ were reported as and set to zero in the tables and calculations. The plasma concentration-time data for these drugs were subjected to pharmacokinetic analysis by non-compartmental methods using the WinNonlin™.

Statistical Analysis

Summary statistics (mean and %CV) were calculated for the concentration data at each sampling time and for the derived pharmacokinetic parameters. The pharmacokinetic parameters were then subjected to statistical analysis by using a cross-over analysis of variance (ANOVA) model. The effects due to sequence, subject within sequence, period, and treatment were extracted. Cmax and AUC values were log-transformed, and 90% confidence intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean were calculated.

Reviewer's remarks

This reviewer used WinNonlin program to calculate 90% confidence intervals for the ratio of the means (Cmax and AUCinf) between treatments (A vs. B and A vs.C); see Table 5).

RESULTS

Analytical Method

Pre-Study Validation: The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

In study Validation Results

Table 3. In-study validation information for DL, 3-OH DL and PSE

	DL	3-OH DL	PSE
Linearity	Satisfactory: Standard curve range from 0.025 to 10.0 ng/mL; $r^2 \geq 0.999$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.998$	Data not submitted
Accuracy	Satisfactory: 7.6% (% Bias) at 0.075 ng/mL; 9.4% at 0.998 ng/mL; 12.1% at 7.48 ng/mL.	Satisfactory: -10.3% (% Bias) at 0.075 ng/mL; -6.4% at 1.0 ng/mL; -4.1% at 7.5 ng/mL.	Data not submitted
Precision	Satisfactory: (%CV) -8.1 at 0.075 ng/mL; -5.1 at 0.998 ng/mL; -1.9 at 7.48 ng/mL.	Satisfactory: 7.0% at 0.075 ng/mL; 5.5% at 1.0 ng/mL; 6.7% at 3.5 ng/mL.	Data not submitted
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted	Data not submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite and for PSE following administration of Clarinex-D-12 tablets, DL bilayer tablets and Drixoral tablets are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for PSE, DL and its metabolite are summarized in Table 4. Individual DL and 3-OH DL C_{max} and AUC(inf) values following the administration of the Clarinex D-12 and DL tablets are shown in Figures 3 and 4, respectively. Likewise, individual C_{max} and AUC_{inf} for PSE following administration of Clarinex D-12 and Drixoral tablets are represented in Figures 5 and 6, respectively.

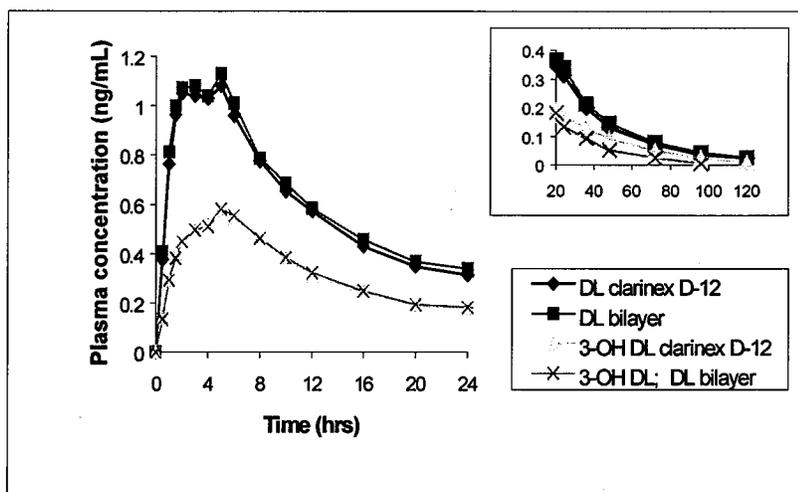


Figure 1. Mean DL and 3-OH DL and plasma concentration-time profiles following single administration of controlled-released (12-hr) Clarinex tablet and DL bilayer Tablet (reference product).

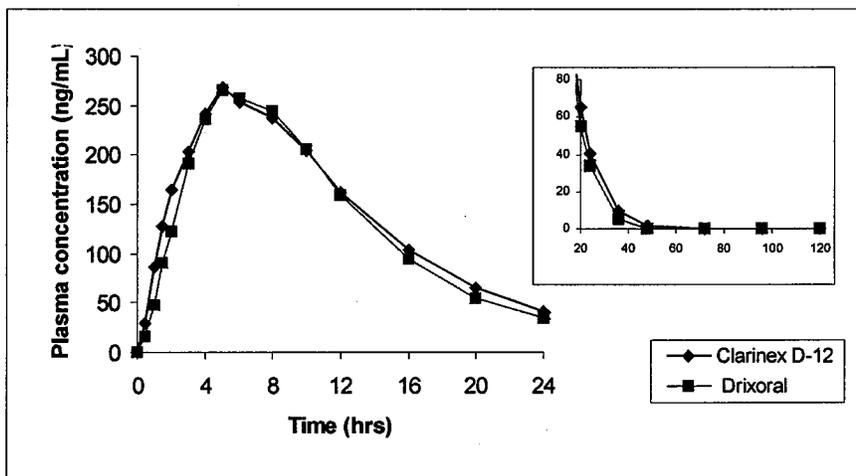


Figure 2. Mean PSE plasma concentration-time profiles following single administration of controlled-released (12-hr) Clarinex tablet and Drixoral tablets (reference product for PSE).

Table 4. Mean (%CV) pharmacokinetic parameters of DL, 3-OH DL and PSE following single administration of Clarinex (12-hr) tablets, Drixoral and the DL bilayer tablet

Treatment	Mean (%CV) PK Parameters				
	C _{max} (ng/mL)	T _{max} (hr)	AUC _t (ng*hr/mL)	AUC _{inf} (ng*hr/mL)	T _{1/2} (hr)
Desloratadine					
Clarinex D-12	1.20 (33)	4 (1.6-16)	23.9 (67)	29 (133)	22.3 (95)
DL bilayer	1.24 (31)	4 (1.5-10)	25.3 (69)	29.3 (112)	21.3 (66)
3-OH Desloratadine					
Clarinex D-12	0.504 (23)	5 (0-8)	13.7 (39)	14.9 (36)	27.6 (27)
DL bilayer	0.496 (25)	5 (0-6)	13.9 (36)	15.2 (34)	26.9 (27)
Pseudoephedrine					
Clarinex D-12	273 (24)	5 (3-8)	3122 (29)	3309 (28)	5.24 (15)
Drixoral	277 (20)	6 (1-12)	2924 (21)	3103 (20)	4.85 (15)

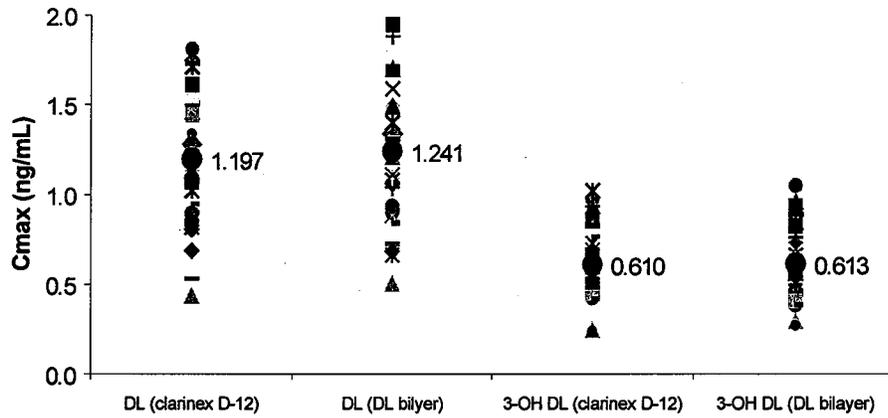


Figure 3. Individual DL and 3-OH DL C_{max} values following single administration of Clarinex D-12 tablets and DL bilayer tablets.

APPEARS THIS WAY
ON ORIGINAL

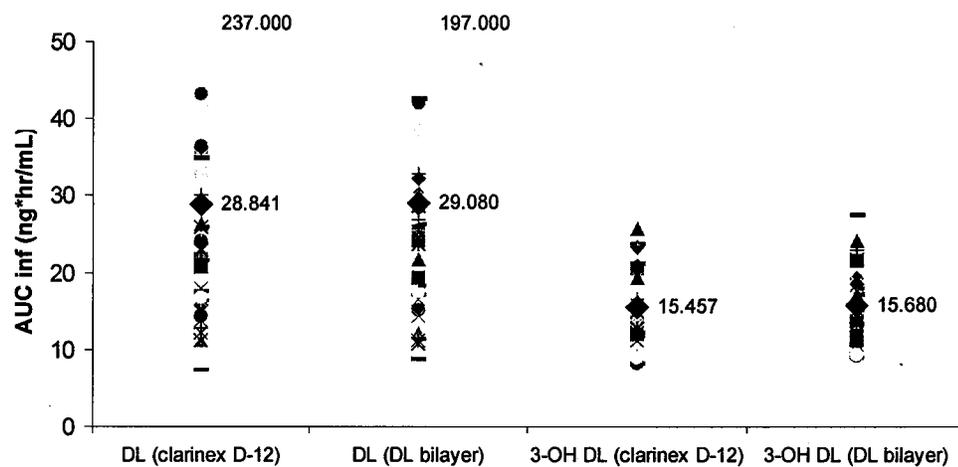


Figure 4. Individual DL and 3-OH DL AUC inf values following single administration of Clarinex D-12 tablets and DL bilayer tablets. The values 237 and 197 represent high values for subject 19, a potential slow metabolizer.

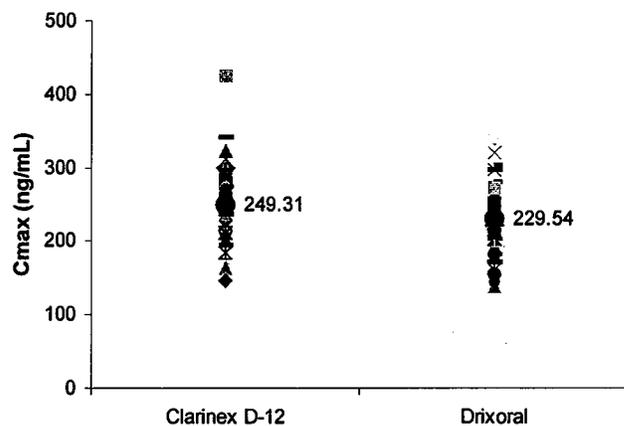


Figure 5. Individual PSE Cmax values following single administration of Clarinex D-12 tablets and Drixoral® tablets.

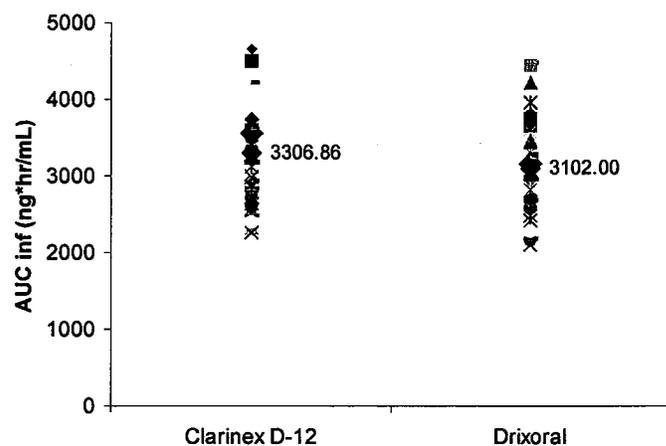


Figure 6. Individual PSE AUCinf values following single administration of Clarinex D-12 tablets and Drixoral® tablets.

Preliminary statistical analysis was performed to examine the extreme pharmacokinetic values and the impact of outliers on the overall results. It was found that exclusion of outliers did not change the overall bioequivalence conclusion of the study. Therefore, all subjects were included in the final statistical analysis.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL, its metabolite and PSE are presented in Table 5. The CIs of AUC(I) and Cmax for DL and its metabolite after Clarinex D-12 relative to DL bilayer tablets met the 80-125% bioequivalence guideline. The CIs of AUC(I) and Cmax for DL D-12 relative to Drixoral also met the 80-125% bioequivalence guideline.

The results indicated that the Clarinex D-12 and DL tablets were bioequivalent with regard to DL and its metabolite and the DL D-12 and Drixoral® tablets were bioequivalent with regard to PSE.

Table 5. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of PSE following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
Desloratadine					
Clarinex D-12/ DL bilayer	AUCinf	95.8	96.3	90-102	84.7-109.4
	Cmax	95.9	98.9	91-101	91.9-106.4
3-OH DL					
Clarinex D-12/ DL bilayer	AUCinf	97.3	97.5	94-101	88.3-105.1
	Cmax	98.8	99.5	96-102	92.4-107.2
Pseudoephedrine					
Clarinex D-12/ Drixoral	AUCinf	105	105.7	101-110	92.9-120.2
	Cmax	109	108.5	102-116	99.9-117.8

GENERAL COMMENTS

In order to show bioequivalency of the immediate release layer containing DL, the sponsor used as a bilayer tablet that contains placebo for PSE as a reference for DL. The use of this formulation (not approved formulation) as a reference for the DL portion of Clarinex D-12 was proposed by the sponsor in a Pre-NDA meeting with the agency. The OCPB team accepted this formulation as a reference most likely based on the following bases:

- The sponsor has previously shown that DL follows linear pharmacokinetics in the range of _____
- The sponsor proposed and conducted clinical trial to determine the safety and efficacy of this formulation.
- The lack of an approved reference for this product.

Because the sponsor has provided data on the safety and efficacy of this product and given the nature of the reference used, this reviewer is of the opinion that the data generated in this bioequivalence study referent to DL be disregarded. This agency should rely on the clinical trials to generate any conclusions about the safety and efficacy of the drug.

CONCLUSION

- The Clarinex D-12 and DL-bilayer tablets (not approved reference) were bioequivalent with regard to DL and 3-OH DL and PSE. However, given the nature of the reference used, this reviewer is of the opinion that the data generated in this bioequivalence study referent to DL be disregarded. This agency should rely on the clinical trials to generate any conclusions about the safety and efficacy of the drug.
- The Clarinex D-12 and Drixoral® tablets were bioequivalent with regard to PSE.

Dissolution

The Clarinex (12-hr) tablet formulation and DL bilayer formulation used in this study proposed dissolution method and specifications are listed below.

Table D1. Proposed dissolution method for Clarinex D-12 tables

Method	
Apparatus:	USP apparatus II (paddle)
Speed:	50 rpm
Temperature:	37 °C ± 0.5 °C
Medium:	0-1 hours: 0.1N HCL 1-8 hours: 0.1M PO4 buffer pH7.5
Volume:	1000 mL
Detection:	UV at _____

Table D2. Proposed dissolution specifications for Clarinex D-12

Time (hours)	Percent PSE sulfate release (sponsor's)	Percent PSE sulfate release (this reviewer's)
1		29-44
2		50-66
6	NLT %	NLT 80%
	DL dissolved	
0.5	Q %	

Table D3. Components for formula number 3538

Ingredients	mg/tablet
-------------	-----------

Immediate Release Layer

Sustained Released Layer

Approximate tablet weight

Table D4. Dissolution data for Clarinex D-12 tablets/PSE

Batch number 75882-053 (formula 3538)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
	Percent PSE sulfate dissolved/dosage form													
0.5													25	1.6
1													37	1.6
2													57	1.2
4													76	1.2
6													87	1.4
8													93	1.4
	Percent DL dissolved/dosage form													
0.5													88	11.5
1													96	7.38

**"THE BIOAVAILABILITY OF PSEUDOEPHEDRINE FROM CONTROLLED-
RELEASE (12-HOUR) FORMULATIONS: A FOUR-WAY CROSSOVER
STUDY"**

Name of Sponsor: Schering-Plough Corporation
Included Protocols: P01352
Development Phase of Study: I
Study Initiation Date: 07 MAR 2000
Study Completion Date: 05 JUN 2000
Sponsor's Project Physician: Mark Marino, M.D.
Sponsor's Project Director: Sauzanne Khalilieh, Pharm.D.
Date of the Report: 04 AUG 2000
Report Number: 1519639

OBJECTIVE

- to determine the bioequivalence of pseudoephedrine sulfate standard formulation relative to pseudoephedrine sulfate formulations with fast, slow and very fast dissolution rates.

SUBJECTS

A total of 19 subjects entered the study and 16 completed all four-treatment periods. These subjects (8 males and 11 females) were between the ages of 19 and 42 years inclusive (mean=30.6 years) with a BMI between 17.6 and 27 kg/m² (mean=23.1 kg/m²). Eleven subjects were Caucasian, 5 were Black, 2 were Asian and 1 was classified as other.

Subject No. 14 withdrew due to noncompliance after completing Periods 1, 2, and 3. Subject No. 16 (anemia) withdrew from the study prior to receiving treatment in Period 3 and Subject No. 18 (personal reasons) withdrew from the study after completing Periods 1 and 2

STUDY DESIGN AND TREATMENT ADMINISTRATION

Subjects were confined to the study site at least 12 hours prior to each treatment administration. In the morning of Day 1 following a 10-hour overnight fast, each subject received one of the following treatments based on his/her subject number and the study period.

Treatment A: SCH 483 tablets, 2.5-mg desloratadine/
120-mg pseudoephedrine-standard batch.

Treatment B: SCH 483 tablets, 2.5-mg desloratadine/
120-mg pseudoephedrine-fast batch.

Treatment C: SCH 483 tablets, 2.5-mg desloratadine/
120 mg pseudoephedrine-slow batch.

Treatment D: SCH 483 tablets, 2.5-mg desloratadine/
120 mg pseudoephedrine-very fast batch.

Each treatment administration was separated by at least a 7-day washout period.

FORMULATION

The DL D-12 tablet(s) were manufactured, packaged and supplied to the Investigator by SPRI, Kenilworth, NJ, USA. The following formulations (Table 1) were used:

Table 1. Formulations for DL D-12 Tablet

Tablet Strength	2.5 mg DL/120 mg Pseudoephedrine Standard Batch	2.5 mg DL/120 mg Pseudoephedrine Fast Batch	2.5 mg DL/120 mg Pseudoephedrine Slow Batch	2.5 mg DL/120 mg Pseudoephedrine Very Fast Batch
Formula. No.	3538	3636	3637	3638
Batch No.	75882-53	53664-025	53664-032	53664-035
FMR No.	99627D02	00506D09	00507D09	00508D09
Manf. Date	5/26/99	5/11/99	5/11/99	5/11/99
Manf. Site	Kenilworth, NJ	Kenilworth, NJ	Kenilworth, NJ	Kenilworth, NJ
Recertification Date	May, 2000	August, 2000	August, 2000	August, 2000
Batch Size (tablets)				

Batch No. 3538 is the same as the to-be marketed formulation. Refer to the end of this study review for information regarding tablet formulation, dissolution method and dissolution data.

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Blood samples for PSE determinations were drawn immediately prior to drug administration (0 hour) and then at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 36, and 48 hours after dosing.

Analytical Method

Plasma samples were analyzed for pseudoephedrine concentrations using a method with a lower limit of quantitation (LOQ) of 10 ng/mL and a linear range of 10 to 401 ng/mL in human plasma.

SAFETY MEASUREMENTS

Safety was assessed by monitoring adverse events, laboratory safety tests (CBC, blood chemistries and urinalysis), pre and poststudy physical examinations, vital signs and electrocardiograms.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Individual plasma concentration-time data were used to calculate the pharmacokinetic parameters using model-independent methods. The data were analyzed using WinNonlin.

Statistical Analysis

Summary statistics were calculated for the concentration data and the derived pharmacokinetic parameters for each pseudoephedrine treatment. The derived pharmacokinetic parameters [C_{max}, T_{max}, AUC(tf), AUC(I)] were analyzed using a crossover analysis of variance model. The effects due to subject, period and treatment were extracted. The C_{max} and AUC values were log-transformed and the following were calculated using the pooled residual error and associated degrees of freedom from the ANOVA:

- 90% confidence intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean. CIs were also constructed for original-scale of C_{max} and AUC values.
- Power to detect a 20% difference in treatment means for an alpha level of 0.05 (two-tailed).

In addition, to assess the effect of gender on the pharmacokinetics of pseudoephedrine, female-to-male ratios based on log-transformed C_{max} and AUC values were computed. Ninety percent confidence intervals were calculated using pooled residual error and associated degrees of freedom from ANOVA models that extracted the effects due to gender, subjects within gender, period, and treatment

Reviewer's remarks

This reviewer used WinNonlin program to calculate 90% confidence intervals for the ratio of the means (C_{max} and AUC_{inf}) between treatments (A vs. B, C vs. A; and A vs. D; A see Table 4).

RESULTS

Analytical Method

Pre-Study Validation:

Sensitivity: The limit of reliable quantitation was set at the concentration of the _____ for pseudoephedrine. The between-batch %CV for QC samples at this concentration was 7.4% in human plasma, EDTA, and 11.5% in human plasma, heparin.

Recovery Data: Observed % recovery (%CV) data for pseudoephedrine were 76.94 (3) at 30.0 ng/ml; 67.5 (7.1) at 150.1 ng/mL; and 66.3 (1.8) at 280.2 ng/mL) and for _____ (internal standard) was _____

Stability Data:

Long Term (Frozen): Samples of pseudoephedrine in human plasma {EDTA} stored at a nominal temperature of -20°C were stable for 149 days, when compared to freshly prepared samples.

Short Term (Benchtop): Pseudoephedrine was stable in human plasma (EDTA) at room temperature for 7 hours. Pseudoephedrine is stable in human plasma (heparin) at room temperature for 19 hours.

Freeze- Thaw: Pseudoephedrine was stable in human plasma (EDTA) plasma after three freeze-thaw cycles and in human plasma heparin after multiple freeze and thaw cycles.

Cross-Validation Between Human Plasma Using Heparin as the Anticoagulant Versus EDTA as the Anticoagulant: In assessing cross-matrix compatibility, a cross-validation batch, short term, freeze-thaw and long term evaluations were performed. The cross-validation batch involved the use of calibration standards and quality control samples prepared in human plasma using EDTA as the anticoagulant (i.e. the validated matrix) versus replicate quality control samples using heparin as the anticoagulant (i.e. the unvalidated matrix). According to the sponsor, since all heparin quality control (Qc) sample concentrations fell within tolerance limits of +20%, +15%, $\pm 15\%$ and $\pm 20\%$ for low, medium, high and lower limit of quantitation (LLOQ) Qc samples respectively, the cross matrix assessment was deemed acceptable.

In study Validation Results**Table 2.** In-study validation information for Pseudoephedrine

	Human Plasma EDTA	Human Plasma Heparin
Linearity	Satisfactory: Standard curve range from 10 to 399.4 ng/mL; $r^2 \geq 0.996$	Satisfactory: Standard curve range from 10 to 400 ng/mL; $r^2 \geq 0.996$
Within batch Accuracy	Satisfactory: 116.8% (% nom) at 10 ng/mL; 106.9% at 30.1 ng/mL; 106.6 % at 150.6 ng/mL; 103.7 at 281.2 ng/mL.	Satisfactory: 92.6% (% nom) at 10 ng/mL; 93.5% at 30.1 ng/mL; 88.8 % at 150.3 ng/mL; 91.7% at 280.5 ng/mL.
Within batch Precision	Satisfactory: 5% (% CV) at 10 ng/mL; 6.5% at 30.1 ng/mL; 5.5 % at 150.6 ng/mL; 7.3 at 281.2 ng/mL..	Satisfactory: 5.7% (% CV) at 10 ng/mL; 2.8% at 30.1 ng/mL; 7.4 % at 150.3 ng/mL; 2.7 at 280.5 ng/mL..
Specificity	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for PSE following administration of the four formulations are presented in Figure 1. The mean pharmacokinetic parameters for PSE are summarized in Table 4 and the individual C_{max} and $\text{AUC}(\text{inf})$ values following the administration of the four formulations are shown in Figures 2 and 3,

respectively. The estimates of bioequivalence and the 90% confidence intervals for the log-transformed C_{max} and AUC values for Treatments B, C and D, relative to Treatment A, are included in Table 4. A total of 19 subjects entered the study, and 16 completed all four-treatment periods. Subject 14 did not complete Treatment 2; Subject 16 did not complete Treatments 2 and 4; and Subject 18 did not complete Treatments 2 and 4. These subjects were therefore excluded from the statistical analysis. Female-to-male ratios and 90% confidence intervals of the pharmacokinetic parameter are summarized in Table 5.

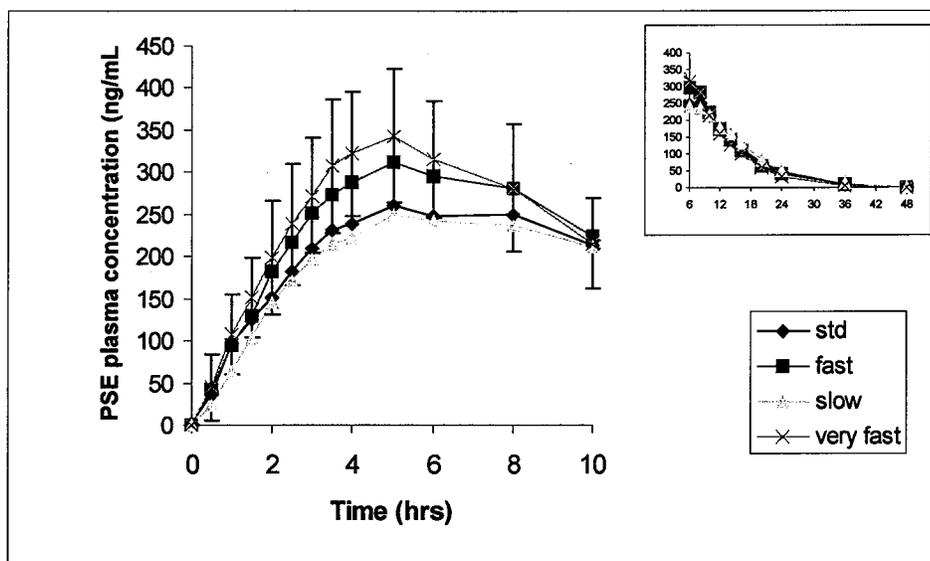


Figure 1. Mean PSE plasma concentration-time profiles following single administration of controlled-released (12-hr) Clarinex tablet formulations. The insert refers to the terminal phase of the profile.

Table 3. Mean (%CV) pharmacokinetic parameters of PSE following single administration of controlled-released (12-hr) Clarinex tablet formulations

Treatment	Mean (%CV) PK Parameters			
	C _{max} (ng/mL)	T _{max} (hr)	AUC _t (ng*hr/mL)	AUC _i (ng*hr/mL)
A (standard)	273 (21)	6.5 (28)	3869 (34)	4063 (32)
B (Fast)	317 (18)	5.16 (20)	3958 (25)	4117 (24)
C (Slow)	266 (22)	6.19 (21)	3910 (22)	4107 (20)
D (Very fast)	343 (21)	4.97 (14)	3874 (22)	4066 (21)

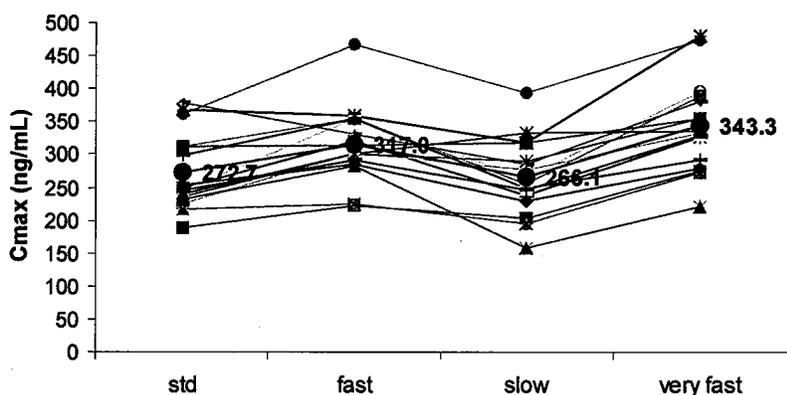


Figure 2. Individual Cmax values following single administration of the Clarinex tablet formulations

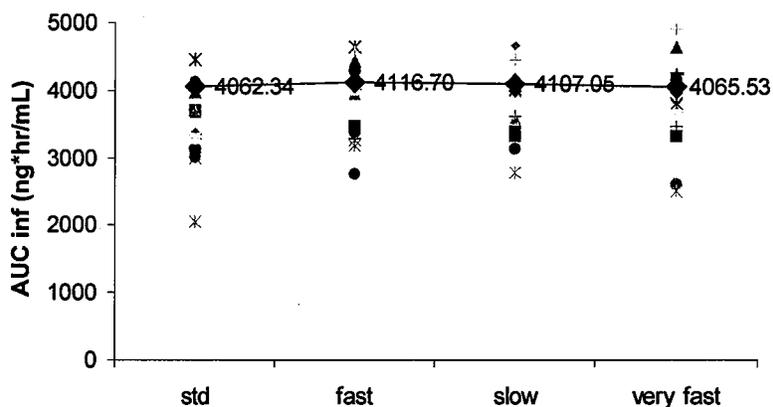


Figure 3. Individual AUC inf values following single administration of the Clarinex tablet formulations

Table 4. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
TrtB/trtA	AUCt	105		97-113	
	AUCinf	104	103.9	97-111	96.8-11.5
	Cmax	117	117.8	110-124	110.9-125.1
TrtC/trtA	AUCt	104		96-112	
	AUCinf	104	103.2	97-111	96.8-11.5
	Cmax	97	97.1	92-103	91.5-103.2
TrtD/trtA	AUCt	103		95-111	
	AUCinf	102	103.1	95-110	96.08-110.7
	Cmax	126	126.2	119-134	118.8-134

*A: standard batch; B: fast batch; C: slow batch; D: very fast batch

Relative to Treatment A, Treatment B and Treatment C meet the 80-125 limits for both AUC and Cmax (Table 4). However, for Treatment B, the upper confidence limit for Cmax was 125.1. Treatment D met the guideline for AUC but not for Cmax. The results indicate that Treatment D is not equivalent to treatment A.

Table 5. PK parameters of PSE in male and female volunteers following single-dose oral administration of controlled-release (12-hr) Clarinex tablet formulations.

Parameter	Female (n=8)	Male (n=8)	Ratio F/M)	90%CI
AUCinf (ng*hr/mL)	4199	3977	106	101-111
AUCt(ng*hr/mL)	4028	3778	107	102-113
Cmax (ng/mL)	332	268	124	119-129

CONCLUSIONS

- Treatment B (fast batch) and C (slow batch) were bioequivalent to Treatment A (standard batch). However, Treatment D (very fast batch) was not equivalent to treatment A.
- Females tend to have statistically significant higher Cmax values of PSE than males

GENERAL COMMENTS

This study was considered pivotal by this reviewer for setting the Clarinex D-12 dissolution specifications. Refer to the following section (dissolution) for details on the rationale for setting the dissolution specifications.

The sponsor increased the _____

_____ Since this change correspond to a Level II change on the manufacturing process, according to SUPAC guidance, no BE bridging studies are needed. The sponsor provided dissolution data for tablets generated with this new _____ specification. This change in : _____ released of PSE at the different times point (especially at _____ to the edge of the _____ without being out of specifications (tablets under stability evaluation).

COMMENTS TO SPONSOR

- This reviewer recommends, based on the BE data submitted, the following dissolution specifications for Clarinex D-12:

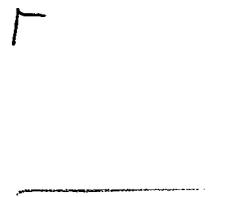
Table D2. Proposed dissolution specifications for Clarinex D-12

Time (hours)	Percent PSE sulfate release (sponsor's)	Percent PSE sulfate release (this reviewer's)
1		29-44
2		50-66
6	NLT 7%	NLT 7%
	DL dissolved	
0.5	Q= 7%	

COMMENTS TO CHEMISTRY REVIEWER

1. Treatments B (fast batch) and C (slow batch) were bioequivalent to Treatment A (standard batch). However, Treatment D (very fast batch) was not equivalent to treatment A.
2. The sponsor has increased the _____ of the tablets (Level II change on the manufacturing process, according to SUPAC guidance) to improve their _____.
The _____ of the tablets in this study (all formulas) was compared to _____ used in the stability studies. According to the chemistry reviewer, this change in _____ was shifted the _____ of PSE at different times point (specially at _____) to the edge of the _____ without being out of specifications (tablets under stability evaluation). Because the chemist concerns about product failing of specifications, it was decided to decrease the lower range at _____ (see Table D9). A value of _____ corresponds to the lowest value observed during stability studies. This value (_____) is within 10% margin of variability (average release at _____), and is supported by the data presented for the slow release tablet (Table D8), which was bioequivalent to the standard formulation.

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Table D6. Components for formula number 3538 (standard batch)	
Ingredients	mg/tablet
<u>Immediate Release Layer</u>	
	
<u>Sustained Released Layer</u>	
	
Approximate tablet weight	

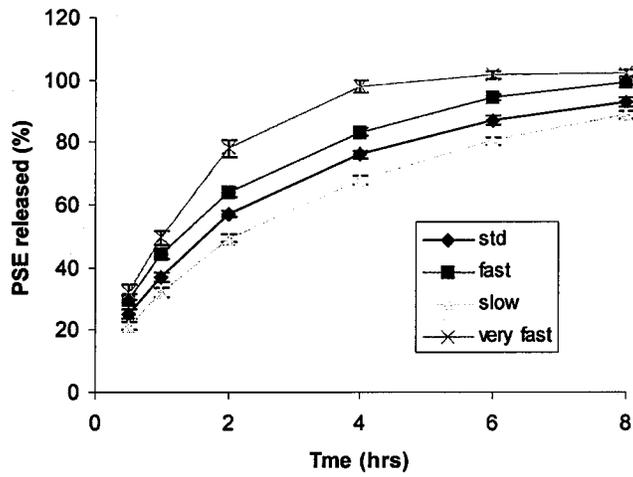


Figure 1D. Mean in vitro PSE sulfate released profiles for very fast, fast, standard and slow extended release formulations of Clarinex D-12 tablets.

Table D7. Dissolution data for PSE from Clarinex D-12 tablets

Standard formulation (3538)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												25	1.6
1													37	1.6
2													57	1.2
4													76	1.2
6													87	1.4
8												└	93	1.4

Very fast formulation (3638)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												32	2.4
1													50	2.3
2													78	2.7
4													98	1.9
6													102	1.2
8												└	102	0.9

Fast formulation (3637)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												30	1.6
1													44	1.8
2													64	1.3
4													83	1.2
6													94	0.9
8												└	100	1.1

Slow formulation (3636)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5	✓												21	1.2
1													32	1.3
2													49	1.2
4													68	1.4
6													80	1.2
8												└	89	1.2

Table D8. Dissolution data for DL from Clarinex D-12 tablets

Standard formulation (3538)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.5													88	12.0
1.0													96	7.7

Very fast formulation (3638)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.25	✓												86	19.3
0.5	✓												95	12.6
0.75													97	9.1
1												✓	99	6.6

Fast formulation (3637)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.25	✓												91	11.5
0.5	✓												100	6.0
0.75													102	4.1
1												✓	103	3.3

Slow formulation (3636)														
Time (hr)	1	2	3	4	5	6	7	8	9	10	11	12	average	stdev
0.25	✓												79	21.6
0.5													94	17.8
0.75													98	14.4
1												✓	101	11.9

COMMENTS TO CHEMISTRY REVIEWER

- Treatments B (fast batch) and C (slow batch) were bioequivalent to Treatment A (standard batch). However, Treatment D (very fast batch) was not equivalent to treatment A.
- The sponsor has increased _____ of the tablets (Level II change on the manufacturing process, according to SUPAC guidance) to improve their _____. The _____ of the tablets in this study (all formulas) was _____ compared to _____ in-process _____ sed in the stability studies. According to the chemist reviewer, this change in _____ has shifted the _____ of PSE at the different times point (especially at _____) to the edge of the _____ without being out of specifications (tablets under stability evaluation). Because of the chemist concerns product failing of specifications, it was decided to decrease the lower range at _____ (see Table D9). A value of _____ corresponds to the lowest value observed during stability studies. This value _____ is within 10% margin of variability (average release at _____) and is supported by the data presented for the slow release tablet (Table D8), which was bioequivalent to the standard formulation.

Office of Clinical Pharmacology and Biopharmaceutics				
<i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
	Information		Information	
NDA Number	21-313	Brand Name	Clarinet-D™ 12 hour tablet	
OCBP Division (I, II, III)	II	Generic Name	Desloratadine (DL)/pseudoephedrine sulfate)	
Medical Division	DPADP	Drug Class	Antihistamine	
OCBP Reviewer	Sandra Suarez-Sharp	Indication(s)	SAR	
OCBP Team Leader	Young Moon Choi (acting)	Dosage Form	Tablet (bilayer: (immediate/extended release)	
		Dosing Regimen	2.5/120mg DL/PSE One tablet bid	
Date of Submission	December 8, 2000	Route of Administration	Oral	
Estimated Due Date of OCPB Review	September 2001	Sponsor	Schering Corp.	
PDUFA Due Date	October, 2001	Priority Classification	Standard	
Division Due Date	September, 2001			
7 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	4	
multiple dose:	X	1	1	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
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 -				
solution as reference:				
alternate formulation as reference:	X	3	3	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		5	5	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. • Please see comment to executive summary, comments to sponsor		
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1. Was the to-be-marketed formulation used in the pharmacokinetic studies? 2. Are the proposed dissolution method and specifications supported by the data provided by the sponsor? 3. Were DL and PSE from the DL D-12 tablet equivalent to the reference product? Did PSE affect the BA of DL (and viseversa) from the DL D-12 formulation? 4. Was the bioavailability of DL and PSE from the DL D-12 tablet affected by the presence of food? 5. What were the PK parameters of DL, its metabolite and PSE following multiple administration of DL D-12 tablet? 		
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-313, HFD-850 (Electronic Entry or Lee), HFD-570 (Hilfiker), HFD-870 (Fadiran, Hunt, Malinowski), CDR (B. Murphy)

**APPEARS THIS WAY
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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sandra Suarez
10/12/01 02:41:46 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
10/12/01 03:16:17 PM
BIOPHARMACEUTICS
I concur