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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-297

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-297
Proprietary Drug Name:	Clarinex™ 5mg Tablets
Generic Name:	Desloratadine
Indication:	Treatment of Chronic Idiopathic Urticaria (CIU).
Dosage Form:	Tablet
Strength:	5 mg
Route of Administration:	Oral
Dosage and administration:	**Adults and children (age 12 and older):** The recommended starting dose of clarinex tablets is 5 mg once daily.
Applicant:	Schering Corporation
Clinical Division:	DPADP (HFD-570)
Submission Date:	August 30, 2000
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader :	Emmanuel Fadiran, Ph. D.

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1. EXECUTIVE SUMMARY

A New Drug Application (NDA 21-165) for Clarinex™ (Desloratadine) 5 mg tablets was filed (10/20/99) for the treatment of seasonal allergic rhinitis and has received an approvable action. The sponsor has submitted another NDA for Clarinex™ 5-mg tablets (NDA 21-297) for the treatment of chronic idiopathic urticaria and it's the subject of the present review.

Desloratadine (SCH 34117; DL) is a long-acting tricyclic histamine H1-receptor antagonist developed by Schering Corporation. Desloratadine the major active metabolite of loratadine (CLARITIN®), has been investigated and shown to possess peripheral antihistaminic effects with no sedative or other central nervous system effects at the clinically recommended dose. Desloratadine was developed for its more desirable pharmacokinetic profile compared to loratadine, exhibiting less extensive first-pass metabolism and a longer plasma elimination half-life.

Clarinex tablets are indicated for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal congestion and for the treatment of chronic idiopathic urticaria in patients 12 years of age and older. The recommended dose of Clarinex™ tablets is 5 mg once daily.

In support of this application, the sponsor has submitted the results of two clinical safety and efficacy studies as well as the results of one pharmacokinetic/pharmacodynamic (PK/PD) study. The clinical development program for Clarinex 5-mg tablets consisted primarily of two phase III multicenter trials involving over 400 patients ages 12 and above with CIU treated with Clarinex or placebo for up to 6 weeks. The to-be-marketed formulation was used in the clinical and pharmacokinetic studies. The batch used in the PK studies was [redacted] scale production batch.

This review summarizes the multiple dose clinical pharmacokinetics, safety and tolerability of DL 5 mg tablets done in a single histamine challenge wheal and flare study (study P01196). This PK/PD study was conducted to determine the effect of chronic dosing of DL 5 mg over 28 days in suppressing the histamine induced wheal and flare reaction. The results from this clinical pharmacology study show that DL and its metabolite (3-OH DL) have an accumulation factor that ranges from 1.64 to 1.75 and from 2.19 to 2.37, respectively, following administration of the Clarinex 5 mg tablet formulation daily for 28 days (Table 1). In addition, DL showed an antihistaminic activity (suppression of histamine induced wheal and flare reaction) at one hour post-administration. The suppression of the histamine induced wheal and flare reaction did not change over the 28-day administration of the 5 mg DL tablet indicating the absence of tachyphylaxis through this period (Figure 1, Table 2). However, because the clinical relevance of the histamine induced wheal and flare reaction is not well understood, the results of the present study should be used as a supportive information only.

Table 1. Mean (%CV) DL and 3-OH DL pharmacokinetic parameters following multiple administration of Clarinex™ tablets 5 mg for 28 days.

		DL				
PK parameters	**Mean**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28***
Cmax (ng/mL)	Arithmetic	2.83 (39)	3.65 (48)	3.76 (38)	3.77 (44)	3.89 (43)
	Geometric	2.67	2.42	3.57	3.56	3.63
Tmax (hr)	Arithmetic	2.86 (19)	2.71 (27)	3.21 (25)	2.86 (19)	3.08 (34)
	Geometric	NC	NC	NC	NC	NC
AUC (0→24h)	Arithmetic	29.6 (36)	49.8 (56)	51.1 (57)	52.2 (57)	54 (54)
	Geometric	28.1	45.7	46.5	47.8	49.4
R	Arithmetic	NA	1.64 (23)	1.67 (23)	1.72 (22)	1.75 (20)
	Geometric	NA	NC	NC	NC	NC
		3-OH DL				
PK parameters	**Mean**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
Cmax (ng/mL)	Arithmetic	1.03 (21)	1.85 (20)	1.98 (22)	1.95 (18)	1.97 (17)
	Geometric	1.0	1.81	3.57	1.92	1.94
Tmax (hr)	Arithmetic	3.21 (25)	3.86 (36)	3.5 (42)	3.5 (42)	3.69 (36)
	Geometric	NC	NC	NC	NC	NC
AUC $_{(0\rightarrow 24h)}$	Arithmetic	13.2 (18)	29.5 (20)	30.9 (23)	31.5 (21)	31.1 (18)
	Geometric	13.0	29.0	30.1	30.8	30.6
R	Arithmetic	NA	2.13 (14)	2.27 (16)	2.33 (18)	2.37 (13)
	Geometric	NA	NC	NC	NC	NC

Table 2. Difference in Mean Minimum Change from Baseline in Wheal Area between DL and Placebo

Mean	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
(Difference in LS Means)	-9.5	-11.07	-10.43	-12.01	-12.49
p Value	0.05	0.027	0.02	0.023	0.026
95% CI	(-18.99, -0.01)	(-20.79,-1.35)	(-19.09,-1.77)	(-22.23, -1.80)	(-23.3, -1.66)

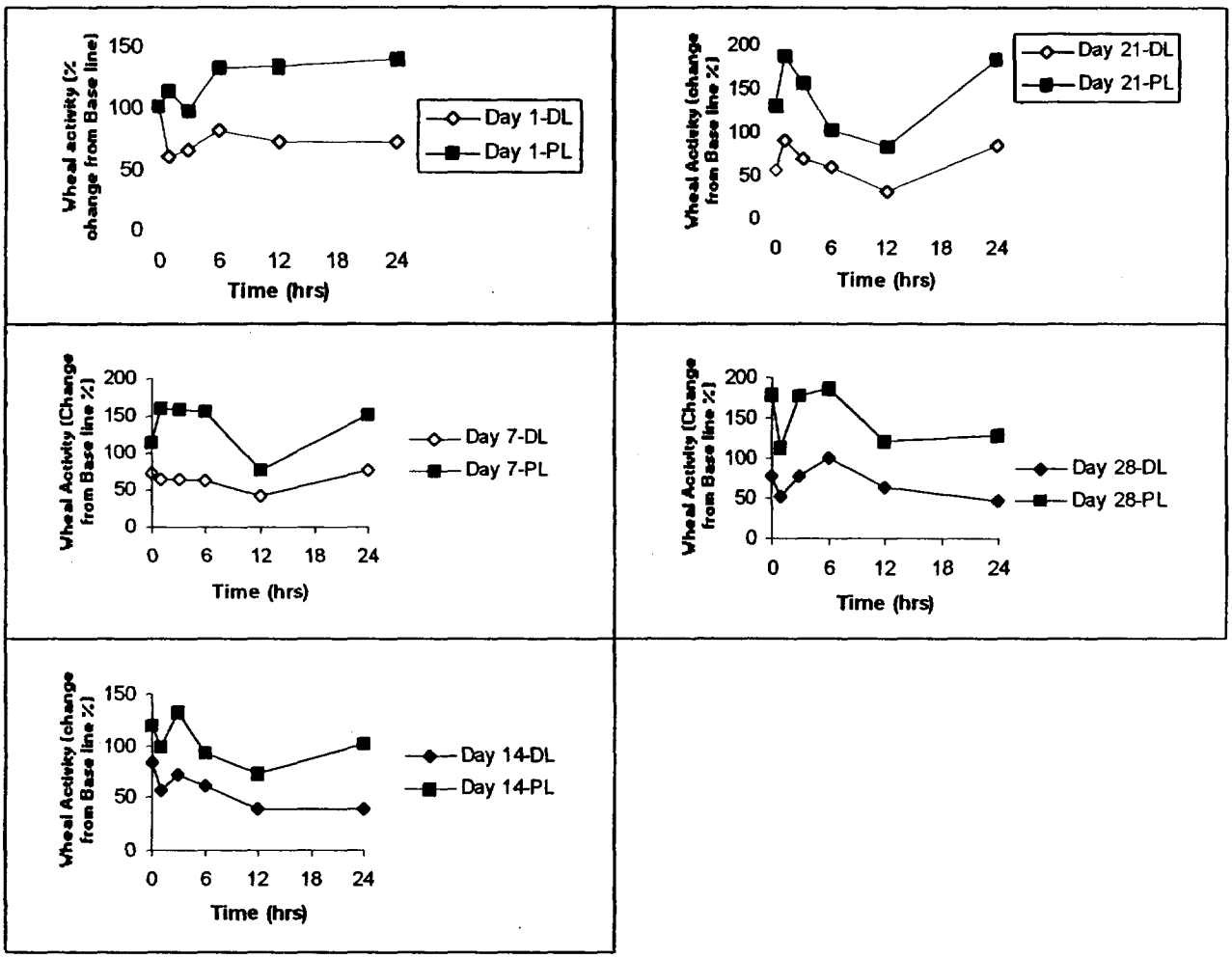

Figure 1. Wheal activity expressed as percentage change from baseline for DL and placebo (PL) groups following multiple dosing of Clarinex 5 mg QD for 28 days.

2. COMMENTS TO SPONSOR

1. Based on the dissolution data submitted to the previous NDA (21-165) and this NDA it is recommended that the dissolution specification should be changed to not less than — % (Q) at 30 min. The sponsor's dissolution method and specification should reflect the comments and agreements made in the previous NDA submitted for clarinex 5-mg tablets (NDA 21-165).
2. The relationship between percentage reduction in wheal and flare areas and plasma DL/metabolite concentrations should be explored for future submissions involving the wheal and flare determinations.

3. COMMENTS TO THE MEDICAL OFFICER

1. A comparison of steady-state C_{max} and $AUC_{(0\text{-}24\ hr)}$ values observed in this study with those from a previous study (P00117) show that after once-daily dosing for 28 days, the pharmacokinetics of SCH 34117 and SCH 45581 display moderate accumulation (R~2). The DL and 3-OH DL accumulation factors from this study (1.64-1.75 and 2.13-2.37, respectively) are similar to those observed from a previous study (P00117; R=1.70-1.85 for DL)
2. DL has antihistamine activity at one hour on Day 1 as shown by a statistically significant difference in the change from baseline in Wheal Area between DL and Placebo. However, this difference was not significant at 3 hours (p=0.163) and 6 hours (p=0.063) and 12 hours (p=0.05) post administration of the drug, but at 24 hours. In addition, the suppression of the histamine induced wheal and flare reaction did not change over the 28-day administration of 5-mg DL tablet indicating lack of tachyphylaxis. However, this information could only be considered as supportive information, since the clinical relevance of the histamine induced wheal and flare reaction is not yet well understood.

4. LABELING COMMENTS

The following changes are suggested for the pharmacodynamics section under clinical pharmacology (see attached label):

Pharmacodynamics:

[

Draft

]

Note: The underlined text highlights this reviewer' s proposed comments to the label.

5. RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-297 submitted on August 30, 2000. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB. The data presented in this NDA showed that DL has antihistamine activity (reduction of the histamine induced wheal and flare reaction) at one hour. In addition, the suppression of the histamine induced wheal and flare reaction does not change over a 28-day administration period of 5-mg DL tablet indicating no reduction of effect (lack of tachyphylaxis). However, this information could only be considered as supportive information, since the clinical relevance of the histamine induced wheal and flare reaction is not yet well understood. Please forward the above comments (page 6) along with the labeling comments to the sponsor.

Reviewer /S/ May 22, 2001

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

/S/ May 22, 2001

cc
NDA 21-297/N-000: Division File
HFD-870: Malinowski, Hunt
HFD-570: Fadiran, Rosebraugh, Ostroff, Suarez-Sharp

The present review has been focused in the following issues.

6. QUESTION BASED REVIEW

Q1. What is the rationale for the proposed dose of DL (5 mg DQ) for the treatment of CIU?

Pharmacokinetic studies (NDA 21-165) 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.

The safety and efficacy data obtained for DL during clinical trials (NDA 21-165) demonstrated that it is effective in the treatment of seasonal allergic rhinitis (SAR), well tolerated, and characterized by an adverse event profile similar to that previously observed with loratadine. Therefore, the DL 5.0-mg dose was identified as the appropriate therapeutic dose of DL in the treatment of SAR in subjects 12 years of age and older. Since loratadine 10 mg is also approved for the management of CIU, the clinical program for DL in CIU also utilized the DL 5 mg dose.

Q2. What is the dissolution method proposed for this formulation? Is this method discriminative enough?

Table 2.1 shows that the sponsor's proposed dissolution method and specification submitted in the present NDA and the one presented in NDA 21-165 (Clarinex 5 mg for the treatment of SAR are the same.

In the previous NDA submitted to the agency (NDA 21-165) the biopharm reviewer found this method acceptable. However, it was recommended at that time to change the specifications to Q= [redacted]% at 30 min. It seems that the sponsor has kept its originally proposed specifications (see Table 2.1).

In the present submission, the sponsor did not provide individual dissolution data and dissolution profiles. Based on the average data provided in Table 2.2, a dissolution specification of [redacted]% (Q) at 30 min may be a more discriminative specification. Therefore, it is recommended to the sponsor to change the dissolution specification to no less than [redacted] % (Q) at 30 min.

Table 2.1. Proposed product dissolution method and specification

Provided in this NDA		**Presented in NDA 21-165**	
Method	**Specification**	**Method**	**Specification**
Apparatus: USP apparatus II (paddle) **Sampling time(s)**: 15, 30, 45 and 60 min **Speed:** 50 rpm **Temperature**: 37 °C **Medium:** 0.1 N HCL **Volume:** 500 mL	Q= [redacted]% at 45 min	**Apparatus**:USP apparatus II (paddle) **Speed:** 50 rpm **Temperature**: 37 °o **Medium:** 0.1 N HCL **Volume:** 500 mL	Q= [redacted]% at 45 min

Table 2.2. Dissolution profile results for Clarinex 5 mg NDA 21-297

Collection time (min)	DL units tested /range/ mean % dissolved.
15	12 [redacted] 83
30	12 [redacted] 93
45	12 [redacted] 97
60	12 [redacted] 100

Q3. What are the pharmacokinetics of DL and its metabolite following multiple administration for 28 days? How does it compare with previous studies submitted under NDA 21-165?

The derived pharmacokinetic parameters for DL (SCH 34117) and 3-OH DL (SCH 45581) from study (P01196) after single and multiple dosing are presented in Table 3.1.

Table 3.1. Mean (%CV) DL and 3-OH DL pharmacokinetic parameters following multiple administration of Clarinex™ tablets 5 mg for 28 days.

		DL				
PK parameters	**Mean**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28***
Cmax (ng/mL)	Arithmetic	2.83 (39)	3.65 (48)	3.76 (38)	3.77 (44)	3.89 (43)
	Geometric	2.67	2.42	3.57	3.56	3.63
Tmax (hr)	Arithmetic	2.86 (19)	2.71 (27)	3.21 (25)	2.86 (19)	3.08 (34)
	Geometric	NC	NC	NC	NC	NC
AUC (0→24h)	Arithmetic	29.6 (36)	49.8 (56)	51.1 (57)	52.2 (57)	54 (54)
	Geometric	28.1	45.7	46.5	47.8	49.4
R	Arithmetic	NA	1.64 (23)	1.67 (23)	1.72 (22)	1.75 (20)
	Geometric	NA	NC	NC	NC	NC
		3-OH DL				
PK parameters	**Mean**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
Cmax (ng/mL)	Arithmetic	1.03 (21)	1.85 (20)	1.98 (22)	1.95 (18)	1.97 (17)
	Geometric	1.0	1.81	3.57	1.92	1.94
Tmax (hr)	Arithmetic	3.21 (25)	3.86 (36)	3.5 (42)	3.5 (42)	3.69 (36)
	Geometric	NC	NC	NC	NC	NC
AUC (0→24h)	Arithmetic	13.2 (18)	29.5 (20)	30.9 (23)	31.5 (21)	31.1 (18)
	Geometric	13.0	29.0	30.1	30.8	30.6
R	Arithmetic	NA	2.13 (14)	2.27 (16)	2.33 (18)	2.37 (13)
	Geometric	NA	NC	NC	NC	NC

N=14: n=13*; NA= not applicable; NC=not calculated

The mean SCH 34117 C_{max} and $AUC_{(0\text{-}24\ hr)}$ values were similar in magnitude to values previously observed (Figure 3.1). In a previous Phase I study (P00117), SCH 34117 was administered once daily for up to 14 days. In this study (P01196), SCH 34117 was administered for 28 days. According to the sponsor, the similarity in C_{max} and $AUC_{(0\text{-}24\ hr)}$ within this study (ie, between Days 7, 14, 21, and 28) as well as between this study and a previous study demonstrated that the pharmacokinetics of SCH 34117 do not change following daily dosing for 4 weeks.

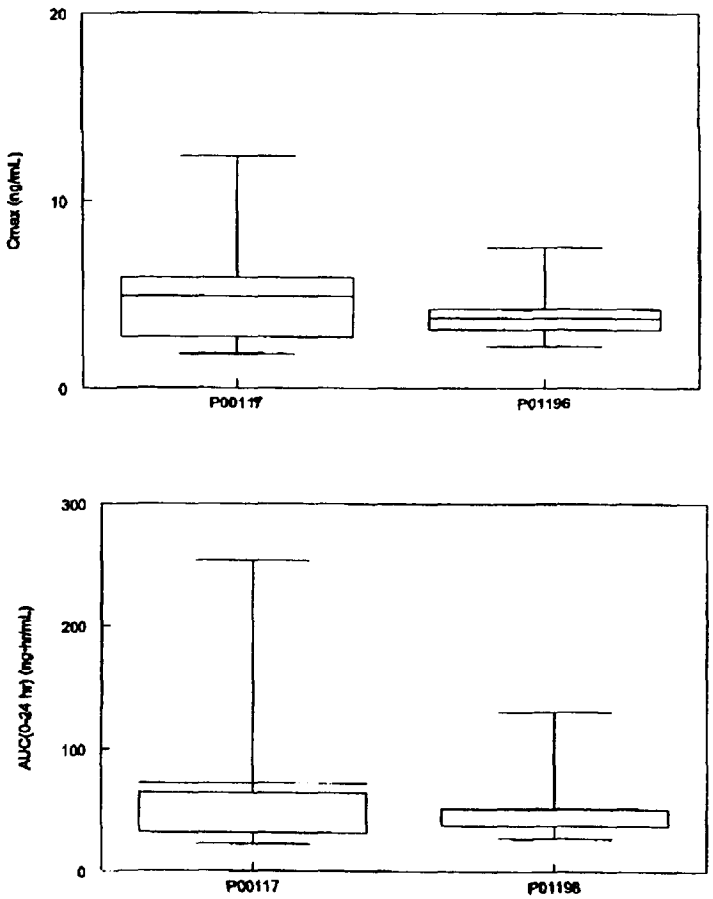

Figure 3.1. Comparison of C_{max} and $AUC_{(0\text{-}24\ hr)}$ values (Day 14 data) of SCH 34117 following oral administration of 5 mg SCH 34117 tablet in study no. P01196 and historical values (Day 10 data) in healthy subjects administered 5 mg SCH 34117 once daily for 10 Days (P00117).

Following daily dosing, SCH 34117 accumulated to a moderate degree (accumulation factor (R) values ranged from 1.6 to 1.8). The R values for the metabolite ranged from 2.2 to 2.4 indicating also a moderate accumulation (Table 3.1).

The half-life of DL has been previously reported (NDA 21-165) to be 27 hours. In the present submission, this reviewer calculated the mean elimination half-life for DL and was found to be much lower than the previously reported (14.5- 17 hours, data not shown). The underestimation might be due to the relatively short sampling duration (24

hrs) compared to longer sampling duration used in NDA 21-165 (t=at least 72 hrs). For this reason, this reviewer recommends not to update the label to reflect the PK findings from this study.

Q4. Is DL effective in reducing the induced histamine wheal and flare reaction? Does DL produce a tachyphylactic effect?

According to the sponsor, significant differences in histamine induced wheal activity were noted between DL and placebo as early as 1 hour and differences were also evident at the 24-hour time point on Day 1. However, it is important to mention that differences were not statistically significant at 3 hours (p=0.163), at 6 hours (p=0.063) at 12 hours (p=0.05) on Day 1; at 0 hr, and 12 hrs on Day 7; at 0 hrs, 6 hrs and 12 hrs on Day 14; and at 6 hrs and 24 hours at Day 21.

Minimum histamine induced wheal area as measured by change from baseline was significantly less with the DL 5 mg treatment than placebo for all days tested (1, 7, 14, 21, and 28) with $p<0.05$ (Table 4.1). In addition, minimum histamine induced wheal area did not change substantially within the DL 5 mg group across all study days indicating a lack of tachyphylaxis over the 28-day treatment period (Table 4.1).

Table 4.1. Difference in Mean Minimum Change from Baseline in Wheal Area between DL and Placebo

Mean (Difference in Means)	**Day 1** LS-9.5	**Day 7** -11.07	**Day 14** -10.43	**Day 21** -12.01	**Day 28** -12.49
p Value	0.05	0.027	0.02	0.023	0.026
95% CI	(-18.99, -0.01)	(-20.79,-1.35)	(-19.09,-1.77)	(-22.23, -1.80)	(-23.3, -1.66)

7. 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.

The sponsor has stated that the safety and efficacy of loratadine is supported by extensive clinical experience in the treatment of allergic rhinitis and chronic allergic skin disorders. In addition, the sponsor believes that, although DL is not presently marketed, patients worldwide have been safely exposed to it as a metabolite of loratadine, which has been marketed internationally since 1988 and in the US since 1993.

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).

The safety and efficacy data obtained for DL during clinical trials (NDA 21-165) demonstrated that it is effective in the treatment of SAR, well tolerated, and characterized by an adverse event profile similar to that previously observed with loratadine. Therefore, the DL 5.0-mg dose was identified as the appropriate therapeutic dose of DL in the

treatment of SAR in subjects 12 years of age and older. Since loratadine 10 mg is also approved for the management of CIU, the clinical program for DL in CIU also utilized the DL 5-mg dose.

In support of this application, the sponsor has submitted the results of clinical safety and efficacy studies as well as the results of one pharmacokinetic /pharmacodynamic study. The clinical development presented in this NDA includes two Phase-III studies (Study P00220 and Study P00221), conducted under identical protocols. A total of 416 subjects were randomized and received at least one dose of study drug: 211 received DL 5.0 mg QD and 205 received placebo QD for 6 consecutive weeks. In addition, one clinical pharmacology study was conducted that may lend additional support to the effect of DL in histamine-mediated skin disorders (P01196).

Clinical Safety and Efficacy Studies

P00220: Randomized, double-blind, placebo-controlled, parallel-group, multicenter study to determine the safety and Efficacy of DL tablets. Subjects received DL 5.0 mg QD or placebo QD for 6 consecutive weeks.

P00221: Randomized, double-blind, placebo-controlled, parallel-group, multicenter to determine the Safety and Efficacy of DL tablets. Subjects received DL 5.0 mg QD or placebo QD for 6 consecutive weeks.

Pharmacokinetic Studies

The PK/PD study (P01196) was conducted to determine the effect of chronic dosing DL 5 mg over 28 days in suppression of a histamine induced wheal and flare reaction.

P01196: Randomized, third-party blinded, placebo-controlled, parallel-group, longitudinal study to evaluate the suppression of wheal and flare following administration of DL 5.0 mg QD or placebo QD for 28 days in normal volunteers.

7.1 INTRODUCTION

7.1.1 PHARMACOKINETICS

The following pharmacokinetics of DL and its metabolite were presented in the previous NDA 21-165.

Absorption: Following oral administration of DL 5 mg once daily for 10 days to normal healthy volunteers, the mean time to maximum plasma concentrations (T_{max}) was approximately 3 hours and mean steady state peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of 4 ng/mL and 56.9 ng·hr/ml were observed, respectively. Food had no effect on the bioavailability (C_{max} and AUC) of DL.

Distribution: DL and 3-hydroxy DL are 82 to 87% and 85 to 89%, bound to plasma proteins, respectively. Protein binding of DL and 3-hydroxy DL was unaltered in subjects with impaired renal function.

Metabolism: DL (a major metabolite of loratadine) is extensively metabolized to 3-

hydroxy DL, an active metabolite, which is subsequently glucuronidated.

Disposition and Elimination: The mean elimination half-life of DL was 27 hours. C_{max} and AUC values increased in a dose proportional manner following single oral doses between 5 and 20 mg. The degree of accumulation after 14 days of dosing was consistent with the half-life of the drug. A human mass balance study documented a recovery of approximately 87% of the ^{14}C- DL dose, which was equally distributed in urine and feces as metabolic products. Analysis of plasma 3-hydroxy DL showed similar T_{max} and half-life values compared to DL.

Special Populations:
Geriatric: In older subjects (≥ 65 years old; n=17) following multiple-dose administration of CLARINEX Tablets, the mean C_{max} and AUC values for DL were 20% greater than in younger subjects (< 65 years old). The mean plasma elimination half-life of DL was 33.7 hr in subjects ≥ 65 years old. The pharmacokinetics for 3-OH DL appeared unchanged in older versus younger subjects. These age-related differences are unlikely to be clinically relevant and no dosage adjustment is recommended in elderly subjects.

Renally Impaired: pharmacokinetics following a single dose of 7.5 mg were characterized in patients with mild (n=7; creatinine clearance 51-69 mL/min/1.73m^2), moderate (n=6; creatinine clearance 34-43 mL/min/1.73m^2), and severe (n=6; creatinine clearance 5-29 mL/min/1.73m^2) renal impairment or hemodialysis dependent (n=6) patients. In patients with mild and moderate insufficiency, median C_{max} and AUC values increased by approximately 1.2 and 1.9-fold, respectively, relative to subjects with normal renal function. In patients with severe renal dysfunction or who were hemodialysis dependent, C_{max} and AUC values increased by approximately 1.7- and 2.5-fold, respectively. Minimal changes in 3-OH DL concentrations were observed. DL and 3-OH DL were poorly removed by hemodialysis. Dosage adjustment for patients with renal impairment is recommended.

Hepatically Impaired: DL pharmacokinetics were characterized following a single oral dose in patients with mild (n=4), moderate (n=4), and severe (n=4) hepatic dysfunction as defined by the Child-Pugh classification of hepatic dysfunction and 8 subjects with normal hepatic function. Patients with hepatic dysfunction, regardless of severity, had approximately a 2.4-fold increase in AUC as compared with normal subjects. The apparent oral clearance of DL in patients with mild, moderate, and severe hepatic dysfunction was 37, 36, and 28% of that in normal subjects, respectively. An increase in the mean elimination half-life of DL in patients with hepatic dysfunction was observed. For 3-OH DL, the mean C_{max} and AUC values for patients with hepatic dysfunction were not significantly different from subjects with normal hepatic function. Dosage adjustment for patients with hepatic impairment is recommended.
Drug Interactions: In two controlled clinical pharmacology studies in healthy male (n=12 in each study) and female (n=12 in each study) volunteers, DL 7.5 mg once daily was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 200 mg every 12 hours for 10 days. Although increased plasma concentrations (Cmax and AUC 0-24

hrs) of DL and 3-OH DL were observed, there were no clinically relevant changes in the safety profile of DL, as assessed by electrocardiographic parameters (including the corrected QT interval), clinical laboratory tests, vital signs, and adverse events.

Pharmacokinetic/Pharmacodynamic Correlation. No studies have been conducted.

7.1.2 CHEMISTRY OVERVIEW

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

Structural formula:

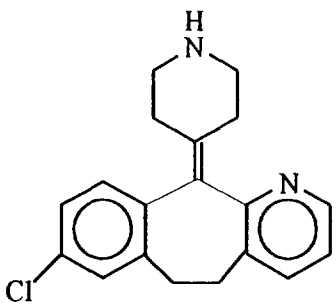

Figure 1. Structural formula of DL.

Molecular formula: $C_{19}H_{19}ClN_2$

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.

7.1.3 FORMULATION

The following table summarizes the composition of the 5-mg tablet as proposed in NDA 21-165:

Core Ingredients	mg/Tablet
DL (SCH 34117)	5.0
Corn Starch NF	[redacted]
Dibasic Calcium Phosphate Dehydrate USP	
Microcrystalline Cellulose NF	
Talc USP	
Blue	
Clear	
Carnauba Wax NF	
White Wax NF	
Core weight	106.31

7.1.4 INDICATION (as per proposed label)

CLARINEX Tablets are indicated for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiophatic urticaria in patients 12 years of age and older.

7.1.5 DOSAGE AND ADMINISTRATION (as per propose label)

In adults and children 12 years of age and over; the recommended dose of CLARINEX Tablets is 5 mg once daily. In patients with liver or renal insufficiency, a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data.

8. SAFETY AND EFFICACY

According to the medical officer (Dr. Rosebraugh), the clinical data presented in this NDA is conclusive that DL 5 mg once daily provides a statistically significant reduction in pruritus after a one week interval. Based on the totality of the data and on placebo drop out rates, DL 5 mg once daily also provides clinical improvement in CIU patients. Medication risks are appropriate for the degree of clinical benefit derived. Mean pruritus AM NOW scores for days 1-8 time point provide questionable support for a 24 hour dosing interval since the difference between placebo and DL did not meet or exceed 0.5 units in study P00220, although it did in study P00221. However, it may be reasonable to extrapolate this information from SAR data (NDA 21-165). Also, the to-be-marketed dose of 5 mg once daily is not fully supported by a dose-ranging pharmacodynamic component in this submission (only the 5 mg dosage was studied). However, data suggest that the dose shown to be effective for SAR would also likely be effective for CIU, as has been shown to be true of the parent drug, loratadine.

" A Study Evaluating the Suppresion of Wheal and Flare Following Multiple-Dose Administration of Desloratadine (5 mg) to Normal Volunteers"

Study No. P01196

OBJECTIVE

The pharmacokinetic objective of this study was to characterize the single and multiple dose pharmacokinetics of SCH 34117 (DL) and its metabolite, SCH 45581 (3-OH DL) following oral administration of 5 mg SCH 34117 to healthy adult subjects.

This PK/PD study was conducted to determine the effect of chronic dosing DL 5 mg over 28 days in suppression of a histamine induced wheal and flare reaction.

SUBJECTS

Twenty-eight subjects (25 males plus 3 females) ages of 20-44 years inclusive (mean=29.9 years), weighing between 58.8-92.6 kg (mean=76.6 kg) and having BMIs between 19.9-28.5 (mean 24.6) were randomized and treated in the study. Ten subjects were Caucasian, 12 were Black, 3 were Asian, 2 were Hispanic and 1 was other. Twenty-four subjects completed the study. Four subjects dropped out of the study, 2 for personal reasons not related to the study (Subject No. 28 who received 5 mg DL and Subject No. 20 who received placebo) and 2 due to adverse events rated unlikely to be related to the therapy.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a third party blind, randomized, placebo controlled, multiple dose, parallel study of SCH 34117 (DL) vs. placebo in normal healthy subjects.

Group	Treatment Day
5mg SCH 34117	Days 1-28
Matching Placebo	Days 1-28

FORMULATION

Table 1. Formulations and batch numbers used in this study.

	DL TABLET	PLACEBO TABLET
Tablet Strength	5 mg	placebo
Formula No.	408	3391
Batch No.	38833-146	38833-072
Batch Size	[redacted]	
FMR No.	99592D09	98500D02
Manufacturing Date	4/20/98	11/24/97
Recertification Date	10/2000	11/2000
Mfg. Site	Kenilworth, NJ	Las Piedras, Puerto Rico

METHODOLOGY: PHARMACODYNAMIC AND PHARMACOKINETIC MEASUREMENTS

Subjects were screened for reactivity to histamine and entered into the study. Subjects were given baseline applications of histamine (5 mg/mL) on Day -1 via the skin prick method and then given either placebo or 5 mg of DL daily for 28 days.

Subjects had repeated histamine applications at specified times (predose, and 1, 3, 6, 12 and 24 hours after dosing) on Days 1, 7, 14, 21 and 28 as well as pharmacokinetic sampling for DL and 3OH-DL at the same times.

Histamine reactions were assessed by measuring the area of the wheal and flare (using a tape and pen method) 10 minutes after the application of histamine and by the measurement of skin blood flow at 0, 5 and 10 minutes after the application of histamine with a laser Doppler flow meter. Subjects were monitored for adverse events throughout the trial.

Analytical Method

Plasma samples were assayed for DL and 3-OH DL concentrations using [redacted] assay

SAFETY MEASUREMENTS

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

DATA ANALYSIS

Pharmacokinetic Data Analysis

Individual plasma concentration-time data of both DL and 3-OH DL were used to calculate the pharmacokinetic parameters using model independent methods. The data were analyzed using WINNONLIN (Version 2.1).

The area under the plasma concentration-time curve from time 0 to 24 hours (AUC[0-24 hr]) was calculated using the linear trapezoidal method. The accumulation index (R) was determined as follows:

$$R = \frac{AUC_{(0 \rightarrow 24hr)ss}}{AUC_{(0 \rightarrow 24hr)day1}}$$

where AUC(0-24 hr) at steady state is the area under the curve on Days 7, 14, 21,and 28.

To identify the existence of slow metabolizers of DL, metabolite to parent ratios were calculated for AUC(0-24 hr) for each subject. A subject was categorized as a slow metabolizer if the ratio (expressed as a percent) was <10%. This criterion has been used previously.

Pharmacodynamic Data Analysis

Analysis of the Doppler Flowmeter Data

Doppler flowmeter data were analyzed for each time point and day as described above for two locations (wheal area and flare area) as a change from preprick

administration. This change was to be computed as the difference between 0 minutes (preprick administration) and the mean of 5 and 10 minutes (postprick administration).

Analysis of Secondary Variables

Actual and change from baseline wheal and flare areas were analyzed for each of Days 1, 7, 14, 21 and 28 at 0, 1, 3, 6, 12 and 24 hours postdose in addition to the daily minimums. In addition, actual AUCs were analyzed at each day for the wheal and flare areas.

Minimum Wheal and Flare Area

Minimum area was determined by the SAS MIN function. Specifically, MIN=MIN (of nonmissing hour [hr] 01, 03, 06, 12, 24) for each day of wheal and flare. Change from Baseline minimum area was computed by subtracting the minimum area from the Baseline (0 hour, Day 1) evaluation.

AUC

AUCs were computed using the sum of trapezoids for each day of wheal and flare, where each trapezoid is defined as follows: (hours between two consecutive observations a and b)*(obs a + obs b)/2, starting with the observation at Hour 1.

Statistical Analysis

Pharmacokinetic Data

Summary statistics, including means, and coefficients of variation for the means were to be provided for the pharmacokinetic parameters. Means, standard deviations and %CV were to be reported for the concentration data at each time point.

Pharmacodynamic Data

Analysis for each of the wheal and flare area included independent t-tests on the actual and change from Baseline difference from DL to placebo for each day and time point, as well as the actual minimum areas and AUCs for each day.

The primary variable is the minimum wheal area. The primary time point is at Day 28. A 95% confidence interval of the Day 28 difference between DL and placebo was to be computed on the primary variable.

RESULTS

Analytical Method

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

In-Study Validation

Limit of Quantitation

The lower and upper limits of quantitation were [redacted] ng/mL and [redacted] ng/mL for SCH 34117 and [redacted] ng/mL and [redacted] ng/mL for SCH 45581, respectively.

Table 2. In-study validation information for SCH 34711 and SCH 45581

	SCH 34711	SCH 45581
Linearity	Satisfactory: Standard curve range from	Satisfactory: Standard curve range from
Accuracy	Satisfactory:	Satisfactory:
Precision	Satisfactory:	Satisfactory:
Specificity	Satisfactory: submitted	Satisfactory: submitted

Pharmacokinetic Results

DL and 3-OH DL concentrations at Time 0 on Day 1 were not quantifiable; Subject No. 28 had discontinued treatment and therefore had no concentration-time data at this time point.

The mean plasma DL (SCH 34117) and 3-OH DL (SCH 45581) concentration-time data and the derived pharmacokinetic parameters after single and multiple dosing are presented in Figure 1 and Table 3 and Figure 2 and Table 3, respectively.

Figures 3 and 4 show the individual Cmax and $AUC_{0\rightarrow\infty}$ for DL and Figures 5 and 6 show likewise for 3-OH DL.

Plasma SCH 34117 concentrations showed relatively high intersubject variability (CV ~50%). Following daily dosing, SCH 34117 accumulated to a moderate degree (R values ranged from 1.6 to 1.8 (Table 3). On Days 7, 14, 21, and 28 mean C_{max} and $AUC_{(0-24\ hr)}$ values were similar (range 3.7 to 3.9 ng/mL and 50 to 54 ng×hr/mL, respectively). The mean SCH 34117 C_{max} and $AUC_{(0-24\ hr)}$ values were similar in magnitude to values previously observed. In previous Phase I studies, SCH 34117 was administered once daily for up to 14 days. In this study, SCH 34117 was administered for 28 days. According to the sponsor, the similarity in C_{max} and $AUC_{(0-24\ hr)}$ within this study (ie, between Days 7, 14, 21, and 28) as well as between this study and previous studies demonstrated that the pharmacokinetics of SCH 34117 do not change following daily dosing for 4 weeks.

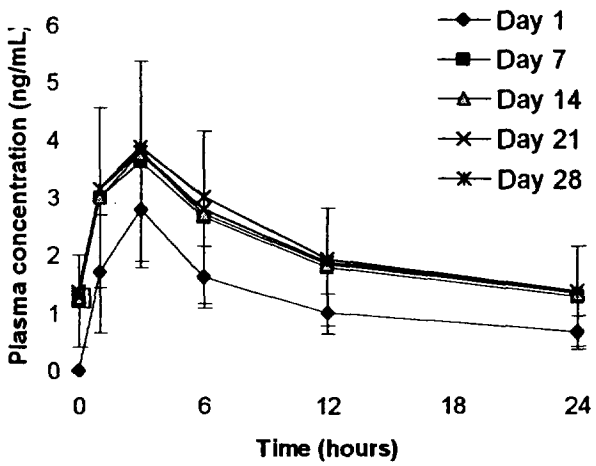

Figure 1. Mean DL plasma concentration-time profiles following multiple administration of Clarinex 5 mg QD for 28 days. Bars represent mean ±SD.

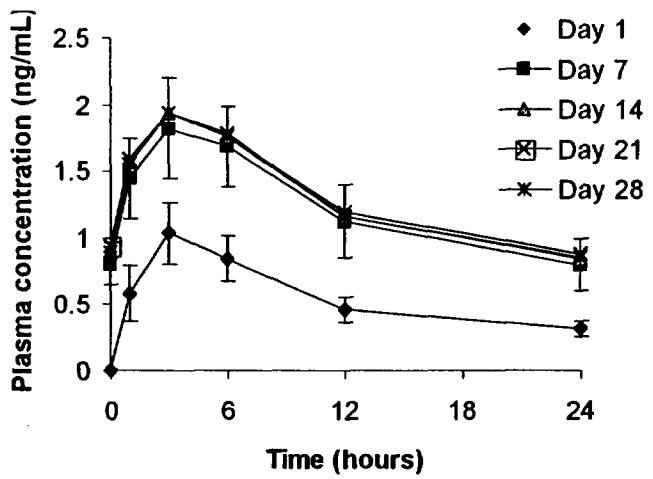

Figure 2. Mean 3-OH DL plasma concentration-time profiles profiles following multiple administration of Clarinex 5 mg QD for 28 days. Bars represent mean ±SD.

Following SCH 34117 administration, SCH 45581 concentrations were quantifiable in plasma; the concentrations showed low intersubject variability (CV~20%). According to the sponsor, this is consistent with previous observations in healthy subjects. The R values ranged from 2.2 to 2.4 indicating a moderate accumulation (Table 3).

Table 3. Mean (%CV) DL and 3-OH DL pharmacokinetic parameters following multiple administration of Clarinex™ tablets 5 mg for 28 days.

		DL				
PK parameters	**Mean**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28***
Cmax (ng/mL)	Arithmetic	2.83 (39)	3.65 (48)	3.76 (38)	3.77 (44)	3.89 (43)
	Geometric	2.67	2.42	3.57	3.56	3.63
Tmax (hr)	Arithmetic	2.86 (19)	2.71 (27)	3.21 (25)	2.86 (19)	3.08 (34)
	Geometric	NC	NC	NC	NC	NC
AUC (0→24h)	Arithmetic	29.6 (36)	49.8 (56)	51.1 (57)	52.2 (57)	54 (54)
	Geometric	28.1	45.7	46.5	47.8	49.4
R	Arithmetic	NA	1.64 (23)	1.67 (23)	1.72 (22)	1.75 (20)
	Geometric	NA	NC	NC	NC	NC
		3-OH DL				
PK parameters	**Mean**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
Cmax (ng/mL)	Arithmetic	1.03 (21)	1.85 (20)	1.98 (22)	1.95 (18)	1.97 (17)
	Geometric	1.0	1.81	3.57	1.92	1.94
Tmax (hr)	Arithmetic	3.21 (25)	3.86 (36)	3.5 (42)	3.5 (42)	3.69 (36)
	Geometric	NC	NC	NC	NC	NC
AUC (0→24h)	Arithmetic	13.2 (18)	29.5 (20)	30.9 (23)	31.5 (21)	31.1 (18)
	Geometric	13.0	29.0	30.1	30.8	30.6
R	Arithmetic	NA	2.13 (14)	2.27 (16)	2.33 (18)	2.37 (13)
	Geometric	NA	NC	NC	NC	NC

N=14: n=13*; NA= not applicable; NC=not calculated

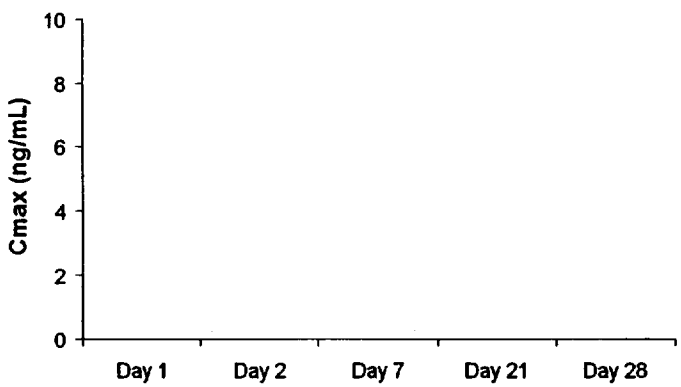

Figure 3. Individual DL Cmax values following multiple administration of Clarinex 5 mg QD for 28 days. Bars represent mean ±SD.

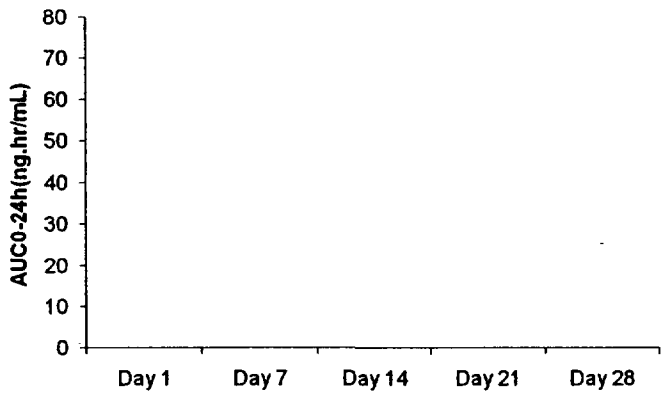

Figure 4. Individual DL $AUC_{0\rightarrow24}$ values following multiple administration of Clarinex 5 mg QD for 28 days. Bars represent mean ±SD.

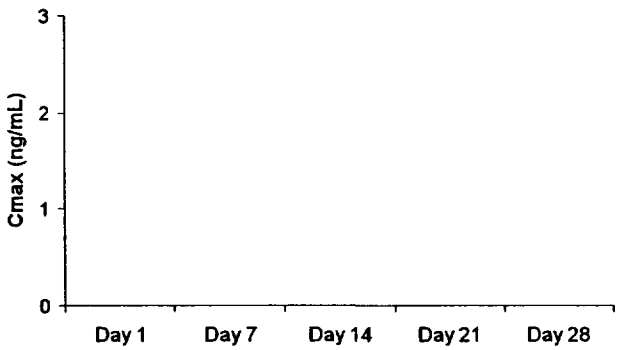

Figure 5. Individual 3-OH DL Cmax values following multiple administration of Clarinex 5 mg QD for 28 days. Bars represent mean ±SD.

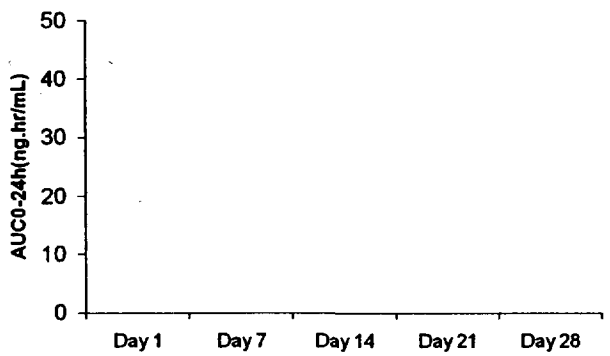

Figure 6. Individual 3-OH DL $AUC_{0\rightarrow24}$ values following multiple administration of Clarinex 5 mg QD for 28 days. Bars represent mean ±SD.

Pharmacodynamic Results

Figure 7 shows the wheal activity expressed as percentage change from baseline for DL and placebo groups following multiple dosing of Clarinex 5 mg QD. Figure 8 and Table 4 show the difference in minimum change from baseline in wheal area between DL and placebo.

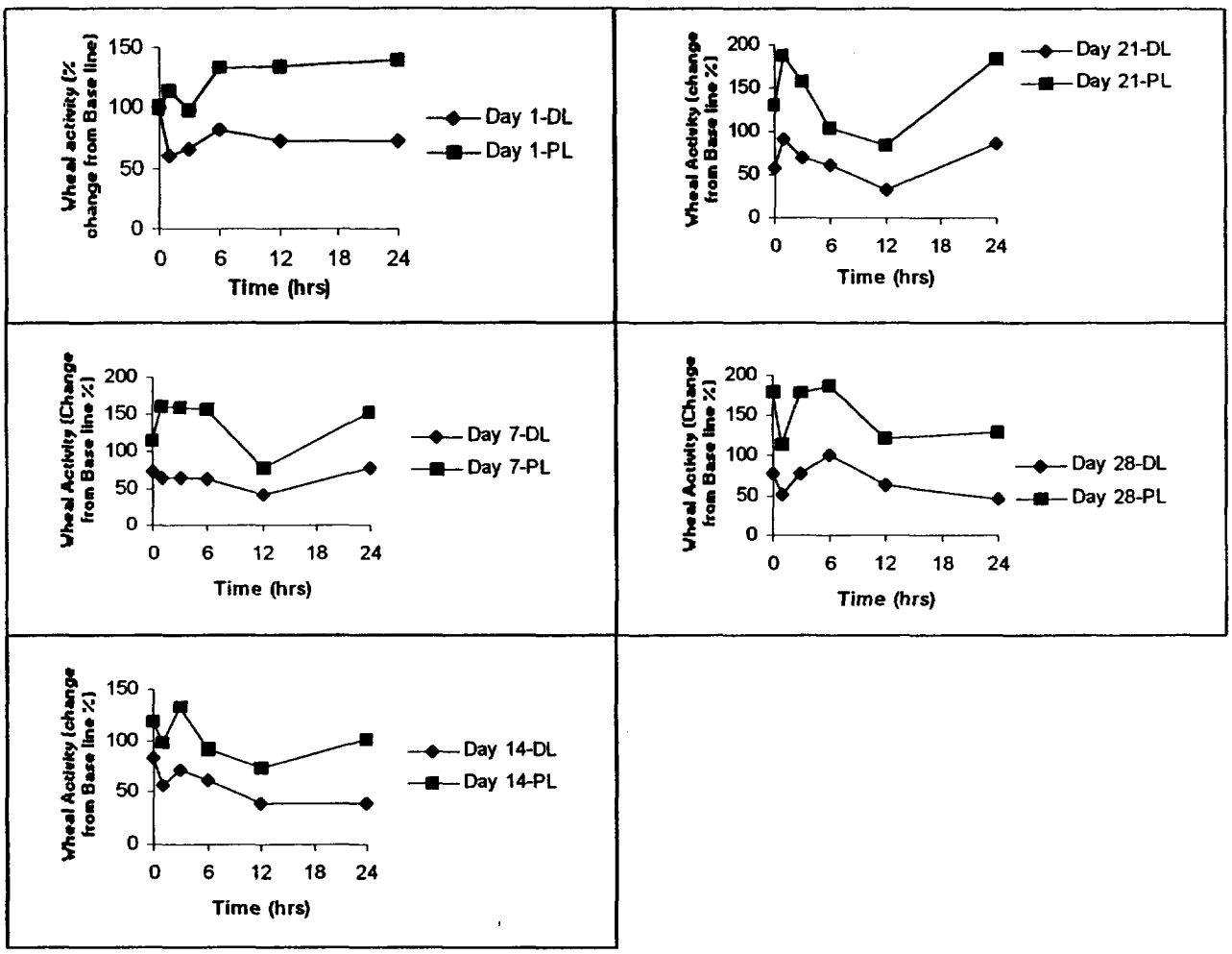

Figure 7. Wheal activity expressed as percentage change from baseline for DL and placebo (PL) groups following multiple dosing of Clarinex 5 mg QD.

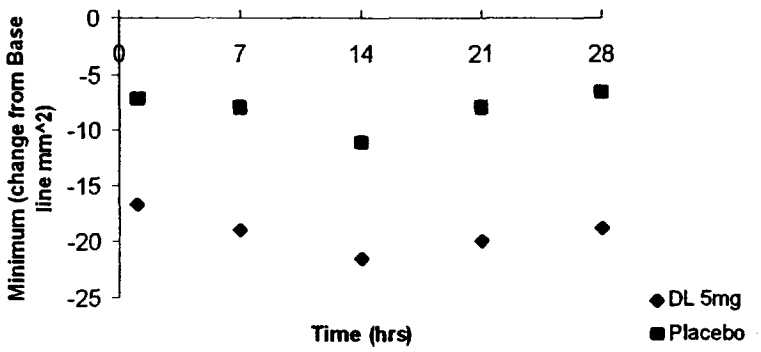

Figure 8. Minimum change from baseline in Wheal Area between DL and Placebo groups following multiple dosing of Clarinex 5 mg QD. Dots represent LS means as a function of time.

Minimum histamine induced wheal area as measured by change from Baseline was significantly less with the DL 5 mg treatment than placebo for all days tested (1, 7, 14, 21, and 28) with $p<0.05$ (Table 6). In addition, minimum histamine induced wheal area did not change substantially within the DL 5 mg group across all study days indicating a lack of tachyphylaxis over the 28-day treatment period (Table 4).

According to the sponsor, significant differences in histamine induced wheal activity were noted between DL and placebo as early as 1 hour and differences were also evident at the 24-hour time point on Day 1. However, it is important to mention that differences were not significant at 3 hours ($p=0.163$), at 6 hours ($p=0.063$) at 12 hours ($p=0.05$) on Day 1; at 0 hrs, and 12 hrs on Day 7; at 0 hrs, 6 hrs and 12 hrs on Day 14; and at 6 hrs and 24 hours at Day 21.

Table 4. Difference in Mean Minimum Change from Baseline in Wheal Area between DL and Placebo

Mean (Difference in LS Means)	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
	-9.5	-11.07	-10.43	-12.01	-12.49
p Value	0.05	0.027	0.02	0.023	0.026
95% CI	(-18.99, -0.01)	(-20.79,-1.35)	(-19.09,-1.77)	(-22.23, -1.80)	(-23.3, -1.66)

The flare response was analyzed as categorical data (flare present vs. flare absent) due to the complete suppression of the flare in a majority of subjects. The DL 5 mg treatment group had a greater effect of completely inhibiting the flare response vs. placebo for Days 7, 14, 21 and 28 ($p\leq 0.013$) (Table 5).

Table 5. Flare response (Absent or Present) in DL or Placebo

No. of subjects with:	**Day 1**		**Day 7**		**Day 14**		**Day 21**		**Day 28**	
	DL	**Placebo**	**DL**	**Placebo**	**DL**	**Placebo**	**DL**	**Placebo**	**DL**	**Placebo**
Flare absent	4	3	13	6	14	7	13	2	13	5
Flare present	10	11	1	8	0	7	1	10	0	6
Fisher Exact Test	P=1.0		P=0.013		P=0.006		P<.001		P=0.003	

Generally, no differences between the 5 mg DL group and placebo were found for wheal blood flow as measured by Laser Doppler for any test day. Significant differences ($p<0.05$) between DL 5 mg and placebo in histamine induced increases in flare blood flow were found for 16 out of 30 time points during the study with a strong trend for a reduction in the increase or flare blood flow by DL 5 mg for all time points.

COMMENTS

PK Comments

- The half-life of DL has been previously reported (NDA 21-165) to be 27 hours. In the present submission, this reviewer calculated the mean elimination half-life for DL and it was found to be much lower than the previously reported (14.5- 17 hours, data not shown). The underestimation might be due to the relatively short sampling duration (24 hrs) compared to longer sampling duration used in NDA 21-165 (t=at least 72 hrs). For this reason, this reviewer recommends not to update the label to reflect the PK findings from this study.

PD Comments

- The relationship between percentage reduction in wheal and flare areas and plasma DL/metabolite concentrations should be explored for future submissions involving the wheal and flare determinations.
- DL has antihistamine activity at one hour on Day 1 since there was a significant difference in the change from baseline in Wheal Area between DL and Placebo. However, this difference was not significant at 3 hours (p=0.163), 6 hours (p=0.063) and 12 hours post administration, but at 24 hours. In addition, the suppression of the histamine induced wheal and flare reaction did not change over the 28-day administration of 5-mg DL tablet indicating lack of tachyphylaxis. However, this information could only be considered as supportive information, since the clinical relevance of the histamine induced wheal and flare reaction is not yet well understood.

CONCLUSION

- The steady-state Cmax and $AUC_{(0\text{-}24\ hr)}$ values observed in this study show that after once-daily dosing for 28 days, the pharmacokinetics of SCH 34117 and SCH 45581 accumulate moderately ($R \sim 2$).
- The suppression of the histamine induced wheal and flare reaction did not change over the 28-day administration of 5 mg DL tablet indicating no reduction of effect (lack of tachyphylaxis). However, this information could only be considered as supportive information, since the clinical relevance of the histamine induced wheal and flare reaction is not yet well understood.

Dissolution

Table 6 compares the sponsor's proposed dissolution method and specification with the one presented for NDA 21-165. Table 7 shows the dissolution profile results for this formulation.

In the previous NDA submitted to the agency (NDA 21-165) the biopharm reviewer found this method acceptable. However, it was recommended at that time to change the specifications to Q= [redacted]% at 30 min. It seems that the sponsor has kept its originally proposed specifications (see Table 6).

In the present submission, the sponsor did not provide individual dissolution data and dissolution profiles. Based on the average data provided in Table 7, a dissolution specification of [redacted]% (Q) may be a more discriminative specification. Therefore, it is recommended to the sponsor to change the dissolution specification to not less than [redacted]% (Q) at 30 min.

Table 6. Proposed product dissolution method and specification

Proposed in this NDA		**Presented in NDA 21-165**	
Method	**Specification**	**Method**	**Specification**
Apparatus: USP apparatus II (paddle) **Sampling time(s)**: 15, 30, 45 and 60 min **Speed:** 50 rpm **Temperature**: 37 °C **Medium:** 0.1 N HCL **Volume:** 500 mL	Q=[redacted]% at 45 min	**Apparatus**: USP apparatus II (paddle) **Speed:** 50 rpm **Temperature**: 37 °C **Medium:** 0.1 N HCL **Volume:** 500 mL	Q=[redacted]% at 45 min

Table 7. Dissolution profile results for Clarinex 5 mg NDA 21-297

Collection time (min)	**DL units tested/range/mean % dissolved.**
15	12 [redacted] 83
30	12 [redacted] 93
45	12 [redacted] 97
60	12 [redacted] 100

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
5/22/01 11:00:13 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
5/22/01 11:04:25 AM
BIOPHARMACEUTICS
I concur

Memorandum

DATE: 18 June 2001

FROM: Curtis J. Rosebraugh, MD, MPH

TO: DFS file

RE: Desloratadine, NDA 21-297, DSI Audit

In October 2000, the Pulmonary and Allergy Division determined that there was not a need for a site audit of any of the investigators associated with the above NDA. This decision was based on several factors. These factors included, but are not limited to the following: 1) There was not an excessive number of subjects enrolled at any one site. 2) None of the sites unduly influenced the results of any of the studies included in this submission. 3) [redacted] and 4) This NDA is closely related to an earlier NDA (21-165) for desloratadine for the treatment of SAR for which an approvable action has been taken. . In all respects except filing status, NDA 21-297 may be considered an "efficacy supplement" to NDA 21-165. An audit of the latter NDA has been completed and included review of five investigators/sites (see MO review of NDA 21-165) during which no major problems were found.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Curtis Rosebraugh
6/18/01 03:43:49 PM
MEDICAL OFFICER

Edits incorporated

Mary Purucker
6/18/01 03:48:30 PM
MEDICAL OFFICER