

**CLINICAL REVIEW: Clarinex-D 12-Hour ER Tablets
(NDA 21-313)**

Appendix: Study P00362

Antihistamine Comparison (Study P00362):									[S8/p00362/63]
Total Symptom Score, Excluding Nasal Congestion (Reflective, AM+PM)									
	DL D-12			DL5			PSE		
	N	mean	% change	N	mean	% change	N	mean	% change
Baseline	213	15.19		212	14.66		221	14.86	
Change from Baseline to:									
Day 1	210	-3.37	-22.5	207	-2.36	-16.9	214	-2.18	-15.2
Day 2	213	-5.50	-36.0	211	-3.69	-25.5	220	-4.20	-28.7
Day 3	211	-6.13	-40.3	211	-4.45	-30.4	218	-4.56	-31.1
Day 4	209	-6.35	-41.6	211	-5.29	-36.0	217	-5.07	-34.3
Days 1-8	213	-6.19	-40.3	212	-4.79	-32.6	221	-4.82	-32.6
Days 9-15	204	-7.29	-47.1	203	-6.08	-40.8	209	-5.96	-39.7
Pairwise Comparison p-values									
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE		
Day 1	0.005*			0.018*			0.671		
Day 2	0.002*			<0.001*			0.213		
Day 3	<0.001*			<0.001*			0.793		
Day 4	0.005*			0.021*			0.623		
Days 1-8	<0.001*			<0.001*			0.943		
Days 9-15	0.003*			0.008*			0.797		

*= p<0.05

Shaded: Relevant treatments for antihistamine comparison

The table below summarizes the data for the reflective decongestant comparisons (nasal congestion score, AM+PM) for the various intervals studied. The cells representing the most relevant comparison on this endpoint, DL D-12 vs. DL5, are shaded. DL D-12 was statistically superior to DL5 during the early timepoints, but the difference did not quite reach statistical significance for the Day 9-15 analysis. During the primary endpoint (Days 1-15), DL D-12 was unexpectedly superior to PSE on nasal congestion. Although DL D-12 was numerically superior to PSE on nasal congestion at each time point, the table below shows that the difference between the two groups was greatest during the first week.

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(4) Pregnancies

Pregnancy was a criterion for exclusion in these studies. All female subjects of childbearing potential were required to have a negative HCG serum pregnancy test at the Screening visit and to use medically acceptable methods of birth control during the treatment period. Two unintended pregnancies were reported, one in the DL group and 1 in the PSE group [S8/ISS/41]. The subject in the PSE treatment group had an elective abortion. The pregnancy for the other subject, who was in the DL treatment group of Study P00362, is being followed, and, at the time of the NDA submission no complications had been reported to date. The 120-Day Safety Update information for this NDA was cross-referenced a "global safety update report", which was submitted to NDA 21-300 (Clarinex Syrup) on April 6, 2001. There is no additional information regarding the outcome of this pregnancy in that submission [NDA 21-300, Submission dated 4/6/01; Pages 87 and 536 of 930]. **Reviewer's Comment: This study was performed in the Fall of 1999. Further follow-up data on the outcome of this pregnancy should be available.**

(5) Drug-demographic interactions

The Applicant provided summaries of the effects of age, race, and gender on the incidence of adverse events, treatment-related AEs, and SAEs [S8/ISS/28-34]. However, there were too few subjects in the age groups 12 to <18, and ≥ 65 years (the subgroup definitions in regard to age was 12 to <18 years, 18 to <65 years, and ≥ 65 years), or who were non-Caucasians to allow meaningful comparisons with respect to age or race [S8/ISS/29]. There were no differences in the patterns of overall AEs and treatment-related AEs among the treatment groups based on gender. The overall incidence of AEs was slightly greater in females than males, across treatment groups. The incidence of treatment-related AEs was greater in females than in males who received DL D-12 (29.1% versus 22.4%) or PSE (30.6% versus 18.2%). This gender difference was not seen in regard to the incidence of treatment-related AEs among subjects in the DL group. [S8/ISS/33]. Regarding vital signs, more women than men were found to have a heart rate >90 bpm at the final visit [S8/ISS/337]. At baseline, 1.2% of women and 5.1% of men in the DL D-12 group had a heart rate ≥ 90 bpm. At the final visit, 8.3% of women and 3.8% of men had a heart rate ≥ 90 bpm. This gender difference was not evident when heart rate was expressed as percent change from baseline [S8/ISS/354], and was not evident in the PSE group.

(6) Drug-Disease Interactions

Other antihistamine products have been associated with adverse cardiovascular effects. Specifically, terfenadine and astemizole have been associated with prolongation of the QT interval and the development of the potentially fatal ventricular arrhythmia, torsades de pointes. For this reason, the NDA specifically addresses safety issues with regard to the cardiovascular system. Referencing data from the development program for desloratadine in adult and adolescent subjects with SAR (NDA 21-265), the Applicant

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states that out of the 2346 subjects who received desloratadine, no severe or serious AEs related to the cardiovascular system were reported. Further, in that database the frequency and pattern of adverse events in the desloratadine is described as “similar to those in the placebo group,” and the Applicant states that ECGs performed in the 20mg dose group showed a modest increase in heart rate (4.5bpm) compared to placebo and a decrease in the QTc interval (1% to 4%, compared to a 1% increase in the placebo group) [S8/ISS/61]. As discussed above, in the clinical program for DL D-12, the incidence and pattern of adverse events in the DL D-12 group was similar to the PSE group. The table below summarizes the cardiovascular adverse events from the two Phase 3 studies (all, and those that were judged by the investigator to be treatment-related). The ECG data from this database is discussed above.

Incidence of Adverse Events Associated with the Cardiovascular System, by Treatment Group and Body System/Organ Class (Studies P00355 and P00362, All Randomized Subjects)						
[Number (%) of Subjects]						[S8/ISS/63]
	DL D-12 (N = 414)		DL (N = 412)		PSE (N = 422)	
Subjects with Cardiac Adverse Event	12	(2.9)	3	(< 1)	14	(3.3)
All Adverse Events						
Cardiovascular Disorders, General	3	(< 1)	1	(< 1)	1	(< 1)
Cardiac Murmur (NOS)	1	(< 1)	0		0	
ECG Abnormal	0		0		1	(< 1)
Edema Legs	1	(< 1)	1	(< 1)	0	
Hypertension	1	(< 1)	0		0	
Heart Rate and Rhythm Disorders	8	(1.9)	1	(< 1)	11	(2.6)
Palpitation	2	(< 1)	1	(< 1)	7	(1.7)
Premature Atrial Contractions	1	(< 1)	0		0	
Tachycardia	5	(1.2)	0		4	(< 1)
Vascular (Extracardiac) Disorders	2	(< 1)	1	(< 1)	2	(< 1)
Migraine	2	(< 1)	1	(< 1)	2	(< 1)
Treatment-Related Adverse Events						
Heart Rate and Rhythm Disorders	7	(1.7)	1	(< 1)	11	(2.6)
Palpitation	1	(< 1)	1	(< 1)	7	(1.7)
Premature Atrial Contractions	1	(< 1)	0		0	
Tachycardia	5	(1.2)	0		4	(< 1)
Vascular (Extracardiac) Disorders	0		1	(< 1)	1	(< 1)
Migraine	0		1	(< 1)	1	(< 1)

(7) Drug-Drug Interactions

No specific drug-drug interactions were studied in the Phase 3 clinical development program.

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D. Adequacy of Safety Testing

The safety testing performed in the clinical studies in this application is sufficient. Although the studies submitted include only a total of 523 subjects exposed to DL D-12 (109 subjects in the five Phase 1 PK/PD studies and 414 subjects in the two Phase 3 studies), this extent of exposure is considered sufficient given the extensive experience with the individual components and with the combination product containing PSE and loratadine, the parent drug of desloratadine. The duration of exposure in the Phase 3 studies (2 weeks) is consistent with what is customarily expected for efficacy studies for drugs to treat SAR. The safety assessments incorporated into the Phase 3 studies (adverse events, vital signs, clinical laboratory studies, and ECGs [1-3 hours after administration of study drug on the last study day]) are sufficient. The safety implications of the poor metabolizer phenotype is discussed in subsection E, below, and in Section III of this Medical Officer Review.

E. Summary of Critical Safety Findings and Limitations of Data

The data submitted in this NDA that is intended to establish the safety profile of DL D-12 is primarily derived from the two Phase 3 studies. The three treatment arms in these studies were DL D-12, and each of its components, DL (2.5mg BID) and PSE (120mg QD). Thus, this data can establish the safety profile of DL D-12 in relation to its components, but not in relation to placebo. The data submitted indicate that DL D-12 is not associated with increased risk, as compared to the risk associated with its component medications. Acceptable safety of the PSE component in relation to placebo can be inferred from the fact that PSE (at the same dose) is currently approved for SAR. A separate NDA (NDA 21-265) has been submitted in support of the safety and efficacy of DL in SAR. NDA 21-265 has been determined to be sufficient for approval, from a clinical perspective. However, the dose of DL in NDA 21-265 (5mg QD) differs from the dose of DL proposed in DL D-12 (2.5mg QD). Nonetheless, the safety data from NDA 21-265 may be used as supportive safety data for DL D-12. Additional supportive data for DL D-12 can be derived from the parent drug, loratadine, which is approved both as a single agent and as a combination product with PSE for SAR.

The proposed label includes adverse reaction data from the Phase 3 studies. Because there were no placebo treatment arms in these studies, the data does not allow for a direct comparison with placebo. Thus the label will provide data on the absolute frequencies of the various adverse reactions experienced in the DL D-12 group, and a comparison of these frequencies with the PSE group (a currently approved dose) and the DL group (not a currently approved dose). While it would be optimal to have placebo data for direct comparison, such data is not available from the Phase 3 studies. Therefore, the proposed approach is acceptable. The specific text of the proposed label will be discussed in a separate labeling review document.

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As discussed in detail in Section III of this Medical Review, pharmacokinetic studies indicate that there exists a population of subjects who metabolize desloratadine poorly, leading to very high systemic exposures of desloratadine. The NDA does not contain sufficient data to assure the safety of DL D-12 in these poor metabolizers.

F. Four-Month Safety Update

In a submission dated April 6, 2001 the Applicant, referencing previous discussions with the Division, states that the four month safety update information is cross-referenced to the global safety update report submitted to NDA 21-300 (CLARINEX™ SYRUP) on April 6, 2001. That submission is currently being reviewed as part of the clinical review of NDA 21-300 and will not be reviewed here. Aspects of the four-month safety update pertaining to the safety of desloratadine in poor metabolizers have been reviewed by Dr. Chowdhury in his Medical Team Leader secondary review, dated October 10, 2001.

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Dosing, Regimen, and Administration Issues

VIII. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The proposed dosing regimen of DL D-12 is one tablet BID. This dose is acceptable. The accepted dose of pseudoephedrine is 120mg. Although dose-ranging studies with DL were not included in this NDA, the dose of the desloratadine component (2.5mg) is based on the approved dose of the parent drug (5mg BID, as a component of Claritin D-12 [loratadine 5mg/ pseudoephedrine 120mg]), and pharmacokinetic studies demonstrating that administration of DL 5mg gives the same systemic exposure (plasma AUC) as administration of 10 mg of loratadine. The dosing interval is justified based on the accepted dosing interval of pseudoephedrine (BID) and the data from the two pivotal studies indicating that the antihistamine effect of DL D-12 is still present at the end of the dosing interval. The endpoint used to assess the end of dosing interval antihistamine efficacy was the change from baseline to Days 1-15 AM+PM instantaneous total symptom score, excluding nasal congestion. In both studies DL D-12 was statistically superior to PSE on this endpoint.

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Use in Special Populations

IX. USE IN SPECIAL POPULATIONS

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The Applicant states that no clinically important differences between males and females were observed in regard to the mean DL, 3-OH DL, and pseudoephedrine pharmacokinetic parameters [S3/3.F.3/page 141/189].

In the two pivotal clinical studies, there were no differences in the patterns of overall AEs and treatment-related AEs among the treatment groups based on gender. The overall incidence of AEs was slightly greater in females than males, across treatment groups. The incidence of treatment-related AEs was greater in females than in males who received DL D-12 (29.1% versus 22.4%) or PSE (30.6% versus 18.2%). This gender difference was not seen in regard to the incidence of treatment-related AEs among subjects in the DL group. [S8/ISS/33]. Regarding vital signs, more women than men were found to have a heart rate >90 bpm at the final visit [S8/ISS/337]. At baseline, 1.2% of women and 5.1% of men in the DL D-12 group had a heart rate ≥90 bpm. At the final visit, 8.3% of women and 3.8% of men had a heart rate ≥90 bpm. This gender difference was not evident when heart rate was expressed as percent change from baseline [S8/ISS/354], and was not evident in the PSE group.

In regard to efficacy, the Applicant examined the response to treatment, by gender, for both clinical studies [S8/p00355/p63 and 65; S8/p00362/p63 and 65]. In both studies, DL D-12 was numerically more effective than PSE on the antihistamine comparison and numerically superior to DL on the decongestant comparison for both men and women. The mean changes in relevant symptom scores for men and women are illustrated in the tables below.

Study P00355: Mean Changes in Symptom Scores, by Gender [S8/p00355/p198-9, 246-7]			
Antihistamine Comparison (reflective AM+PM total symptom score, excluding congestion, Days 1-15)		DL D-12	PSE
	Men	-7.21	-4.81
	Women	-6.22	-5.38
Decongestant Comparison (reflective AM+PM nasal congestion score, Days 1-15)		DL D-12	DL
	Men	-1.03	-0.73
	Women	-0.89	-0.65

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Study P00362: Mean Changes in Symptom Scores, by Gender [S8/p00362/p195-6, 241-2]		
Antihistamine Comparison (reflective AM+PM total symptom score, excluding congestion, Days 1-15)	DL D-12	PSE
Men	-6.26	-4.40
Women	-6.77	-5.69
Decongestant Comparison (reflective AM+PM nasal congestion score, Days 1-15)	DL D-12	DL
Men	-0.85	-0.64
Women	-0.96	-0.78

The Applicant did not state whether DL D-12 was *statistically* superior on the primary endpoints for both men and women. The Biometrics reviewer (Dr. Zhou) found that in Study P00355, DL D-12 was statistically superior to the appropriate comparator on both primary endpoints in both men and women. In Study P00362, DL D-12 was statistically superior on the antihistamine component in both men and women, and was statistically superior on the decongestant component in women and approached statistical significance in men ($p= 0.0553$).

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Previous studies have evaluated the pharmacokinetics of DL in the elderly (P00275) as well as patients with renal (C98-355) and hepatic impairment (C98-354). According to the Applicant, based on these data there was no alteration in the safety profile and no dosage adjustment was recommended [S3/3.F.3/page 141/189].

The Applicant provided summaries of the effects of age, race, and gender on the incidence of adverse events, treatment-related AEs, and SAEs in the two pivotal clinical studies [S8/ISS/28-34]. However, there were too few subjects in the age groups 12 to <18, and ≥ 65 years (the subgroup definitions in regard to age was 12 to <18 years, 18 to <65 years, and ≥ 65 years), or who were non-Caucasians to allow meaningful comparisons with respect to age or race [S8/ISS/29]. The same concern applies to subgroup analyses based on age or race with regard to efficacy.

C. Evaluation of Pediatric Program

This application did not contain a pediatric program. The Applicant has requested a waiver of the "Pediatric Use Information" requirements (21 CFR 314.55(a)) for the

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pediatric age groups below 12 years [S20/peduse/page 1]. The Applicant asserts that DL D-12 does not represent a meaningful therapeutic benefit over existing treatments and is not likely to be used in a substantial number of patients below the age of 12 years because the dose of pseudoephedrine (120mg BID) is not recommended for such patients. The request for a waiver of the pediatric use information requirements is appropriate.

D. Comments on Data Available or Needed in Other Populations

The Application does not include assessments in patients with hepatic or renal impairment. There is no clinical information available regarding the safety of this product during pregnancy. As discussed in Section VI of this Medical Officer Review, two pregnancies occurred during the clinical trial, one in the PSE group, and one in the DL group. The subject in the PSE group elected to have an abortion. The follow-up of the pregnancy in the DL group is incomplete.

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Conclusions and Recommendations

4. The phrase ' _____ ' should be deleted. There is no need to further describe the extended release layer in this section.
5. The label should include information regarding the poor metabolizer phenotype. Such information would include the prevalence of the phenotype and its effect on desloratadine exposures.
6. Insert the following statement in Line 175 (Pharmacodynamics Section), prior to the sentence beginning "No clinically meaningful changes...": _____

7. The phrase ' _____ ' should be deleted from the description of the clinical studies. The comparators were used as "placebos".
8. The Clinical Trials section states that Clarinex-D 12 HOUR tablet was superior to both comparators (desloratadine alone, and pseudoephedrine alone) on the total symptom score. _____
_____ endpoint of either _____

9. The dose of desloratadine used in the studies is mistakenly stated to be _____ twice daily [line 206]. The actual dose was 5mg once daily.
10. Instantaneous symptom scores in both studies support the end of dosing interval efficacy. However, while DL D-12 was statistically superior to the comparators the magnitude of the effect at the end of the dosing interval was small. Therefore, the word _____ [line 207] should be deleted.
11. The Clinical Trials section states that _____
_____ es 207-208]. In Study P00355, DL D-12 was not statistically superior to the appropriate comparator on either primary comparison at Day 1 (DL D-12 vs. PSE for total symptoms, excluding nasal congestion; and DL D-12 vs. DL5 for nasal congestion). Therefore, it is not appropriate to include this phrase in the label.
12. The table of adverse events should include all AEs, not only those deemed _____

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Appendix: Study P00355

XI. APPENDIX

A. Individual Study Review: STUDY #P00355: "Efficacy and safety of desloratadine (sch 34117) + pseudoephedrine, bid, versus its components in the treatment of subjects with seasonal allergic rhinitis"

(1) Study Description

This parallel group study compared three treatment groups: desloratadine 5mg QD (DL5), pseudoephedrine 120mg BID (PSE), and desloratadine 2.5mg + pseudoephedrine 120mg BID (DL D-12). This was a two-week study in subjects with seasonal allergic rhinitis (SAR) performed during the Fall season, 1999. The original protocol for this study was dated July 13, 1999 [S8/P00355/893-1419]. There were no protocol amendments [S8/P00355/892].

(a) Design

This was a randomized, multicenter, parallel group, double-dummy, double-blind study. There was no placebo. Randomization was performed in a 1:1:1 ratio.

(b) Duration

The treatment period was 2 weeks. The period between the screening visit (Visit 1) and the baseline visit (Day 1) ranged from 3 to 14 days.

(c) Study Centers

The study was conducted at 20 medical centers across the US.

(d) Population

The study population was subjects 12 years of age and older with at least a 2-year history of seasonal allergic rhinitis (SAR).

(e) Study Treatments

The subjects in the three treatment groups received the following [S8/P00355/908]:

<u>Treatment</u>	<u>AM Dose</u>	<u>PM Dose</u>
1. DL D-12*	DL D-12 + DL5 placebo	DL D-12
2. DL5	DL5 + DL D-12 placebo	DL D-12 placebo
3. PSE*	PSE 120 mg + DL5 placebo	PSE 120 mg

*(DL D-12 and PSE 120 mg were identical in appearance.)

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Appendix: Study P00355

(f) Objective

Primary objective: to assess the efficacy of DL D-12, a twice daily bilayer tablet antihistamine/decongestant containing 2.5 mg of immediate release desloratadine and 120 mg of sustained release pseudoephedrine compared to its components in subjects with seasonal allergic rhinitis. **Reviewer's Note: The stated objective is to compare DL D-12 to its components; however, this comparison is complicated because the dosing schedules of the antihistamine component (desloratadine) differ between the combination product (2.5mg BID) and the comparator (5mg QD).**

Secondary objective: to evaluate the safety profile of DL D-12 using the following parameters: patient reported adverse events, ECG, vital sign evaluations and laboratory results.

(g) Inclusion Criteria

Inclusion criteria of note include the following:

1. Subjects must be 12 years of age and older, of either sex and of any race.
2. Subjects must have at least a two-year documented history of seasonal allergic rhinitis.
3. Subjects must have a positive skin test (prick or intradermal) response to an appropriate seasonal allergen within the 12 months prior to Visit 1. For the skin prick test, a positive response is defined as a wheal diameter at least 3 mm larger than diluent control. For the intradermal test, a positive response is defined as a wheal diameter of at least 7 mm larger than diluent control.
4. Subjects must be clinically symptomatic at the Screening Visit. Nasal rhinorrhea (anterior or posterior) must be at least moderate (score of at least 2); nasal stuffiness must be at least moderate; total nasal symptom score must be at least 6 and a total nonnasal score must be at least 5 to qualify, as evaluated jointly by the subject and Investigator.
5. The seven run-in diary "reflective" scores for the three days prior to Baseline, and the AM of Baseline visit, must total a minimum of 42 for the total nasal score, a minimum of 35 for the total non-nasal score and a minimum of 14 for the congestion and rhinorrhea.
6. Subject must be in general good health.

(h) Exclusion Criteria

Exclusion criteria of note include:

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1. Subjects with asthma who require chronic use of inhaled or systemic corticosteroids.
2. Subjects with current or history of frequent, clinically significant sinusitis or chronic purulent postnasal drip.
3. Subjects with rhinitis medicamentosa.
4. Subjects with a history of allergies to more than two classes of medication or who are allergic to or cannot tolerate antihistamines.
5. Subjects who have had an upper respiratory tract or sinus infection that required antibiotic therapy without at least a 14 day washout prior to screening, or who have had a viral upper respiratory infection within 7 days prior to screening.
6. Subjects who have nasal structural abnormalities, including large nasal polyps and marked septal deviation, that significantly interfere with nasal air flow.
7. Subjects who, in the opinion of the Investigator, are dependent upon nasal, oral or ocular decongestants, nasal topical antihistamines, or nasal steroids.
8. Subjects on immunotherapy (desensitization therapy), unless on a regular maintenance schedule prior to the Screening visit and staying on this schedule for the remainder of the study. Subjects may not receive desensitization treatment within 24 hours prior to a follow-up visit.

(i) Prohibited Medications

Subjects who took the following medications prior to screening were required to have the specified minimum washout period, and were not allowed to take the medications during the study.

<u>Medication</u>	<u>Washout Period</u>
- Nasal or inhaled cromolyn sodium or nedocromil	2 weeks
- Corticosteroids - nasal, ocular, oral, inhaled, intravenous or rectal	1 month
- Corticosteroids – intramuscular or intra-articular	3 months
- High-potency dermatological corticosteroids - mid-strength, potent, or superpotent by Stoughton-Cornell scale	1 week
- Antihistamines, short acting (e.g., chlorpheniramine)	12 hours
- Clemastine, long-acting OTC forms of chlorpheniramine	48 hours
- Long-acting antihistamines (cetirizine, terfenadine, fexofenadine, hydroxyzine)	10 days
- Loratadine	10 days
- Azelastine and other topical antihistamines	10 days
- Accolate, Singulair, Zileuton	10 days

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Decongestant Comparison (Study P00362):									[S8/p00362/65]
Nasal Congestion Score (Reflective, AM+PM)									
	DL D-12			DL5			PSE		
	N	mean	% change	N	mean	% change	N	mean	% change
Baseline	214	2.55		213	2.56		221	2.56	
Change from Baseline to:									
Day 1	212	-0.58	-23.1	211	-0.37	-15.0	220	-0.49	-18.9
Day 2	214	-0.84	-32.8	212	-0.53	-20.7	220	-0.68	-26.2
Day 3	212	-0.89	-35.5	212	-0.60	-23.9	218	-0.68	-26.1
Day 4	210	-0.89	-35.2	212	-0.72	-28.1	217	-0.81	-30.9
Days 1-8	214	-0.87	-34.1	213	-0.66	-25.8	221	-0.75	-28.9
Days 9-15	205	-0.98	-38.6	204	-0.84	-32.9	209	-0.93	-35.8
Pairwise Comparison p-values									
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE		
Day 1	0.236			0.006*			0.115		
Day 2	0.023*			<0.001*			0.040*		
Day 3	0.005*			<0.001*			0.334		
Day 4	0.301			0.037*			0.283		
Days 1-8	0.066			0.001*			0.154		
Days 9-15	0.518			0.058			0.207		

*=p<0.05

Shaded cells: relevant treatments for antihistamine comparison

Finally, the table below summarizes the data on the reflective, AM+PM, total symptom scores (*including nasal congestion*) for the Day 1-15 comparison. This table shows that DL D-12 was slightly, but statistically significantly superior to both DL5 and PSE on this endpoint. Thus, when compared on the same endpoint, DL D-12 was shown to be statistically superior to DL5 and PSE. As noted in the review of Study 00355, this superiority would not fulfill the Agency's customary requirement regarding the efficacy of combination drugs because of the different dosing regimens for desloratadine.

Total Symptom Score (<i>including nasal congestion</i>), Reflective, AM+PM (Study P00362, ITT population):										[S8/p00362/221]
	DL D-12			DL5			PSE			
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	213	17.74		212	17.21		221	17.41		
Change from Baseline to Day 1-15	213	-7.56	-42.0%	212	-6.09	-35.1%	221	-6.11	-35.0%	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	0.001*			0.001*			0.957			

*p<0.05

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End Of Dosing Interval (Instantaneous Scores)

The instantaneous scores are intended to assess the end of dosing interval efficacy. The Applicant proposes that the AM+PM instantaneous score is most appropriate for the antihistamine comparison because both of the treatments being compared (DL D-12 and PSE) are dosed twice-daily. However, the Applicant proposes that the AM instantaneous score is most appropriate for the decongestant comparison because one of the treatments being compared (DL5) is dosed once-daily. **Reviewer's Comment: This approach to the analysis of the decongestant activity will exclude the PM instantaneous scores. The daytime end of dosing interval efficacy is an important aspect of the overall assessment of efficacy of DL D-12. Because this is a double-dummy study, with DL5 intended as a "placebo" in regard to decongestant activity, it is not necessary to exclude the PM scores. Therefore, the AM+PM instantaneous nasal congestion scores will also be discussed.**

The table below provides the end of dosing interval data for the antihistamine comparison, for the entire 2-week treatment period (Days 1-15). For this interval, as well as all of the other intervals except Day 1, the DL D-12 group was superior to the PSE group in regard to instantaneous mean total symptom scores, excluding nasal congestion. The relative improvement seen with DL D-12 for Days 1-15, while statistically significant, was small, considering the improvement seen with PSE, which is not felt to have antihistamine activity (-42.1% vs. -35.7%). As seen with the reflective scores, DL5 did not appear to have significant antihistamine activity. The relative reduction in instantaneous symptoms was similar to PSE and inferior to DL D-12.

End of Dosing Interval, Antihistamine Comparison (Study P00362):								[S8/p00362/69]	
Total Symptom Score, Excluding Nasal Congestion (Instantaneous, AM+PM)									
	DL D-12			DL5			PSE		
	N	mean	%change	N	mean	%change	N	mean	%change
Baseline	213	14.84		212	14.37		221	14.70	
Change from Baseline to Days 1-15	213	-6.30	-42.1	212	-5.19	-35.2	221	-5.28	-35.7
Pairwise Comparison p-values									
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE		
	0.010*			0.005*			0.816		

*= p<0.05

Shaded cells: relevant treatments for antihistamine comparison

The table below provides the end of dosing interval data for the decongestant comparison, for the entire 2-week treatment period (Days 1-15). As discussed above, this analysis uses only the AM data. For this interval (but not for the Days 9-15 interval), the DL D-12 group was superior to the DL5 group in regard to instantaneous nasal congestion score improvement. The relative improvement seen with DL D-12 for Days 1-15, while statistically significant, was small, considering the improvement seen with DL5, which is not felt to have decongestant activity (-31.4% vs. -25.5%). Finally, as

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(NDA 21-313)**

Appendix: Study P00362

seen with the reflective scores, DL D-12 was statistically superior to PSE on the instantaneous nasal congestion score.

End of Dosing Interval, Decongestant Comparison (Study P00362):										[S8/p00362/71]
Nasal Congestion Score (Instantaneous, AM)										
	DL D-12			DL5			PSE			
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	214	2.55		213	2.57		220	2.54		
Change from Baseline to Days 1-15	214	-0.82	-31.4%	213	-0.66	-25.5%	220	-0.76	-28.5%	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	0.395			0.019*			0.131			

*= p<0.05

Shaded cells: relevant treatments for antihistamine comparison

As discussed above, the Applicant has chosen to present the AM instantaneous nasal congestion scores as the most appropriate comparison to illustrate end of dosing interval efficacy. This reviewer believes that the AM+PM comparison would be more appropriate. However, using AM+PM instantaneous nasal congestion scores does not alter the conclusions drawn from the AM instantaneous comparison. The improvement in instantaneous nasal symptoms scores (Day 1-15) seen with DL D-12 (-33.6%) was superior to the improvement seen with DL5 (-27.8%), with a p-value of 0.022 [S8/p00362/74].

Other Secondary Endpoints

Additional secondary endpoints included:

- Other subject-evaluated reflective and instantaneous total symptom scores, excluding nasal congestion (AM and PM)
- Other subject-evaluated reflective and instantaneous nasal congestion scores (AM and PM)
- Subject-evaluated total symptom score (reflective and instantaneous, AM, PM and AM+PM)
- Individual symptom scores, reflective and instantaneous (AM and PM)
- Joint subject-investigator evaluation of overall condition of SAR
- Joint subject-investigator evaluation of therapeutic response

Each of the subject-evaluated scores were analyzed at Days 1, 2, 3, 4, and Week 1 (Days 1-8), Week 2 (Days 9-15), and for the average over the 2-week treatment period (Days 1-15).

The following tables summarize the Day 1-15 comparisons for total symptom scores, excluding nasal congestion, and nasal congestion scores, both reflective and instantaneous. **The results of these comparisons do not alter the conclusions drawn based upon the comparisons considered above (AM+PM scores, and end of dosing**

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(NDA 21-313)**

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interval scores). The results support the conclusion that DL D-12 provides a small, but statistically significant benefit over DL5 for the decongestant effect (nasal congestion score), and over PSE for the antihistamine effect (total symptom scores, excluding nasal congestion). As seen in the prior analyses, DL5 did not seem to have an antihistamine effect (the effect was indistinguishable from PSE and inferior to the effect seen with DL D-12).

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Total Symptom Scores, Excluding Nasal Congestion: Change and Percent Change Between Baseline and Days 1-15, Instantaneous and Reflective (ITT population, Study No. P00362)										
Time Point	DL D-12			DL			PSE			
	N	Mean	Mean % Change	N	Mean	Mean % Change (DL D-12 vs. DL)	N	Mean	Mean % Change	p-value (DL D-12 vs. PSE)
AM Reflective										
Baseline	213	15.01		212	14.53	0.084	219	14.52		0.079
Days 1-15	213	-6.49	(-42.4)	212	-5.34	(-36.3)	219	-5.05	(-34.6)	<0.001
AM Instant.										
Baseline	213	14.79		212	14.57	0.458	220	14.61		0.534
Days 1-15	213	-6.09	(-40.4)	212	-5.13	(-34.2)	220	-5.13	(-34.7)	0.017
PM Reflective										
Baseline	213	15.37		212	14.79	0.040	221	15.18		0.506
Days 1-15	213	-6.80	(-43.3)	212	-5.35	(-35.3)	221	-5.50	(-35.8)	0.001
PM Instant.										
Baseline	213	14.88		212	14.18	0.031	221	14.78		0.747
Days 1-15	213	-6.51	(-43.3)	212	-5.25	(-35.5)	221	-5.43	(-36.3)	0.009

Nasal Congestion Scores: Change and Percent Change Between Baseline and Days 1-15, Instantaneous and Reflective (ITT population, Study P00362)										
Time Point	DL D-12			DL			PSE			
	N	Mean	Mean % Change	N	Mean	Mean % Change (DL D12 vs. DL)	N	Mean	Mean % Change	p-value (DL D12 vs. PSE)
AM/PM NOW										
Baseline	214	2.52		213	2.53	0.793	221	2.53		0.950
Days 1-15	214	-0.85	(-33.6)	213	-0.70	(-27.8)	221	-0.79	(-30.2)	0.367
AM PRIOR										
Baseline	214	2.57		213	2.58	0.880	219	2.57		0.938
Days 1-15	214	-0.89	(-34.5)	213	-0.72	(-28.1)	219	-0.80	(-30.2)	0.182
PM PRIOR										
Baseline	214	2.53		213	2.54	0.798	221	2.54		0.756
Days 1-15	214	-0.94	(-37.0)	213	-0.75	(-29.1)	221	-0.85	(-32.6)	0.171
PM NOW										
Baseline	214	2.50		213	2.50	>0.999	221	2.52		0.695
Days 1-15	214	-0.88	(-35.2)	213	-0.74	(-28.8)	221	-0.82	(-30.9)	0.372

Analysis of the Day 1-15 reflective individual antihistamine symptom scores (rhinorrhea, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate) revealed results which were similar to those seen with the total symptom scores (excluding nasal congestion). In this analysis, DL D-12 was statistically superior to DL5 for each of the individual symptoms, with the exception of rhinorrhea (p=0.65) and itching of ears/palate (p=0.056), and DL D-12 was statistically superior to PSE on each of the individual symptom scores, with the exception of rhinorrhea (p=0.051) [S8/p00362/76-77].

The overall condition of SAR was evaluated jointly by the subject and investigator, and recorded on a scale of 0-3. For this parameter, although the differences between groups were small, DL D-12 was statistically superior to both DL5 and PSE at Day 1-15. Note that in Study P00355 these differences did not reach statistical significance.

Overall Condition of SAR, determined by subject and investigator jointly (Study P00362, ITT population) [S8/p00362/79]									
	DL D-12			DL5			PSE		
	N	mean	%change	N	mean	%change	N	mean	%change
Baseline	213	2.66		211	2.58		219	2.60	
Change from Baseline to Day 1-15	213	-1.07	-36.8%	211	-0.85	-31.0%	219	-0.90	-31.9%
Pairwise Comparison p-values									
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE		
	0.041*			0.006*			0.452		

*p<0.05

An evaluation of the therapeutic response was performed by the subject and investigator jointly. The response was recorded on a scale of 1 (complete relief) to 5 (treatment failure). For Day 1-15, DL D-12 was statistically superior to both DL5 and PSE (2.87 vs. 3.19 and 3.19) [S8/p00362/80]. Note that this difference did not reach statistical significance in Study P00355.

(d) Statistical/Analytical Issues

The applicant reports that there was a baseline imbalance between the DL D-12 group and the DL group in AM+PM reflective, PM reflective, and PM instantaneous total symptom score, excluding congestion. This imbalance was not important because these parameters are relevant to the DL D-12 versus PSE comparison, not the DL D-12 versus DL comparison. Further, the Applicant states that an analysis of covariance, which included baseline score as a covariate, did not result in inferences that were different than those drawn from the protocol-specified ANOVA, discussed above [S8/p00362/80].

In calculating the average over Days 1-15, no data were imputed for subjects who discontinued early. A total of 46 subjects discontinued early, 14 in the DL D-12 group, 14 in the DL group, and 18 in the PSE group. Four subjects were not included in the

antihistamine efficacy analysis because they did not have baseline or endpoint diary data for the primary variable of total symptom score, excluding nasal congestion (1 in the DL D-12 group, 2 in the DL group, and 1 in the PSE group). Two of these four subjects also did not have endpoint diary data for the primary endpoint of nasal congestion and were not included in the decongestant efficacy analysis.

The Applicant states that the test for treatment-by-center effect was not significant ($p > 0.65$) for either of the primary efficacy variables [S8/p00362/81].

(e) Reviewer's Comments on Efficacy

This randomized, double-blind, double-dummy study was designed to demonstrate that DL D-12 has superior antihistamine effects as compared with PSE, and that DL D-12 has superior decongestant effects, as compared with DL5.

The pre-specified primary endpoint in regard to the antihistamine effect was the change from baseline in the reflective AM+PM total symptoms score, excluding nasal congestion. The primary comparison on this variable was DL D-12 versus PSE. The results of the study demonstrated that DL D-12 was statistically superior to PSE on this variable. While the Applicant did not pre-specify the effect size that would be considered to be clinically significant, the study was powered to demonstrate a difference between groups of 1.6. The actual difference between groups was demonstrated to be 1.37. Thus, the conclusion can be that DL D-12 is slightly, but statistically, superior to PSE on this measure of antihistamine activity.

The pre-specified primary endpoint in regard to the decongestant effect was the change from baseline in the reflective AM+PM nasal congestion score. The primary comparison on this variable was DL D-12 versus DL5. The results of the study demonstrated that DL D-12 was statistically superior to DL5 on this variable. The difference between groups was small, but statistically significant.

The various secondary analyses of symptom scores supported the conclusions drawn from the primary endpoints. Instantaneous symptom scores demonstrated that the efficacy of DL D-12 is maintained at the end of the dosing interval. Assessments of the overall condition of SAR and of the therapeutic response, which were performed jointly by the subject and investigator, also showed a statistically significant benefit of DL D-12 over both comparators.

Two additional noteworthy observations from this study are: 1) the DL5 treatment did not appear to demonstrate antihistamine activity that could be distinguished from the effects of PSE; and 2) the DL D-12 treatment had significantly greater decongestant activity than did the PSE treatment. Similar findings were noted in Study P00355.

(4) Safety Review

Studies P00355 and P00362 were performed under identical protocols. Safety data from the two studies will be considered collectively. The review of this data can be found in the Overview of Safety section of this review.

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this page is the manifestation of the electronic signature.**

/s/

Eugene Sullivan
10/11/01 11:00:05 AM
MEDICAL OFFICER

Badrul Chowdhury
10/11/01 05:01:07 PM
MEDICAL OFFICER

I concur. Also see my team leader memorandum dated October 10, 2001.

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CLINICAL REVIEW

Application Type 21313
Submission Number N000
Submission Code BZ

Letter Date July 29, 2005
Stamp Date August 1, 2005
PDUFA Goal Date February 1, 2006

Reviewer Name Sally Seymour, M.D.
Review Completion Date January 26, 2006

Established Name Desloratadine/pseudoephedrine sulfate
(Proposed) Trade Name Clarinex-D 12 Hour Extended Release Tablet
Therapeutic Class Antihistamine/decongestant
Applicant Schering-Plough

Priority Designation S

Formulation Tablet
Dosing Regimen One tablet twice a day
Indication Relief of nasal and non-nasal symptoms of seasonal
allergic rhinitis including nasal congestion
Intended Population Adults and children 12 years of age and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Clarinex D 12 Hour Extended Release is a bilayer tablet consisting of immediate release desloratadine 2.5mg and pseudoephedrine 120mg in an extended release layer. The original NDA for Clarinex-D 12 Hour Extended Release Tablets was submitted December 27, 2000. An Approvable action was taken on the application on October 26, 2001, primarily due to CMC issues.

In this complete response, Schering modified the formulation of Clarinex-D 12 Hour Extended Release Tablets to address CMC concerns raised during the first review cycle. In this response, the Applicant demonstrated that the modified formulation of Clarinex-D 12 Hour Extended Release Tablets is bioequivalent to the phase 3 formulation used in two pivotal clinical studies that supported the safety and efficacy of the phase 3 formulation of Clarinex-D 12 Hour Extended Release Tablets. Because the Applicant demonstrated bioequivalence between the phase 3 formulation and the to-be-marketed formulation, the safety and efficacy data from the clinical trials conducted with the phase 3 formulation can be extrapolated to the new to-be marketed formulation. The Applicant also adequately addressed the clinical deficiency regarding poor metabolizers of desloratadine. In addition, the Applicant has agreed to address labeling issues identified by the Division. Therefore, assuming the Applicant formally submits the agreed-upon labeling changes, from a clinical perspective, the recommendation is for Approval.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In the original NDA, the Applicant's clinical development program consisted of 5 clinical pharmacology studies and two pivotal clinical studies. According to the Medical Officer Review by Dr. Eugene Sullivan, the two pivotal clinical studies established the efficacy and safety of 2.5mg/pseudoephedrine sulfate 120mg tablets (DL/PSE-12).

In response to CMC issues raised by the Agency in the Approvable letter, the Applicant modified the formulation of the DL/PSE-12. The Applicant conducted four clinical pharmacology studies to support the new formulation of DL/PSE-12. Study P02040 demonstrated bioequivalence between the phase 3 formulation and the to-be-marketed formulation of DL/PSE-12. Study P02041 documented the multiple dose and steady state pharmacokinetics of DL/PSE-12. Study P02042 demonstrated that food did not have an effect on the oral bioavailability of DL/PSE-12. Study P02043 compared the bioavailability of pseudoephedrine from controlled release formulations of DL/PSE to establish dissolution specifications.

1.3.2 Efficacy

The clinical program for Clarinex-D 12 Hour Extended Release Tablets was designed to support the indication of the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion, in adults and children 12 years of age and older. The Applicant conducted two pivotal clinical trials with the phase 3 formulation of DL/PSE-12. The pivotal trials were reviewed in the first cycle and determined to support the proposed indication. Because the clinical pharmacology Study P02040 in this complete response demonstrated bioequivalence between the phase 3 formulation and the to-be-marketed formulation, the efficacy data from clinical trials conducted with the phase 3 formulation can be extrapolated to the new to-be marketed formulation. No new efficacy studies were included in this submission.

1.3.3 Safety

The safety of Clarinex-D 12 Hour Extended Release Tablets is primarily supported by the safety data in the two pivotal clinical trials with the phase 3 formulation of DL/PSE-12. Again, because the clinical pharmacology Study P02040 in this complete response demonstrated bioequivalence between the phase 3 formulation and the to-be-marketed formulation, the safety data from clinical trials conducted with the phase 3 formulation can be extrapolated to the new to-be marketed formulation. The safety data from the clinical pharmacology studies conducted for this complete response did not suggest a new safety signal. In addition, a safety update was submitted, which included a literature review and post-marketing adverse events for the single ingredients, desloratadine, pseudoephedrine, and the combination product, Clarinex-D 24 Hour Extended Release Tablets. The safety update did not suggest a new safety signal. Finally, the safety of Clarinex-D 12 Hour Extended Release Tablets is also supported by substantial safety experience with desloratadine reported in other NDAs for desloratadine products, including NDA# 21-605 for Clarinex-D 24 Hour Extended Release Tablet.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for Clarinex-D 12 Hour Extended Release Tablets is one tablet twice a day for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion.

1.3.6 Special Populations

The Approvable letter included a clinical deficiency regarding the safety and mechanism of poor metabolizers of desloratadine. Since the Approvable letter, the Applicant has adequately addressed the safety and mechanism of poor metabolizers of desloratadine for other applications for desloratadine (NDA# 21-363, Clarinex Tablets; NDA# 21-165, Clarinex Tablets; NDA# 21-312 Clarinex Reditabs; NDA# 21-300 Clarinex Syrup; and NDA# 21-297 Clarinex Tablets (CIU)) sponsored by Schering-Plough. No new information was submitted in this complete response regarding poor metabolizers.

During the review period the issue of dose adjustment in patients with renal or hepatic impairment was raised. The Applicant did not perform clinical or pharmacokinetic studies with DL/PSE-12 in subjects with renal or hepatic impairment. Therefore, recommendations regarding usage in patients with renal or hepatic impairment are based upon pharmacokinetic studies with the individual components, desloratadine and pseudoephedrine. The Applicant has performed pharmacokinetic studies with DL in subjects with renal and hepatic impairment for the Clarinet NDAs. According to the product label, the AUC for desloratadine is increased ~1.2 to 2.5 fold in patients with hepatic or renal impairment, relative to subjects with normal renal and hepatic function.

Pseudoephedrine is an OTC medication with extensive clinical experience and the Applicant did not conduct pharmacokinetic studies with pseudoephedrine in subjects with renal or hepatic impairment. The Applicant submitted literature references suggesting that pseudoephedrine is primarily excreted by the kidneys; however, no pharmacokinetic data were available. Since this is a combination product, without specific PK data for pseudoephedrine in patients with renal and hepatic impairment, it is difficult to determine if the dosing frequency of DL/PSE-12 can be adjusted in patients with renal or hepatic impairment and still be safe and effective. Thus, Clarinet D 12 Hour should not be recommended for use in patients with renal or hepatic impairment.

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2 INTRODUCTION AND BACKGROUND

NDA# 21-313 was originally submitted December 8, 2000, by Schering Plough for 2.5mg desloratadine/120mg pseudoephedrine sulfate (DL/PSE-12) tablets. The proposed trade name was Clarinet-D 12 Hour Extended Release Tablets. The proposed indication was the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion. An Approvable action was taken October 26, 2001, primarily for CMC deficiencies. However, there was a clinical issue regarding establishing the safety of high levels of desloratadine exposure in slow metabolizers. In addition to the clinical concern regarding poor metabolizers of desloratadine, two labeling comments were conveyed in the Approvable Letter.

In response to the issues raised by the Agency, the Applicant modified the formulation of the desloratadine 2.5mg/pseudoephedrine sulfate 120mg (DL/PSE -12) tablets. The Applicant conducted four clinical pharmacology studies to support the new formulation of the DL/PSE-12 tablets.

2.5 Presubmission Regulatory Activity

The following is a summary of the pertinent regulatory history with regards to NDA# 21,313.

- December 8, 2000, NDA# 21-313 submitted by Schering Plough
 - 2.5mg desloratadine/120mg pseudoephedrine sulfate tablets
 - proposed trade name - Clarinet-D 12 Hour Extended Release Tablets
 - proposed indication - the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion.
 - Five clinical pharmacology studies and two phase 3 studies
- October 26, 2001, Approvable letter issued
 - primarily CMC deficiencies
- July 20, 2004, Request for teleconference to discuss development program
 - Questions submitted
 - October 20, 2004, Responses to questions regarding development program conveyed to Applicant
- June 6, 2005, correspondence regarding proposal for safety update with response submission

5 CLINICAL PHARMACOLOGY

The Applicant conducted four clinical pharmacology studies to support the modified formulation of DL/PSE-12. The studies are listed below with a detailed review of the individual studies in the Appendices.

- Study P02040 – bioavailability of DL and PSE from extended-release formulations
 - Single dose, open-label, 2 way crossover study in 20 healthy volunteers

- As shown below in Table 1, Study P02040 established the bioequivalence between the phase 3 formulation of DL/PSE-12 (A) and the to-be-marketed formulation of DL/PSE-12 (B).

Table 1. Study P02040 Summary of Key Pharmacokinetic Parameters (N=20)					
Mean Desloratadine PK Parameters					
Parameter	TRT ¹	Mean (%CV)	Pair	Ratio	90% CI
AUC _{if} (ng*h/mL)	A	33.5 (79)	A/B	93.7	85.6 - 102
	B	31.6 (88)			
AUC ₁ (ng*h/mL)	A	36.0 (110)	A/B	98.4	92.7 - 104
	B	36.9 (114)			
C _{max} (ng/mL)	A	1.03 (31)	A/B	99.7	94.2 - 106
	B	1.09 (36)			
Mean 3-OH Desloratadine PK Parameters					
AUC _{if} (ng*h/mL)	A	12.2 (54)	A/B	98.8	92.9 - 105
	B	12.6 (50)			
AUC ₁ (ng*h/mL)	A	15.4 (33)	A/B	99.1	93.3 - 105
	B	15.5 (34)			
C _{max} (ng/mL)	A	0.408 (57)	A/B	100	94.6 - 107
	B	0.430 (56)			
Mean Pseudoephedrine PK Parameters					
AUC _{if} (ng*h/mL)	A	4161 (22)	A/B	107	99.0 - 115
	B	4588 (25)			
AUC ₁ (ng*h/mL)	A	4291 (23)	A/B	107	99.3 - 115
	B	4745 (25)			
C _{max} (ng/mL)	A	254 (16)	A/B	103	97.6 - 109
	B	263 (13)			
¹ Treatment Groups: A= DL/PSE (phase 3 formulation); B = DL/PSE (to-be-marketed formulation) Source: N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 34, 35, 38, 40, 42, 44					

Reviewer's Comment: According to the Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, to establish bioequivalence the 90% confidence interval for the ratio of the geometric means between the products should fall within the interval 80-125% for log-transformed AUC_{0-inf}, AUC_{0-t}, and C_{max}.

- Study P02041 – multiple-dose and steady-state pharmacokinetics of DL/PSE -12
 - Multiple dose, open-label study in 18 healthy volunteers
 - The multiple dose and steady state pharmacokinetics of DL/PSE-12 are shown in Table 6 in the Appendix.
- Study P02042 – influence of food on the oral bioavailability of DL/PSE -12
 - Single dose, open-label, 2 way crossover study in 20 healthy volunteers
 - As shown below in Table 2, Study P02042 demonstrated that food did not have an effect on the oral bioavailability of DL/PSE-12

Table 2 Study P02042 Summary of Key Pharmacokinetic Parameters (N=20)				
Mean Desloratadine PK Parameters				
Parameter	TRT	Mean (%CV)	Ratio (Fed/Fasted)	90% CI
AUC _{0-t} (ng*h/mL)	Fasted	20.9 (48)	105	98-113
	Fed	22.1 (46)		
AUC ₁ (ng*h/mL)	Fasted	21.8 (49)	105	98-113
	Fed	23.0 (47)		
C _{max} (ng/mL)	Fasted	1.13 (43)	106	97-115
	Fed	1.18 (41)		
Mean 3-OH Desloratadine PK Parameters				
AUC _{0-t} (ng*h/mL)	Fasted	12.7 (32)	98.6	94-103
	Fed	12.6 (27)		
AUC ₁ (ng*h/mL)	Fasted	14.1 (31)	99.2	95-104
	Fed	14.1 (26)		
C _{max} (ng/mL)	Fasted	0.51 (36)	102	95-109
	Fed	0.52 (33)		
Mean Pseudoephedrine PK Parameters				
AUC _{0-t} (ng*h/mL)	Fasted	4274 (29)	87.1	84-91
	Fed	3724 (24)		
AUC ₁ (ng*h/mL)	Fasted	4369 (28)	88.2	85-92
	Fed	3840 (23)		
C _{max} (ng/mL)	Fasted	297 (26)	102	98-107
	Fed	305 (21)		
Source: N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 34				

- Study P02043 – bioavailability of PSE from controlled-release (12-hour) formulations
 - Single dose, open-label, 4 way crossover study in 20 healthy volunteers
 - Compared the bioavailability of pseudoephedrine from controlled release formulations of DL/PSE to establish dissolution specifications

It should be noted that the manufacturer of the DL/PSE –12 tablets used in the clinical pharmacology studies (Schering Plough Corporation, New Jersey) is different than the proposed commercial manufacturer (_____). The Applicant conducted in vitro/in vivo correlation studies.

Reviewer's Comment: Interpretation of the pharmacokinetic studies is deferred to the OCPB reviewer, Dr. Sayed Al Habet.

6 INTEGRATED REVIEW OF EFFICACY

The clinical program for Clarinex-D 12 Hour Extended Release Tablets was designed to support the indication of the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion, in adults and children 12 years of age and older. The Applicant conducted two pivotal clinical trials with the phase 3 formulation of DL/PSE-12. The pivotal trials were reviewed in the first cycle and determined to support the proposed indication.

Because the clinical pharmacology Study P02040 in this complete response demonstrated bioequivalence between the phase 3 formulation and the to-be-marketed formulation, the efficacy data from clinical trials conducted with the phase 3 formulation can be extrapolated to the new to-be marketed formulation. No new efficacy studies were included in this submission.

7 INTEGRATED REVIEW OF SAFETY

The safety of Clarinex-D 12 Hour Extended Release Tablets is primarily supported by the safety data in the two pivotal clinical trials with the phase 3 formulation of DL/PSE-12. Again, because the clinical pharmacology Study P02040 in this complete response demonstrated bioequivalence between the phase 3 formulation and the to-be-marketed formulation, the safety data from clinical trials conducted with the phase 3 formulation can be extrapolated to the new to-be marketed formulation. The safety data from the clinical pharmacology studies conducted for this complete response did not suggest a new safety signal. In addition, a safety update was submitted, which included a literature review and post-marketing adverse events for the single ingredients, desloratadine and pseudoephedrine. The safety update did not suggest a new safety signal. Finally, the safety of Clarinex-D 12 Hour Extended Release Tablets is supported by substantial safety experience with desloratadine reported in other NDAs for desloratadine products.

The Applicant submitted a safety update in this complete response, which updates a previous safety summary submitted to NDA# 21-605 for Clarinex-D 24 Hour Extended Release Tablet. The safety summary submitted to NDA# 21-605 covers the period December 21, 2001 to September 30, 2004. The safety update submitted in this response to Approvable covers the period from October 1, 2004, to May 31, 2005. The safety update included the following [N21313\N_000\2005-07-29, update.pdf, pg 7-37]:

- a review of the post-marketing AEs for the single ingredients, desloratadine and pseudoephedrine
- a review of the medical literature for articles relevant to the safety of the single ingredients, desloratadine and pseudoephedrine
- a review of the post-marketing AEs for Clarinex D 24 Hour Extended Release Tablet.

A review of the safety update did not suggest a new safety signal for Clarinex-D 12 Hour Extended Release Tablets. The Applicant markets several desloratadine products (Clarinex Tablets, Syrup, and Reditabs). The post-marketing AEs for desloratadine were provided and are consistent with the adverse events listed in the product label. The Applicant also markets Drixoral Nasal Decongestant as an OTC product, which contains 120mg pseudoephedrine. During the reporting period for this safety update 5 AEs were reported for Drixoral Nasal Decongestant (drug effect decreased (2), psychomotor hyperreactivity, insomnia, and nasal congestion). Although a limited number of AEs were reported with pseudoephedrine, the AE profile for pseudoephedrine is well-described. The Applicant markets Clarinex D 24 Hour Extended Release Tablets. Since approval March 30, 2005, there were 5 cases of AEs reported during the reporting period (confusion regarding package with Clarinex, stomach pain/GERD, weakness and dizziness (2)). The Applicant's medical literature search for relevant articles with

respect to the safety of desloratadine and pseudoephedrine did not identify any new safety signals.

8 ADDITIONAL CLINICAL ISSUES

8.3 Special Populations

8.3.1 Poor Metabolizers

The Approvable letter included a clinical deficiency regarding the safety and mechanism of poor metabolizers of desloratadine. Since the Approvable letter, the Applicant has adequately addressed the safety and mechanism of poor metabolizers of desloratadine for other applications for desloratadine (NDA# 21-363, Clarinet Tablets; NDA# 21-165, Clarinet Tablets; NDA# 21-312 Clarinet Reditabs; NDA# 21-300 Clarinet Syrup; and NDA# 21-297 Clarinet Tablets (CIU)) sponsored by Schering-Plough. No new information was submitted in this complete response regarding poor metabolizers.

8.3.2 Renal and Hepatic Impairment

During the review period the issue of dose adjustment in patients with renal or hepatic impairment was raised. The Applicant did not perform clinical or pharmacokinetic studies with DL/PSE-12 in subjects with renal or hepatic impairment. Therefore, recommendations regarding usage in patients with renal or hepatic impairment are based upon pharmacokinetic studies with the individual components of DL/PSE-12, desloratadine and pseudoephedrine. The Applicant has performed pharmacokinetic studies with DL in subjects with renal and hepatic impairment for the Clarinet NDAs.

According to the proposed product label, in single dose pharmacokinetic studies with 7.5mg desloratadine in patients with mild and moderate renal impairment, median C_{max} and AUC values increased by ~1.2 and 1.9 fold, respectively, relative to subjects with normal renal function. In patients with severe renal impairment or who were hemodialysis dependent, C_{max} and AUC values increased by 1.7 and 2.5-fold, respectively.

According to the proposed product label, in single dose pharmacokinetic studies with desloratadine in patients with mild, moderate, and severe hepatic impairment, AUC values increased by 2.4 fold, respectively, relative to subjects with normal liver function. The apparent oral clearance of desloratadine in subjects with mild, moderate, and severe hepatic impairment was 37, 36, and 28% of that in normal subjects, respectively.

Pseudoephedrine is an OTC medication with extensive clinical experience and the Applicant did not conduct pharmacokinetic studies with pseudoephedrine in subjects with renal or hepatic impairment. According to the proposed product label, pseudoephedrine is primarily excreted unchanged in the urine with the remainder apparently being metabolized in the liver. Therefore

pseudoephedrine may accumulate in patients with renal impairment. Since this is a combination product, without specific PK data for pseudoephedrine in patients with renal and hepatic impairment, it is difficult to determine if the dosing frequency of DL/PSE-12 can be adjusted in patients with renal or hepatic impairment and still be safe and effective. Thus, Clarinex D 12 Hour should not be recommended for patients with renal or hepatic impairment.

9 OVERALL ASSESSMENT

9.1 Conclusions

The clinical program for Clarinex-D 12 Hour Extended Release Tablets was designed to support the indication of the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion, in adults and children 12 years of age and older. The Applicant conducted two pivotal clinical trials with the phase 3 formulation of DL/PSE-12. The pivotal trials were reviewed in the first cycle and determined to support the proposed indication. Because the clinical pharmacology Study P02040 in this complete response demonstrated bioequivalence between the phase 3 formulation and the to-be-marketed formulation, the efficacy and safety data from clinical trials conducted with the phase 3 formulation can be extrapolated to the new to-be marketed formulation.

The safety data from the clinical pharmacology studies conducted for this complete response did not suggest a new safety signal. In addition, a safety update was submitted, which included a literature review and post-marketing adverse events for the single ingredients, desloratadine and pseudoephedrine. The safety update did not suggest a new safety signal. Finally, the safety of Clarinex-D 12 Hour Extended Release Tablets is supported by substantial safety experience with desloratadine reported in other NDAs for desloratadine products, including NDA# 21-605 for Clarinex-D 24 Hour Extended Release Tablet.

9.2 Recommendation on Regulatory Action

Clarinex D 12 Hour Extended Release is a bilayer tablet consisting of immediate release desloratadine 2.5mg and pseudoephedrine 120mg in an extended release layer. The original NDA for Clarinex-D 12 Hour Extended Release Tablets was submitted December 27, 2000. An Approvable action was taken on the application on October 26, 2001, primarily due to CMC issues. In this complete response, Schering modified the formulation of Clarinex-D 12 Hour Extended Release Tablets to address CMC concerns raised during the first review cycle. In this response, the Applicant demonstrated that the modified formulation of Clarinex-D 12 Hour Extended Release Tablets is bioequivalent to the phase 3 formulation used in two pivotal clinical studies that supported the safety and efficacy of the phase 3 formulation of Clarinex-D 12 Hour Extended Release Tablets. The Applicant has adequately addressed the clinical deficiency regarding poor metabolizers of desloratadine. In addition, the Applicant has agreed to address labeling issues identified by the Division (See Section 9.4). Therefore, assuming the Applicant formally submits the agreed-upon labeling changes, from a clinical perspective, the recommendation is for Approval.

9.4 Labeling Review

A detailed labeling review was performed during the first review cycle and the proposed product label is very similar to the product label for the approved Clarinet D 24 Hour Extended Release Tablets. In a fax dated December 27, 2005, the following labeling comment was conveyed to the Applicant:

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In addition, the Project Manager, Anthony Zeccola, also requested the _____ be removed from the tradename for the same reasons (increases prominence of the proprietary name and decreases relative prominence of established name). In a teleconference with the Applicant on January 25, 2006, the Applicant agreed to the Division's requests regarding the package labeling.

In addition, during the review period, the issue of dose adjustment in patients with renal or hepatic impairment was raised. As discussed in Section 8.3.2, in this reviewer's opinion, Clarinet D 12 Hour should not be recommended for patients with renal or hepatic impairment. In a teleconference with the Applicant on January 25, 2006, the Division's recommendation regarding avoiding use in patients with renal or hepatic impairment was conveyed to the Applicant. The Applicant agreed to modify the product label to include language about avoiding use in patients with renal or hepatic impairment.

Submission of the final product label with the agreed upon revisions is pending at the time of finalization of this review.

9.5 Comments to the Applicant

No additional clinical comments will be conveyed to the Applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study P02040

Title: The bioavailability of desloratadine and pseudoephedrine from extended-release (12-hour) formulations: a replicate two-way crossover study

10.1.1.1 Protocol

Study P02040 was a randomized, single-dose, two-sequence, four-period crossover study under fasting conditions in 20 non-smoking male and female healthy subjects, 18-45 years of age. Females of childbearing potential were required to practice barrier contraception for the duration of the study. Pertinent exclusion criteria included clinically significant infectious disease within 4 weeks prior to treatment, blood pressure > 140/90 mmHg, drug, tobacco or alcohol use, Hepatitis B or C positive, HIV positive, recent use of medications (14 days), or recent use of alcohol (72 hours), pregnant or nursing women [N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 86-89].

Reviewer's Comment: The purpose of Study P02040 is to evaluate the bioequivalence of the formulation of DL/PSE-12 used in the phase 3 studies and the new to-be-marketed formulation of DL/PSE-12.

Informed consent was obtained from all subjects prior to initiation of study procedures. Screening procedures were performed within 3 weeks prior to administration of study medication. Screening procedures included: history and physical exam, ECG, chemistry, hematology, HIV screening, hepatitis screening, urinalysis, serum pregnancy screen, and urine drug screen [N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 80].

Eligible subjects were admitted to the study center approximately 12 hours prior to dosing with study medication. A serum pregnancy screen was collected and eligibility was reconfirmed. On study day 1 after an overnight fast (~10 hours), subjects were randomized to receive the following treatments twice in four separate periods in one of two sequences: ABAB or BABA:

- Treatment A – 2.5mg desloratadine/120mg extended release pseudoephedrine (Phase 3 formulation, batch no. 78578-008)
- Treatment B - 2.5mg desloratadine/120mg extended release pseudoephedrine (to be marketed formulation, batch no. 77660-111)

Study medication was administered at 8AM with 240mL of room temperature water. After dosing, subjects were to remain in an upright position for 4 hours. No food was allowed for four hours. Drinking water was permitted during the fasting period except for one hour pre and post-dose [N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 91].

Blood samples for pharmacokinetic measurements were collected before dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, and 120 hours post-dose. Subjects were confined to the study site until the 120 hours (Day 6) post dose sample was collected. Safety monitoring included vital signs, laboratories (chemistry, hematology, urinalysis, and pregnancy), and adverse events. Subjects could have been withdrawn for any reason. Following a 10 day washout period, subjects returned to the study center for the next treatment period [N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 80, 97].

No parameters of clinical efficacy were evaluated in this study. The following pharmacokinetic parameters were determined for desloratadine, 3-OH desloratadine, and pseudoephedrine from the plasma concentration data:

- The maximum observed concentration (C_{max})
- The time of observed C_{max} (T_{max})
- The terminal phase half life ($T_{1/2}$)
- The area under the concentration-time curve from time zero to the last sample with measurable concentration (AUC_{tf})
- The area under the concentration-time curve from time zero to infinity (AUC_l).

The pharmacokinetic parameters were analyzed using a linear mixed effect model on log-transformed AUC_{tf} , AUC_l , and C_{max} . Bioequivalence was assessed by the 90% confidence intervals for the difference between two treatment least squares means [N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 94, 104].

Reviewer's Comment: To establish bioequivalence under fasting conditions, the 90% confidence interval for the ratio of the geometric means between the products should fall within the interval 90-125% for log-transformed AUC_{0-inf} , AUC_{0-t} , and C_{max} .

10.1.1.2 Results

Study P02040 commenced on November 1, 2001, and was completed on December 16, 2001.

10.1.1.2.1 Subject Disposition and Demographics

All 20 subjects who enrolled completed all treatments. The mean age of the subjects was 38 years with an age range of 23 to 45 years. There were 19 males (95%) and 1 female (5%). The majority of the subjects were black. Only one subject was Hispanic and 4 subjects were caucasian [N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 1180].

Reviewer's Comment: The under-representation of female subjects is less than ideal.

All subjects received treatment A and treatment B in a certain sequence. The details of the treatments are displayed in Table 3.

Table 3 Study P02040 Treatment				
Treatment	Product	Sponsor	Batch No.	Expiration Date
A (Phase 3 formulation)	2.5mg desloratadine/120mg extended release pseudoephedrine	Schering Plough	78578-008	Manufactured on August 28, 2001 Kenilworth, NJ
B (to be marketed formulation)	2.5mg desloratadine/120mg extended release pseudoephedrine	Schering Plough	77660-111	Manufactured on July 21, 2001 Kenilworth, NJ

Source: N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 275-281

10.1.1.2.2 Pharmacokinetic Endpoint Outcomes

The data from Study P02040 demonstrate that the key pharmacokinetic parameters for the phase 3 formulation (treatment A) and the to-be-marketed formulation (treatment B) of 2.5mg desloratadine/120mg extended release pseudoephedrine were bioequivalent. According to the FDA, bioequivalence is established when the calculated CI falls between 80-125% for the ratio of the product averages (Guidance to Industry – Statistical Approaches to Establishing Bioequivalence). Table 4 is a summary of the key pharmacokinetic parameters from Study P02040. The data is presented for desloratadine, 3-OH desloratadine, and pseudoephedrine. The 90% confidence interval for the ratio of the means of the products was determined. The 90% confidence intervals for the key pharmacokinetic parameters fell between 80 and 125%.

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Table 4 Study P02040 Summary of Key Pharmacokinetic Parameters (N=20)					
Mean Desloratadine PK Parameters					
Parameter	TRT¹	Mean (%CV)	Pair	Ratio	90% CI
AUC _{0-t} (ng*h/mL)	A	33.5 (79)	A/B	93.7	85.6 - 102
	B	31.6 (88)			
AUC ₁ (ng*h/mL)	A	36.0 (110)	A/B	98.4	92.7 - 104
	B	36.9 (114)			
C _{max} (ng/mL)	A	1.03 (31)	A/B	99.7	94.2 - 106
	B	1.09 (36)			
Mean 3-OH Desloratadine PK Parameters					
AUC _{0-t} (ng*h/mL)	A	12.2 (54)	A/B	98.8	92.9 - 105
	B	12.6 (50)			
AUC ₁ (ng*h/mL)	A	15.4 (33)	A/B	99.1	93.3 - 105
	B	15.5 (34)			
C _{max} (ng/mL)	A	0.408 (57)	A/B	100	94.6 - 107
	B	0.430 (56)			
Mean Pseudoephedrine PK Parameters					
AUC _{0-t} (ng*h/mL)	A	4161 (22)	A/B	107	99.0 - 115
	B	4588 (25)			
AUC ₁ (ng*h/mL)	A	4291 (23)	A/B	107	99.3 - 115
	B	4745 (25)			
C _{max} (ng/mL)	A	254 (16)	A/B	103	97.6 - 109
	B	263 (13)			
¹ Treatment Groups: A= DL/PSE (phase 3 formulation); B = DL/PSE (to-be-marketed formulation) Source: N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 34, 35, 38, 40, 42, 44					

Following oral administration desloratadine is metabolized to 3-OH desloratadine, which is an active metabolite. Desloratadine conversion to 3-OH desloratadine exhibits a phenotypic polymorphism. A slow metabolizer of desloratadine is defined as any subjects with a 3-OH desloratadine to desloratadine ratio of <10%, or has desloratadine half-life >50 hours. Subject number 9 and 19 were identified as slow metabolizers, while subject number 4 behaved like a slow metabolizer in 1 out of 4 periods [N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 36].

10.1.1.2.3 Safety Outcomes

Adverse Events

The adverse event data does not suggest a new safety signal. All 20 subjects received 4 single doses of study medication. Of the 20 subjects who completed the study, 12 adverse events were recorded over the course of the study in 10 subjects. There were no serious adverse events (SAEs) or deaths in the study. All adverse events were mild in severity. Table 5 is a summary of adverse events reported by the subjects.

Table 5 Study P02040 Adverse Events		
Adverse Event	Treatment A	Treatment B
All Adverse Events	5	7
Headache	4	4
Dyspepsia	1	1
Loose stools	0	1
Skeletal pain	0	1

Source: N21313\N_000\2005-07-29, study-report-p02040.pdf, pg 45

Reviewer's Comment: The two slow metabolizers, subjects 9 and 19, each reported an adverse event: dyspepsia and headache, respectively.

Clinical Laboratories

Laboratory studies were performed at screening at the conclusion of the study. The laboratories were reviewed and there were no clinically significant consistent findings.

Vital Signs

Vital signs were measured at screening as well as pre and post dosing during each treatment period. The vital sign data was reviewed and there were no clinically significant change findings noted.

10.1.1.3 Discussion and Conclusions

The data from Study P02040 demonstrate that the key pharmacokinetic parameters for the phase 3 formulation (treatment A) and the to-be-marketed formulation (treatment B) of 2.5mg desloratadine/120mg extended release pseudoephedrine were bioequivalent under fasting conditions in healthy subjects. The safety data from this clinical pharmacology study do not suggest a safety signal.

10.1.2 Study P02041

Title: The multiple-dose and steady-state pharmacokinetics of DL/PSE -12

10.1.2.1 Protocol

Study P02041 was an open-label, multiple-dose, 14 day study in 18 non-smoking male and female healthy subjects, 18-45 years of age. Females of childbearing potential were required to practice barrier contraception for the duration of the study. Subjects must be free of significant disease and have normal physical exam, ECG, and laboratories. Pertinent exclusion criteria included clinically significant infectious disease within 4 weeks prior to treatment, blood pressure > 140/90 mmHg, drug, tobacco or alcohol use, Hepatitis B or C positive, HIV positive, recent use of medications (14 days), or recent use of alcohol (72 hours), pregnant or nursing women [N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 67-68].

Reviewer's Comment: The purpose of Study P02041 is to evaluate the steady state pharmacokinetic profile of DL, 3-OH DL, and pseudoephedrine following twice daily administration of DL/PSE-12 for 14 days.

Informed consent was obtained from all subjects prior to initiation of study procedures. Screening procedures were performed within 3 weeks prior to administration of study medication. Screening procedures included: history and physical exam, ECG, chemistry, hematology, HIV screening, hepatitis screening, urinalysis, serum pregnancy screen, and urine drug screen [N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 60].

Eligible subjects were admitted to the study center approximately 12 hours prior to dosing with study medication. A serum pregnancy screen and laboratories were collected and eligibility reconfirmed. On each study day after an overnight fast (~10 hours), subjects received 2.5mg desloratadine/120mg extended release pseudoephedrine at 8AM. The second dose was administered at 8PM. Study medication was administered twice daily (8AM and 8PM) for 14 consecutive days with 240mL of room temperature water. After dosing, subjects were to remain ambulatory for 4 hours post-dose. No food was allowed for four hours. Meals were standardized and controlled. Drinking water was permitted during the fasting period except for one hour pre and post-dose [N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 70-71].

Blood samples for pharmacokinetic measurements were collected before dosing (0 hour, Day 1, 10, 11, 12, 13, and 14) and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 (pre PM dose), 12.5, 13, 13.5, 14, 16, 18, 20, 22, and 24 hours post the morning dose. Subjects were confined to the study site until the Day 15 post dose sample was collected. Safety monitoring included vital signs, laboratories (chemistry, hematology, urinalysis, and pregnancy), and adverse events. Subjects could have withdrawn from the study for any reason [N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 77].

No parameters of clinical efficacy were evaluated in this study. The following pharmacokinetic parameters were determined for desloratadine, 3-OH desloratadine, and pseudoephedrine from the plasma concentration data:

- The maximum observed concentration (C_{max})
- The minimum observed concentration (C_{min})
- The time of observed C_{max} (T_{max})
- The terminal phase half life ($T_{1/2}$)
- The area under the concentration-time curve from time zero to the last sample with measurable concentration (AUC_{tf})
- The area under the concentration-time curve from time zero to infinity (AUC_i).

10.1.2.2 Results

Study P02041 commenced on November 27, 2001, and was completed on December 18, 2001.

10.1.2.2.1 Subject Disposition and Demographics

All 18 subjects who enrolled completed all 14 days of treatment. The mean age of the subjects was 36 years with an age range of 22 to 45 years. There were 9 males (50%) and 9 female (50%). The majority of the subjects were Caucasian (56%), while the remainder of the subjects were Black (39%) and American Indian (6%) [N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 45].

All subjects received 2.5mg desloratadine/120mg extended release pseudoephedrine, batch number 77660-111 [N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 19].

10.1.2.2.2 Pharmacokinetic Endpoint Outcomes

The data from Study P02041 demonstrate that the mean PK parameters for DL, 3-OH DL, and PSE following morning and evening administration were similar. Table 4 is a summary of the key pharmacokinetic parameters from Study P02041.

Table 6 Study P02041 Summary of Key Pharmacokinetic Parameters (N=18)		
Mean Desloratadine PK Parameters		
Parameter	Period	Mean (%CV)
AUC (ng*h/mL)	0-12 hr	16.4 (28)
	12-24 hr	14.9 (25)
C _{avg} (ng/mL)	0-12 hr	1.37 (28)
	12-24 hr	1.24 (25)
C _{max} (ng/mL)	0-12 hr	1.71 (23)
	12-24 hr	1.50 (23)
Mean 3-OH Desloratadine PK Parameters		
AUC (ng*h/mL)	0-12 hr	10.2 (36)
	12-24 hr	9.69 (38)
C _{avg} (ng/mL)	0-12 hr	0.854 (36)
	12-24 hr	0.807 (38)
C _{max} (ng/mL)	0-12 hr	1.00 (33)
	12-24 hr	0.924 (36)
Mean Pseudoephedrine PK Parameters		
AUC (ng*h/mL)	0-12 hr	4658 (33)
	12-24 hr	4332 (34)
C _{avg} (ng/mL)	0-12 hr	388 (33)
	12-24 hr	361 (34)
C _{max} (ng/mL)	0-12 hr	459 (29)
	12-24 hr	447 (33)
Source: N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 31, 34, 36		

The mean C_{min} for DL and 3-OH DL for Day 10 through Day 14 were statistically significantly different. The mean C_{min} did not continue to increase from Day 10 to Day 14. The mean C_{min} for Day 14 tended to be less than for Day 10. The mean C_{min} for PSE was not statistically significantly different for Day 10 through Day 14. For DL, 3-OH DL, and PSE, the 95%

confidence interval of the ratios of the Cmin fell within 80 to 125%. This suggests that steady state was achieved by Day 10 [N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 29-41].

10.1.2.2.3 Safety Outcomes

Adverse Events

The adverse event data does not suggest a new safety signal. All 18 subjects received 28 doses of study medication. Of the 18 subjects who completed the study, 11 subjects reported adverse events. There were no serious adverse events (SAEs) or deaths in the study. All adverse events were mild in severity except nervousness in one subject, which was considered moderate in severity. Table 7 is a summary of adverse events reported by the subjects.

Table 7 Study P02041 Number of Subjects with Adverse Events	
Adverse Event	Number (%) of subjects
All Adverse Events	11 (61)
Headache	10 (56)
Upper Respiratory Tract Infection	1 (6)
Nervousness	1 (6)
Epistaxis	1 (6)

Source: N21313\N_000\2005-07-29, study-report-p02041.pdf, pg 41

Clinical Laboratories and Vital Signs

Laboratory studies and physical examinations were performed at screening at the conclusion of the study. Vital signs were measured at screening, Day 1, Day 7, and Day 14. According to the Applicant, there were no clinically significant, consistent changes in laboratories, vital signs, or physical examinations.

10.1.2.3 Discussion and Conclusions

The key pharmacokinetic parameters from Study P02041 demonstrate that following 14 days oral administration, steady state conditions were attained by Day 10 for DL, 3-OH DL, and for PSE. In addition, there was no significant difference in PK parameters for DL, 3-OH DL, and PSE over the AM and PM dosing interval. The safety data from this clinical pharmacology study do not suggest a safety signal.

10.1.3 Study P02042

Title: The influence of food on the oral bioavailability of DL/PSE -12 administered to healthy subjects: a two way crossover study

10.1.3.1 Protocol

Study P02042 was a randomized, single-dose, two-way crossover study under fasting and fed conditions in 20 non-smoking male and female healthy subjects, 18-45 years of age. Females of childbearing potential were required to practice barrier contraception for the duration of the study. Pertinent exclusion criteria included clinically significant infectious disease within 4 weeks prior to treatment, blood pressure > 140/90 mmHg, drug, tobacco or alcohol use, Hepatitis B or C positive, HIV positive, recent use of medications (14 days), or recent use of alcohol (72 hours), pregnant or nursing women [N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 65-68].

Reviewer's Comment: The purpose of Study P02042 is to evaluate the influence of food on the bioavailability of DL and PSE from DL/PSE-12.

Informed consent was obtained from all subjects prior to initiation of study procedures. Screening procedures were performed within 3 weeks prior to administration of study medication. Screening procedures included: history and physical exam, ECG, chemistry, hematology, HIV screening, hepatitis screening, urinalysis, serum pregnancy screen, and urine drug screen [N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 59].

Eligible subjects were admitted to the study center approximately 12 hours prior to dosing with study medication. A serum pregnancy screen was collected and eligibility was reconfirmed. On study day 1 after an overnight fast (~10 hours), subjects were randomized to receive one of the following treatments twice in four separate periods:

- Treatment A – 2.5mg desloratadine/120mg extended release pseudoephedrine following a 10 hour fast, batch no. 77660-111)
- Treatment B - 2.5mg desloratadine/120mg extended release pseudoephedrine following a standardized high-fat, high caloric breakfast, batch no. 77660-111

Subjects randomized to Treatment B received the standardized meal and were administered study medication approximately 20 minutes after receiving the meal. Study medication was administered with 240mL of room temperature water. After dosing, subjects were to remain in an upright position for 4 hours. No food was allowed for four hours. Drinking water was permitted during the fasting period except for one hour pre and post-dose [N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 70].

Blood samples for pharmacokinetic measurements were collected before dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, and 120 hours post-dose. Subjects were confined to the study site until the 120 hours (Day 6) post dose sample was collected. Safety monitoring included vital signs, laboratories (chemistry, hematology, urinalysis, and pregnancy), and adverse events. Subjects could have been withdrawn for any reason. Following a 10 day washout period, subjects returned to the study center for the next treatment period. [N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 76].

No parameters of clinical efficacy were evaluated in this study. The following pharmacokinetic parameters were determined for desloratadine, 3-OH desloratadine, and pseudoephedrine from the plasma concentration data:

- The maximum observed concentration (C_{max})
- The time of observed C_{max} (T_{max})
- The terminal phase half life ($T_{1/2}$)
- The area under the concentration-time curve from time zero to the last sample with measurable concentration (AUC_{tf})
- The area under the concentration-time curve from time zero to infinity (AUC_{∞}).

The pharmacokinetic parameters were analyzed using a crossover analysis of variance model. Bioequivalence was assessed by the 90% confidence intervals for the difference between the two treatment means for the log-transformed AUC and C_{max} [N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 73, 82].

Reviewer's Comment: To establish bioequivalence under fasting conditions, the 90% confidence interval for the ratio of the geometric means between the products should fall within the interval 90-125% for log-transformed $AUC_{0-\infty}$, AUC_{0-t} , and C_{max} .

10.1.3.2 Results

Study P02042 commenced on October 1, 2001, and was completed on December 4, 2001.

10.1.3.2.1 Subject Disposition and Demographics

Twenty subjects were enrolled in the study and 19 completed all treatments. One subject discontinued due to person reasons. The mean age of the subjects was 34.5 years with an age range of 18 to 44 years. There were 10 males (50%) and 10 females (50%). The majority of the subjects were Hispanic. Only one subject was Caucasian and 3 subjects were Black. One subject was lost to follow up after the first treatment period [N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 40].

10.1.3.2.2 Pharmacokinetic Endpoint Outcomes

The data from Study P02042 demonstrate that the key pharmacokinetic parameters for 2.5mg desloratadine/120mg extended release pseudoephedrine under fed and fasting conditions were similar. Table 8 is a summary of the key pharmacokinetic parameters from Study P02042. The data is presented for desloratadine, 3-OH desloratadine, and pseudoephedrine. The 90% confidence interval for the ratio of the means was determined. The 90% confidence intervals for the key pharmacokinetic parameters fell between 80 and 125%.

Table 8 Study P02042 Summary of Key Pharmacokinetic Parameters (N=20)				
Mean Desloratadine PK Parameters				
Parameter	TRT	Mean (%CV)	Ratio (Fed/Fasted)	90% CI
AUC _{0-t} (ng*h/mL)	Fasted	20.9 (48)	105	98-113
	Fed	22.1 (46)		
AUC ₁ (ng*h/mL)	Fasted	21.8 (49)	105	98-113
	Fed	23.0 (47)		
C _{max} (ng/mL)	Fasted	1.13 (43)	106	97-115
	Fed	1.18 (41)		
Mean 3-OH Desloratadine PK Parameters				
AUC _{0-t} (ng*h/mL)	Fasted	12.7 (32)	98.6	94-103
	Fed	12.6 (27)		
AUC ₁ (ng*h/mL)	Fasted	14.1 (31)	99.2	95-104
	Fed	14.1 (26)		
C _{max} (ng/mL)	Fasted	0.51 (36)	102	95-109
	Fed	0.52 (33)		
Mean Pseudoephedrine PK Parameters				
AUC _{0-t} (ng*h/mL)	Fasted	4274 (29)	87.1	84-91
	Fed	3724 (24)		
AUC ₁ (ng*h/mL)	Fasted	4369 (28)	88.2	85-92
	Fed	3840 (23)		
C _{max} (ng/mL)	Fasted	297 (26)	102	98-107
	Fed	305 (21)		
Source: N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 34				

10.1.3.2.3 Safety Outcomes

Adverse Events

The adverse event data does not suggest a new safety signal. Nineteen of the 20 subjects received two single doses of study medication. One subject (# 3) discontinued after Period 1 due to personal reasons and received only received one dose of study medication [N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 28].

Three subjects reported adverse events during the course of the study. There were no serious adverse events (SAEs) or deaths in the study. All adverse events were mild in severity. All adverse events were reported with Treatment B (fed). Adverse events reported were: fever, headache, gamma-GT increase, and SGPT increased. The subject with elevated liver enzymes was noted to have a GGT and SGPT/ALT of 254 U/L and 103 U/L upon return to the study center on Day -1 of Period 2. The subject was dosed with study medication on Day 1 and on Day 6 normal levels of SGPT/ALT were noted, however the GGT remained elevated at 130 U/L. the subject was discharged and instructed to return to the study center for repeated liver enzyme test, but was lost to follow-up [N21313\N_000\2005-07-29, study-report-p02042.pdf, pg 37-38].

Clinical Laboratories

Laboratory studies were performed at screening at the conclusion of the study. Other than the laboratory abnormalities noted in Subject number 13 as described above, there were no clinically significant consistent findings in laboratory parameters.

Vital Signs

Vital signs were measured at screening as well as pre and post dosing during each treatment period. There were no clinically significant consistent findings noted in vital signs.

10.1.1.3 Discussion and Conclusions

The data from Study P02042 demonstrate that the key pharmacokinetic parameters for 2.5mg desloratadine/120mg extended release pseudoephedrine in the fed and fasting state were bioequivalent in healthy subjects. Thus, there is no significant food effect and DL/PSE-12 may be administered without regard to meals. The safety data from this clinical pharmacology study do not suggest a safety signal.

10.1.4 Study P02043

Title: The bioavailability pseudoephedrine from controlled-release (12-hour) formulations: a 4 way crossover study

10.1.4.1 Protocol

Study P02043 was a randomized, single-dose, two-sequence, four-way crossover study under fasting conditions in 20 non-smoking male and female healthy subjects, 18-45 years of age. Females of childbearing potential were required to practice double barrier contraception for the duration of the study. Pertinent exclusion criteria included clinically significant infectious disease within 4 weeks prior to treatment, blood pressure > 140/90 mmHg, drug, tobacco or alcohol use, Hepatitis B or C positive, HIV positive, recent use of medications (14 days), or recent use of alcohol (72 hours), pregnant or nursing women [N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 62-63].

Reviewer's Comment: The purpose of Study P02043 is to evaluate the bioequivalence of the DL/PSE-12 and the once daily DL 5/PSE 120 formulation. Both products contain an extended release pseudoephedrine layer; however, the layer is slightly different and the dissolution profile of pseudoephedrine is different. To validate the different dissolution specifications, formulations with a faster and slower dissolution rate were utilized in this study.

Informed consent was obtained from all subjects prior to initiation of study procedures. Screening procedures were performed within 3 weeks prior to administration of study medication. Screening procedures included: history and physical exam, ECG, chemistry, hematology, HIV screening, hepatitis screening, urinalysis, serum pregnancy screen, and urine drug screen [N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 12, 24].

Eligible subjects were admitted to the study center approximately 12 hours prior to dosing with study medication. A serum pregnancy screen was collected and eligibility was reconfirmed. On study day 1 after an overnight fast (~10 hours), subjects were randomized to receive one of following in a specific order:

- Treatment A – 2.5mg desloratadine/120mg extended release pseudoephedrine, standard batch
- Treatment B - 5mg desloratadine/120mg extended release pseudoephedrine, standard batch
- Treatment C - 5mg desloratadine/120mg extended release pseudoephedrine, fast batch
- Treatment D – 2.5mg desloratadine/120mg extended release pseudoephedrine, slow batch

Study medication was administered at 8AM with 240mL of room temperature water. After dosing, subjects were to remain ambulatory for 4 hours. No food was allowed for four hours. Drinking water was permitted during the fasting period except for one hour pre and post-dose [N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 66].

Blood samples for pharmacokinetic measurements were collected before dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 36, and 48hours post-dose. Subjects were confined to the study site until the 48 hours post dose sample was collected. Safety monitoring included vital signs, laboratories (chemistry, hematology, urinalysis, and pregnancy), and adverse events. Follow-up laboratories were drawn at the end of the fourth period only. Subjects could have been withdrawn for any reason. Following at least a 7 day washout period, subjects returned to the study center for the next treatment period [N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 24, 64].

No parameters of clinical efficacy were evaluated in this study. The following pharmacokinetic parameters were determined for pseudoephedrine from the plasma concentration data:

- The maximum observed concentration (C_{max})
- The time of observed C_{max} (T_{max})
- The terminal phase half life ($T_{1/2}$)
- The area under the concentration-time curve from time zero to the last sample with measurable concentration (AUC_{tr})
- The area under the concentration-time curve from time zero to infinity (AUC_{∞}).

The pharmacokinetic parameters were analyzed using an ANOVA model. The statistical comparisons were between Treatment B, C, and D vs. Treatment A as well as between Treatment C and D vs. Treatment B [N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 27].

10.1.4.2 Results

Study P02043 commenced on November 7, 2002, and was completed on December 16, 2002.

10.1.4.2.1 Subject Disposition and Demographics

All 20 subjects who enrolled completed all treatments. The mean age of the subjects was 37 years with an age range of 27 to 44 years. There were 10 males (50%) and 10 females (50%). The majority of the subjects were black. Nineteen (95%) of the subjects were Hispanic [N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 30].

Reviewer's Comment: The under-representation of non-Hispanic subjects is less than ideal.

The details of the study medications are displayed in Table 9.

Treatment	Product	Sponsor	Batch No.	Expiration Date
A	2.5mg desloratadine/120mg extended release pseudoephedrine Standard batch	Schering Plough	77660-111	Manufactured on July 18, 2001
B	5 mg desloratadine/120mg extended release pseudoephedrine Standard batch	Schering Plough	77660-028	Manufactured on August 8, 2001
C	2.5mg desloratadine/120mg extended release pseudoephedrine Slow batch	Schering Plough	56517-16	Manufactured on July 18, 2001
D	5 mg desloratadine/120mg extended release pseudoephedrine Fast batch	Schering Plough	56517-010	Manufactured on August 15, 2001

Source: N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 20

10.1.4.2.2 Pharmacokinetic Endpoint Outcomes

The data from Study P02043 demonstrate that with respect to the pseudoephedrine component, the DL(2.5mg)/PSE(120mg)-standard was bioequivalent to the DL(5mg)/PSE(120mg)-standard and DL(2.5mg)/PSE(120mg)-slow; however, the DL(2.5mg)/PSE(120mg)-standard was not bioequivalent to the DL(5mg)/PSE(120mg)-fast. Both the DL (2.5mg)/PSE(120mg)-slow and the DL(5mg)/PSE(120mg)-fast were bioequivalent to the DL(5mg)/PSE(120mg)-standard. According to the FDA, bioequivalence is established when the calculated CI falls between 80-125% for the ratio of the product averages (Guidance to Industry – Statistical Approaches to Establishing Bioequivalence). Table 10 is a summary of the key pharmacokinetic parameters from Study P02043 [N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 33-34].

Table 10 Study P02043 Summary of Key Pharmacokinetic Parameters			
Mean Pseudoephedrine PK Parameters			
Parameter	TRT	Mean (%CV)	
AUC _{tf} (ng*h/mL)	A - DL(2.5mg)/PSE(120mg), standard	3769 (22)	
	B - DL(5mg)/PSE(120mg), standard	3958 (26)	
	C - DL(5mg)/PSE(120mg), fast	3802 (25)	
	D - DL(2.5mg)/PSE(120mg), slow	3608 (27)	
AUC _i (ng*h/mL)	A - DL(2.5mg)/PSE(120mg), standard	3848 (22)	
	B - DL(5mg)/PSE(120mg), standard	4054 (25)	
	C - DL(5mg)/PSE(120mg), fast	3898 (24)	
	D - DL(2.5mg)/PSE(120mg), slow	3684 (26)	
C _{max} (ng/mL)	A - DL(2.5mg)/PSE(120mg), standard	283 (23)	
	B - DL(5mg)/PSE(120mg), standard	317 (21)	
	C - DL(5mg)/PSE(120mg), fast	358 (23)	
	D - DL(2.5mg)/PSE(120mg), slow	269 (27)	
Relative Bioavailability			
Parameter	Pair	Ratio	90% CI
AUC _{tf} (ng*h/mL)	B/A	104.2	99-110
	D/A	94.9	90-100
	C/A	100.3	95-106
	D/B	91.1	86-96
	C/B	96.3	91-102
AUC _i (ng*h/mL)	B/A	104.7	99-110
	D/A	95.1	90-100
	C/A	100.9	96-106
	D/B	90.8	86-96
	C/B	96.3	91-102
C _{max} (ng/mL)	B/A	111.8	107-117
	D/A	93.9	90-98
	C/A	126.1	120-132
	D/B	84.0	80-88
	C/B	112.8	108-118
Source: N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 33-34			

The Applicant also looked at the effect of gender and did not find a difference in the relative bioavailability between male and female subjects.

10.1.4.2.3 Safety Outcomes

The adverse event data does not suggest a new safety signal. All 20 subjects received 4 single doses of study medication. Of the 20 subjects who completed the study, 2 adverse events were reported: nasal congestion and myalgia. There were no serious adverse events (SAEs) or deaths in the study. All adverse events were mild in severity.

Laboratory studies were performed at screening at the conclusion of the study. The results suggest that there were no clinically significant consistent findings. Vital signs were measured at

screening as well as 48 hours after each treatment. The results suggest that there were no clinically significant findings [N21313\N_000\2005-07-29, study-report-p02043.pdf, pg 35-36].

10.1.4.3 Discussion and Conclusions

The objective of Study P02043 was to validate a widened dissolution specification for pseudoephedrine in DL 5mg/PSE 120mg and DL 2.5mg/PSE 120mg standard formulations by assessing the effect of formulations that have different in vitro dissolution on the exposure of pseudoephedrine. Four different formulations were compared. The fast and slow formulations were compared to the two standard formulations and the two standard formulations were compared to each other.

The data from Study P02043 demonstrate that with respect to the pseudoephedrine component:

- DL(2.5mg)/PSE(120mg)-standard was bioequivalent to the DL(5mg)/PSE(120mg)-standard
- DL(2.5mg)/PSE(120mg)-standard was bioequivalent to the DL(2.5mg)/PSE(120mg)-slow
- DL(2.5mg)/PSE(120mg)-standard was not bioequivalent to the DL(5mg)/PSE(120mg)-fast
- Both the DL (2.5mg)/PSE(120mg)-slow and the DL(5mg)/PSE(120mg)-fast were bioequivalent to the DL(5mg)/PSE(120mg)-standard

Reviewer's Comment: The interpretation of the results of this study with respect to the dissolution specifications is deferred to the clinical pharmacology reviewer.

The safety data from this pharmacokinetic study did not suggest a safety signal.

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