CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-605

MEDICAL REVIEW

DIVISION DIRECTOR'S MEMORANDUM

Date: March 3, 2005

To: NDA 21-605

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Clarinex-D 24 Hour (desloratadine 5 mg and pseudoephedrine sulfate 240 mg) Extended Release Tablets

Applicant: Schering Corporation

Administrative and Introduction

Schering Corporation submitted NDA 21-605 for Clarinex-D 24 Hour (desloratadine 5 mg and pseudoephedrine sulfate 240 mg) Extended Release Tablets on May 3, 2004. The PDUFA due date on this application is March 3, 2005. Clarinex-D 24 Hour Extended Release Tablets is proposed for prescription use in patients 12 years of age and older for relief from symptoms of seasonal allergic rhinitis. The product is particularly intended to be used when both the antihistaminic properties of desloratadine and the nasal decongestant properties of pseudoephedrine are desired. The proposed dose is one tablet once a day. Schering has three products containing desloratadine approved for marketing in the United States. These are Clarinex Tablets 5 mg under three NDAs for three different indications (NDA 21-165, NDA 21-297, NDA 21-363), Clarinex RediTabs (NDA 21-313), and Clarinex Syrup under two NDAs covering different age groups (NDA 21-300, NDA 21-563). The regulatory pathway for this application is 505(b)(2). Schering originally developed the desloratadine molecule and has rights to all relevant data on desloratadine, the data related to the pseudoephedrine formulation used in this product are in the public domain, and Schering has submitted appropriate patent information and certification that there are no relevant patents. The Office of New Drugs in consultation with the Office of Regulatory Policy and Office of Chief Council has confirmed that 505(b)(2) regulatory pathway is appropriate for this application.

Since desloratadine and pseudoephedrine are both marketed products, Schering's original plan was to rely on bioequivalence studies to support approval of Clarinex-D 24 Hour Extended Release Tablets. This is the usual pathway for development of such a product. The bioequivalence program showed that Clarinex-D 24 Hour Extended Release Tablets was not bioequivalent to its components; specifically exposure to desloratadine was lower from the combination product compared to single ingredient desloratadine 5 mg tablet. Schering therefore conducted clinical studies to show efficacy of Clarinex-D 24 Hour Extended Release Tablets. The efficacy studies and other data support approval of this product.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation
Clarinex-D 24 Hour Extended Release Tablets contains an immediate release outer coat of desloratadine 5 mg and an inner core of extended-release pseudoephedrine 240 mg, and a number of commercially used excipients. The desloratadine drug substance used in this product is manufactured by Schering in Avondale, Ireland, and the pseudoephedrine drug substance used in this product is manufactured by [redacted]. The Schering facility in Kenilworth, New Jersey, manufactures the finished dosage form and conducts release and stability testing. All information related to manufacturing and controls of this product and the relevant Drug Master Files (DMFs) are adequate. All manufacturing and testing sites related to this application have acceptable evaluation status. The CMC team recommends approval of this application and I concur with the recommendation.

There are several issues related to the manufacturing and stability of Clarinex-D 24 Hour Extended Release Tablets that are worth noting. The reader is referred to Dr. Peri's review for details.

[redacted] i. There are virtually no in-process controls for the coating process of desloratadine. The final product has large content variability, which is acceptable because it satisfies the USP Content Uniformity acceptance criteria. The USP criteria allows for 85% to 115% variability. [redacted] It is worth noting that the manufacturing and stability issues are related to the desloratadine component, and the desloratadine component of this product is not bioequivalent to the single ingredient desloratadine 5 mg tablet.

The stability data submitted for Clarinex-D 24 Hour Extended Release Tablets support storage at 25°C, however, short excursions between 15°C and 30°C may be permitted. Based on the date, the CMC team has determined that the shelf life of the tablets in bottles will be 24 months and the shelf life of the tablets in blisters will be 12 months.

Clinical Pharmacology and Biopharmaceutics
The applicant submitted results from five clinical pharmacology studies in support of the application. The five clinical pharmacology studies enrolled a total of 154 healthy male and female volunteers between the ages of 18 and 44 years. Of the five clinical pharmacology studies three were conducted with the to-be-marketed formulation and were considered relevant to this NDA. These three studies included a study designed to demonstrate bioequivalence of Clarinex-D 24 Hour Extended Release Tablets to the reference products after a single dose (Study P 00439), a study to assess the effect of high fat high calorie diet on the absorption of desloratadine and pseudoephedrine from Clarinex-D 24 Hour Extended Release Tablets (Study PO 0441), and a study to determine the pharmacokinetic profile of desloratadine and pseudoephedrine following daily administration of Clarinex-D 24 Hour Extended Release Tablets for 14 days (Study PO 0884). The clinical pharmacology studies were reviewed in depth by the Office of Clinical Pharmacology and Biopharmaceutics (OCBP) Reviewer Dr. Al-Habet.

The Cmax and AUC data from the single dose bioequivalence study are shown in Table 1. The 90% CI for the ratio of AUC and Cmax for desloratadine and its major metabolite 3-OH desloratadine were outside the accepted 80% to 125% bioequivalence limit; specifically, the exposure to desloratadine and 3-OH desloratadine from Clarinex-D 24 Hour Extended Release Tablets were lower than that from the marketed Clarinex 5 mg Tablets. The applicant determined from other bioequivalence studies that a 6 mg quantity of desloratadine would be required in the Clarinex-D 24 Hour Extended Release Tablets formulation to give exposure comparable to that from desloratadine 5 mg tablet (data not shown in this document). The lower exposure of desloratadine from the Clarinex-D 24 Hour Extended Release Tablets raises efficacy concerns for the antihistaminic component of this product. To support the efficacy of the lower exposure to desloratadine from this product the applicant conducted two clinical studies. The applicant took this rather unusual approach because the formulation failed to meet the goal of achieving exposure that were bioequivalent to the reference, rather than to make a formulation that would be bioequivalent to its two components.

The food effect study (Study PO 0441) showed that a high fat high calorie diet did not have any effect on the bioavailability of the formulation components (Table 1). The multiple dose study (Study PO 0884) showed that steady state for desloratadine, 3-OH desloratadine, and pseudoephedrine was reached on about day 10.

Table 1. Ratio between test and reference products (test/reference) for geometric LS mean values of PK parameters of desloratadine, 3-OH desloratadine, and pseudoephedrine from various studies

		desloratadine		3-OH desloratadine		pseudoephedrine	
	PK Parameter	Point estimate	90% CI	Point estimate	90% CI	Point estimate	90% CI
Study P 00439 (Single dose) *							
	Cmax	80.2	75-86	80.3	75-86	93	89-97
	AUC inf	85.0	78-92	81.2	72-92	102	94-112
Study PO 0441 (Food effect) †							
	Cmax	104	96.0-113	106	99.0-114	108	104-113
	AUC inf	102	97.0-107	102	97.0-107	92.0	87.0-97.0

* Reference drugs: Marketed 5 mg Clarinex (desloratadine) Tablets and pseudoephedrine 240 mg core from Claritin-D 24 Hour Extended Release Tablets coated with placebo

† Single Clarinex-D 24 Hour Extended Release Tablets administered after overnight fast (reference) or 30 minute after high-fat breakfast (test)

The reference pseudoephedrine used in the pharmacokinetic studies was pseudoephedrine 240 mg core from Claritin-D 24 Hour Extended Release Tablets coated with placebo. This essentially makes the pseudoephedrine comparison as comparison to self, because the pseudoephedrine core of Clarinex-D 24 Hour Extended Release Tablets uses the pseudoephedrine 240 mg core from Claritin-D 24 Hour Extended Release Tablets. This is a problem because for the Claritin-D 24 Hour Extended Release Tablets, Schering was unable to establish bioequivalence for the pseudoephedrine component in a comparison to Afrinol, pseudoephedrine sulfate 120 mg repetab administered twice daily (NDA 20-470, BioPharm Review, March 9, 1995, and Division Director Memo, August 22, 1996).

To place the pseudoephedrine data from this application in some frame of reference, Drs. Al-Habet and Starke reviewed historical data from other NDAs and concluded that exposure to pseudoephedrine from this product is generally similar to exposure to pseudoephedrine from other antihistamine and pseudoephedrine combination products. Details can be found in Dr. Al-Habet's Clinical Pharmacology review addendum and in Dr. Starke's Medical Team Leader memorandum.

Clinical and Statistical

The applicant submitted results from two large clinical studies (Studies P 01875 and P 01884) to support the clinical efficacy and safety of Clarinex-D 24 Hour Extended Release Tablets. These studies were conducted to support efficacy of lower exposure of desloratadine from this product. These studies would not be required if Clarinex-D 24 Hour Extended Release Tablets were bioequivalent to its individual components, which would be the usual pathway of approval of such a combination product. These studies are reviewed in detail in the Medical Officer and Medical Team Leader reviews. Brief comments on the two studies are made in the following sections.

The two studies were essentially identical in design. The studies were double-blind, double-dummy, multi-center, parallel group in design conducted in the United States in patient 12 years of age and older with seasonal allergic rhinitis. The studies had a 7-day run-in period, followed by 15-day double-blind treatment period. The studies compared two formulations of Clarinex-D 24 Hour Extended Release Tables with desloratadine 5 mg tablet (DL), and pseudoephedrine 240 mg sustained release tablet (PSE). Efficacy was assessed by reflective and instantaneous patient scoring of four nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and four non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate) twice daily (AM and PM) on a four point scale (0=none, 1=mild, 2=moderate, and 3=severe). Safety variables included recording of adverse events, physical examination, laboratory tests, and ECG. The primary efficacy endpoint for the antihistamine component was the change from baseline of the mean AM + PM reflective total symptoms score (nasal + non-nasal) excluding nasal stuffiness/congestion averaged over the 15 days of treatment. The primary comparison for this endpoint was between Clarinex-D 24 versus pseudoephedrine. The primary efficacy endpoint for the decongestant component was the change from baseline of the mean AM + PM reflective nasal stuffiness/congestion score averaged over the 15 days of treatment. The primary comparison for this endpoint was between Clarinex-D 24 versus desloratadine. Each treatment arm of the two studies were required to have 350 evaluable patients to give a 90% power to detect a 1.2 point difference between treatment groups for the antihistamine component and a 0.16 point difference between treatment groups for the decongestant component at a two-tailed alpha-level of 0.025.

A total of 1495 patients were randomized to the four treatment arms in Study P 01875 of which 1391 patient (93%) completed the study, and a total of 1357 patients were randomized to the four treatment arms in Study P 01884 of which 1274 (94%) completed the study. Clarinex D-24 Hour Extended Release Tablets were well tolerated in the

studies. There were no new safety signals seen in the studies. Results of the primary and selected efficacy variables of the two studies are shown in Table 2 and Table 3. Of the two Clarinex-D 24 Hour formulations, data from the formulation that is proposed to be marketed is shown in the tables. In both studies Clarinex-D 24 Hour Extended Release Tablets showed consistent statistically significant numerical difference for the antihistamine component and decongestant component over the appropriate individual mono-components, which satisfies the 21 CFR 300.50 Combination Drug regulations. This finding along with the findings from the clinical pharmacology studies is adequate to support efficacy of this product. Furthermore, the known pharmacology of pseudoephedrine makes this a rationale combination. Pseudoephedrine is known to act directly on alpha-adrenergic receptors in the nasal mucosa to produce vasoconstriction and relieve nasal congestion. Since antihistamines generally lack this effect, antihistamine plus pseudoephedrine is accepted as a rational combination product.

It is worth noting that while Clarinex-D 24 Hour Extended Release Tablets in the two studies was statistically superior to pseudoephedrine for antihistamine effect and to desloratadine for the decongestant effect, the combination product was also statistically superior to loratadine for the antihistamine effect and to pseudoephedrine for the decongestant effect. This is not expected, but not surprising because patients are possibly not able to finely discriminate the various symptoms being scored.

Table 2. Efficacy Data from Study P 01875

Treatment Group	Baseline N[a]	Baseline LS Mean [b]	Change from Baseline LS Mean [b]	Change from Baseline %[c]	Pairwise Comparisons vs. DL D-24 Δ	Pairwise Comparisons vs. DL D-24 P-value
Primary Efficacy Analyses						
Total Symptom Score (Excluding Nasal Congestion), Mean AM/PM Reflective						
DL D-24	372	15.01	-6.09	-38.8		
DL	369	14.71	-5.10	-33.5	-0.99	0.001
PSE	377	15.08	-5.08	-32.4	-1.01	0.001
Nasal Stuffiness/Congestion, Mean AM/PM Reflective						
DL D-24	372	2.57	-0.90	-33.4		
DL	369	2.55	-0.74	-28.0	-0.16	0.001
PSE	377	2.56	-0.78	-28.6	-0.12	0.009
Selected Secondary Efficacy Analyses						
Total Nasal Symptom Score (Excluding Nasal Congestion), Mean AM/PM Reflective						
DL D-24	372	6.81	-2.69	-37.8		
DL	369	6.68	-2.24	-32.1	-0.45	0.001
PSE	372	6.83	-2.17	-30.1	-0.52	<0.001
Total Nasal Symptom Score (Including Nasal Congestion), Mean AM/PM Reflective						
DL D-24	372	9.39	-3.60	-36.6		
DL	369	9.23	-2.99	-31.1	-0.61	<0.001
PSE	372	9.39	-2.94	-29.8	-0.66	<0.001
Total Non-nasal Symptom Score, Mean AM/PM Reflective						
DL D-24	372	8.20	-3.40	-39.6		
DL	369	8.03	-2.85	-34.3	-0.55	0.003
PSE	372	8.24	-2.91	-34.1	-0.49	0.008
Total Symptom Score (Excluding Nasal Congestion), Mean AM Instantaneous						
DL D-24	372	14.65	-5.57	-36.6		
DL	367	14.61	-4.61	-30.2	-0.97	0.003

Treatment Group	Baseline N[a]	Baseline LS Mean[b]	Change from Baseline LS Mean[b]	Change from Baseline %[c]	Pairwise Comparisons vs. DL D-24 Δ	Pairwise Comparisons vs. DL D-24 P-value
PSE	371	14.79	-4.56	-29.2	-1.01	0.001
Nasal Stuffiness/Congestion, Mean AM Instantaneous						
DL D-24	372	2.55	-0.80	-30.0		
DL	367	2.57	-0.63	-22.6	-0.17	<0.001
PSE	371	2.58	-0.69	-25.0	-0.11	0.040

[a] Calculation of mean Baseline values included all patients with Baseline and Endpoint data; calculation of mean post Baseline values included all patients with both Baseline and post Baseline data at the specified time point(s).
[b] LS Means are obtained from the two-way ANOVA model with treatment and site effects
[c] Mean percent changes are raw means

Table 3. Efficacy Data from Study P 01884

Treatment Group	Baseline N[a]	Baseline LS Mean[b]	Change from Baseline LS Mean[b]	Change from Baseline %[c]	Pairwise Comparisons vs. DL D-24 Δ	Pairwise Comparisons vs. DL D-24 P-value
Primary Efficacy Analyses						
Total Symptom Score (Excluding Nasal Congestion), Mean AM/PM Reflective						
DL D-24	333	14.84	-5.71	-37.4		
DL	337	15.06	-4.78	-30.8	-0.93	0.003
PSE	337	15.03	-4.95	-32.0	-0.76	0.015
Nasal Stuffiness/Congestion, Mean AM/PM Reflective						
DL D-24	333	2.56	-0.85	-32.3		
DL	337	2.57	-0.65	-24.8	-0.20	<0.001
PSE	337	2.54	-0.70	-27.1	-0.15	0.002
Selected Secondary Efficacy Analyses						
Total Nasal Symptom Score (Excluding Nasal Congestion), Mean AM/PM Reflective						
DL D-24	333	6.73	-2.56	-36.8		
DL	337	6.79	-2.09	-30.0	-0.47	<0.001
PSE	337	6.81	-2.16	-30.9	-0.40	0.003
Total Nasal Symptom Score (Including Nasal Congestion), Mean AM/PM Reflective						
DL D-24	333	9.29	-3.41	-35.7		
DL	337	9.36	-2.74	-28.6	-0.67	<0.001
PSE	337	9.35	-2.87	-30.0	-0.54	0.002
Total Non-nasal Symptom Score, Mean AM/PM Reflective						
DL D-24	333	8.11	-3.15	-37.9		
DL	337	8.27	-2.69	-31.3	-0.46	0.015
PSE	337	8.23	-2.79	-32.8	-0.36	0.053
Total Symptom Score (Excluding Nasal Congestion), Mean AM Instantaneous						
DL D-24	333	14.76	-5.34	-34.4		
DL	337	14.93	-4.48	-27.8	-0.86	0.008
PSE	335	15.14	-4.64	-29.1	-0.70	0.029
Nasal Stuffiness/Congestion, Mean AM Instantaneous						
DL D-24	333	2.56	-0.75	-27.6		
DL	337	2.57	-0.59	-21.1	-0.16	0.001
PSE	335	2.58	-0.61	-22.3	-0.14	0.008

[a] Calculation of mean Baseline values included all patients with Baseline and Endpoint data; calculation of mean post Baseline values included all patients with both Baseline and post Baseline data at the specified time point(s).
[b] LS Means are obtained from the two-way ANOVA model with treatment and site effects
[c] Mean percent changes are raw means

Pharmacology and Toxicology
The applicant did not conduct any new preclinical studies specifically for this application because the active components of Clarinex-D 24 Hour Extended Release Tablets were previously studied by the applicant or others. Within the review period of the application, the applicant submitted results of a 2-year carcinogenicity study (Study SN 97255). The study was conducted by the applicant as a phase-4 commitment for desloratadine NDA (NDA 21-165). The carcinogenicity study was reviewed by Pharmacology and Toxicology reviewer Dr. Pei and by Statistical reviewer Dr. Guo. The review teams concluded that the study did not show any carcinogenicity potential for desloratadine.

Data Quality, Integrity, and Financial Disclosure
No DSI audit for the clinical study sites were conducted because both components of the combination product are approved and there is a significant amount of clinical experience with both. Also, during review of the submission, no irregularities were found that would raise concerns regarding data integrity. DSI audit for the clinical pharmacology study sites was not conducted because the clinical pharmacology program failed to show bioequivalence and thus was not crucial to support approval of the drug product. All studies were conducted in accordance with accepted ethical standards. The applicant provided adequate disclosure of financial interest of the clinical investigators. One investigator had a significant equity interest in Schering. That interest contributed a total of 35 patients to the whole clinical program. Review of the efficacy and safety data of the particular investigator's site did not show any suspicious trends.

Pediatric Considerations
The applicant is proposing an indication down to the age of 12 years and is not proposing to seek approval in patients below 12 years of age. This is acceptable because the fixed dose combination at the proposed dosage would not be suitable for children younger than 12 years of age.

Product Name
The trade name Clarinex is approved and used by Schering for the product line containing desloratadine. The suffix "D 24 Hour" distinguishes this product as containing a decongestant and that the dosing frequency is 24 hours.

Labeling
Schering submitted a product label that generally conforms to the currently marketed Clarinex label and other antihistamine plus decongestant combination products. Relevant information for the two active components is included in the appropriate section of the label. The label has been reviewed by various disciplines. The Division and Schering have agreed on a final labeling text. There are two highlights in the label that is worth noting. First, the labeled indication of this product is specific to seasonal allergic rhinitis.

This is different than the single ingredient desloratadine products, which have both the seasonal and perennial allergic rhinitis indications.

[redacted]

Second, the label will have language to state that Clarinex-D 24 Hour Extended Release Tablets gives less exposure to desloratadine as compared to from single ingredient desloratadine 5 mg tablet, and that clinical studies were necessary to support efficacy of this product. This language will be included in the Pharmacokinetics sub-section of the Clinical Pharmacology section of the label. This will place the description of the clinical studies in the Clinical Trials section of the label in the correct context.

Action

The clinical efficacy and safety data and the supporting pharmacology data are sufficient to support approval of Clarinex-D 24 Hour Extended Release Tablets for use in patients ages 12 years and older for control of symptoms of seasonal allergic rhinitis. The CMC data also support approval of the product. Therefore, the action on this application will be APPROVAL.

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

/s/

Badrul Chowdhury
3/3/05 09:40:57 AM
MEDICAL OFFICER

CLINICAL TEAM LEADER MEMORANDUM

Date:	March 2, 2005
To:	NDA 21-605
From:	Peter Starke, MD Medical Team Leader Division of Pulmonary and Allergy Drug Products, HFD-570
Product:	Clarinex–D® 24 HOUR Extended Release Tablet
Applicant:	Schering Corporation
Re:	First cycle clinical review for seasonal allergic rhinitis indication PDUFA date March 3, 2005

Administrative and Introduction

This is a clinical team leader memorandum for NDA 21-605 from Schering Corporation is for a fixed-combination antihistamine/decongestant tablet product containing desloratadine 5 mg in an immediate-release coating and pseudoephedrine sulfate 240 mg in a sustained-release matrix core. The applicant refers to this product as DL-D-24. The proposed a trade name is Clarinex-D® 24 HOUR. The product is currently intended for to be marketed for prescription use only.

Clarinex-D® 24 HOUR tablets are proposed to be administered once daily to adults and children 12 years of age and older. The proposed indication is for the "relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal congestion, in patients 12 years of age and older. CLARINEX-D 24 HOUR Extended Release Tablets can be administered when the antihistaminic properties of desloratadine and the nasal decongestant activity of pseudoephedrine are desired."

Note: The original proposed indication included both seasonal allergic rhinitis (SAR) and

[redacted]

The Applicant initially planned a submission that would rely on data from previously approved desloratadine 5 mg tablets (NDA 21-165 and NDA 21-312), monographed pseudoephedrine, and five clinical pharmacology bioavailability and bioequivalence studies. However, Study P00439, a pilot open-label, single-dose, randomized, 3-way crossover study failed to demonstrate bioequivalence of desloratadine in the to-be-marketed clinical formulation of Clarinex-D® 24 Hour to the approved individual component, Clarinex 5 mg. A separate study demonstrated that it would take a formulation of this drug product containing 6 mg of desloratadine and 240 mg of pseudoephedrine to produce systemic exposures of desloratadine comparable to the approved Clarinex 5 mg drug product. Because of the lack of bioequivalence, a clinical development program was required and was undertaken.

During this review, a consultation from the Division of Scientific Investigations (DSI) was not requested. Since both components in the combination product are approved and there is a significant amount of clinical experience with each, a DSI audit was not requested for the combination drug product. While there were several irregular findings noted during the course of the reviews, none of the findings were judged to be significant enough to impact upon the regulatory decision for the NDA.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The proposed product provides 5 mg of immediate-release desloratadine applied as an outer coating to an extended-release 240 mg pseudoephedrine sulfate matrix core. Of note, the PSE extended release tablet cores used in Clarinex-D® 24 Hour Tablets are identical in composition and shape to the tablet cores used in the current commercial Claritin-D® 24 Hour tablets (original Rx NDA 20-470, now OTC). The tablets are light blue, oval-shaped, with a trade name branded in black ink on one side.

There are a number of CMC issues for this application, which are discussed in depth in Dr. Prasad's review. The two primary issues of concern are the lack of in-process controls for the application of the desloratadine 5 mg layer and poor stability of the drug product when exposed to heat.

. Since these temperatures are common in everyday life, the result will likely be labeling limitations and requirements for storage of the drug product.

Pharmacology and Toxicology

The application contains no new nonclinical information for either of the active ingredients, desloratadine or pseudoephedrine. The applicant refers to NDA 21-165 (desloratadine tablets) for the nonclinical developmental program of desloratadine. Under NDA 21-165 and as a phase-4 commitment, the sponsor completed a 2-year carcinogenicity study of desloratadine in mice (Study #97255) that was submitted on November 13, 2003. The review team completed review of this study during this review cycle. Please see Dr. Pei's review for further details. The sponsor's currently proposed labeling for the Clarinex D-24 Hour did not mention the study and the sponsor was advised in the 75-day filing letter to update the labeling to include the study results.

Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology program for DL D-24 (SCH 483) comprised five open-label studies in 154 healthy volunteers, as summarized in Table 1. Desloratadine is a long-acting tricyclic histamine antagonist with selective H_1-receptor histamine antagonist activity. It is the major active metabolite of loratadine. Desloratadine appears to exhibit less first-pass metabolism and a longer plasma elimination half-life than loratadine. Pseudoephedrine is a decongestant recognized and monographed as GRAS and GRAE.

A clinical development program was undertaken because bioequivalence study P00439 failed to demonstrate bioequivalence between the desloratadine component in the to-be-marketed DL D-24 (DL 5 mg / PSE 240 mg) formulation and the individual component

desloratadine 5 mg (marketed Clarinex 5 mg). For evaluation of bioequivalence of the PSE component, in study P00439 the sponsor compared DL D-24 to PSE via the same core PSE as it planned for marketing. In other words, in this study the sponsor compared the PSE component to itself. A second study (P01813) demonstrated that a DL 6 mg / PSE 240 mg formulation was in fact bioequivalent to the individual components using DL 5 mg plus extended-release PSE 240 mg. Pertinent bioequivalence studies are briefly discussed below. Please see Dr Al Habet's Clinical Pharmacology and Biopharmaceutics Review for further details of these studies.

Table 1. Summary of Clinical Pharmacokinetic and Bioavailability Studies

Study	Study Type	Treatment Groups	Batch Number*	Ages	N (M,F)	Race
Studies using DL 5 mg / PSE 240 mg						
P00439	OL, SD, 3-way crossover BE of DL and PSE	DL D-24 (5 mg/PSE 240 mg) DL 5 mg PSE 240 mg (Claritin® D24 extended release cores with placebo Claritin D24 coating)	**75882-056** 38833-142 75059-114	31-45	36 M	7 C 11 B
P00441	OL, SD, 2-way crossover BA, Food Effect	DL D-24 (fed state) DL D-24 (fasted state)	**75882-056** **75882-056**	19-44	27 M 11 F	24 C 11 B 3 H
P00884	14 day, OL, MD, steady-state PK	DL D-24 (5 mg/PSE 240 mg)	**75882-056**	21-45	15 M 3 F	14 C 4 B
Studies using DL 6 mg / PSE 240 mg						
P01813	OL, 3-way crossover single dose BE	DL 6 mg/PSE 240 mg DL D-24 (5 mg/PSE 240 mg) DL 5 mg + PSE 240 mg (Claritin® D24 extended release cores with placebo Claritin D24 coating)	76466-068 **75882-056** 38833-142 + 75882-061	19-45	21 M 21 F	37 C 4 B 1 H
P01981	OL, 4-way crossover single dose BA to evaluate PSE core with altered *in vitro* dissolution rates	DL 6 mg/PSE 240 mg DL 6 mg/PSE 240 mg DL 5 mg/PSE 240 mg DL 5 mg/PSE 240 mg	54039-143 54039-144 54039-138 **75882-056**	18-45	13 M 7F	5 C 1 B 14 H

* Batch number **75882-056** is the proposed commercial formulation

Sources: Section 3H, page7, summary.pdf; Section 4C, page 20, invest.pdf

Study P00439

Study P00439 was an open open-label, single-dose, randomized, 3-way crossover bioequivalence study comparing the to-be marketed DL D-24 (DL 5 mg / PSE 240 mg) formulation, DL 5 mg (Clarinex) tablets, and the extended release PSE 240 mg cores coated with a Claritin placebo. The study was performed under fasted conditions in 36 healthy men (12 Caucasians and 24 Blacks) between the ages of 21 and 45 years of age (mean = 39.3 years).

In this study, the desloratadine in the DL D-24 was not bioequivalent to desloratadine from Clarinex 5 mg: the 90% confidence intervals (CI) for DL and 3-OH did not meet the

80%-125% bioequivalence guidelines for both Cmax and AUC(tf) values (Table 3). However, the CI (82%-92%) of 3-OH DL for AUC(l) did meet the 80%-125% bioequivalence guidelines. Following the administration of the DL D-24 tablet, the DL and 3-OH DL C_{max} and AUC values were approximately 15%-20% less than those observed following administration of the DL 5 mg tablet. While the PSE component was bioequivalent, the sponsor did not use an independent reference product, instead choosing as a reference a Claritin-D24 PSE core coated with a Claritin placebo. Since this same PSE core is used in both the Claritin-D24 and Clarinex-D24 products, the PSE comparison was essentially a comparison to self and not to a different reference product.

Despite the lack of bioequivalence of the desloratadine component, the Applicant carried forward the DL-D-24 formulation into two Phase 3 clinical studies, P01875 and P01884, to support the efficacy of DL D-24 as the to-be-marketed formulation.

Of note, in this study two patients were noted to have measurable concentrations (14 ng/mL to 63 ng/mL) of PSE following the administration of DL. Since the Division felt that the data from these two patients would not affect the regulatory decision for this drug product, a DSI audit was not pursued. However, in retrospect this is of interest because of the efficacy findings in the two clinical studies. Please see the clinical section for further discussion.

Table 2. Summary of pharmacokinetics of desloratadine and 3-OH desloratadine in Clarinex-D 24 HOUR compared to Clarinex

Desloratadine PK	DL			3-OH DL		
	Cmax ng/mL	Tmax hr	AUC ng•hr/mL	Cmax ng/mL	Tmax hr	AUC ng•hr/mL
Clarinex-D 24 (DL D24 5/240 mg)						
Study P00439 (single-dose)	1.79	6.78	54.8	0.695	6.09	24.4
Study P00884 (multiple-dose)	2.44	3.68	34.8	1.56	4.65	25.7
Clarinex (DL 5mg)						
Study P00439 (single-dose)	2.23	5.10	63.3	0.832	4.96	28.0

Sources: Hpbio, 6B: Study P00439, p2; Study P00884, p2;

Pharmacokinetic data for pseudoephedrine are summarized in Table 3. Study P00439 used as the reference comparator the same PSE slow release core as used in the to-be-marketed Clarinex-D24 drug product, thus making what is in effect a comparison to self. Therefore, historical data from other NDAs were explored to supplement the data in this NDA, and provide some frame of reference for the Cmax and AUC values of PSE from the Clarinex-D24 Hour drug product. After single-doses, the Claritin-D24 and Clarinex-D24 products (which use the same core PSE) tend to have similar systemic exposure (AUC), about double that seen with Claritin-D12. Single-dose PSE exposure from Allegra-D24, which uses a different release technology, tends to be a little higher than from the Claritin-D 24and Clarinex-D 24 products. With multiple-dose exposure, there are no differences of note between any of drug products.

Of interest, clinical studies were performed for the Claritin-D 24 drug product because the applicant was unable to establish bioequivalence for the PSE component in a comparison between Claritin-D24 and the reference products of Claritin and Afrinol (pseudoephedrine sulfate 120 mg repetab administered BID). [NDA 20-470, Division

Director Memo, August 22, 1996] In particular, in a multiple-dose study, the Cmin and fluctuation index were higher for Claritin-D24 than for Afrinol. [NDA 20-470, Biopharm Review, March 9, 1995] Indeed, for Claritin-D24, in the first two studies did not demonstrate an end-of-dosing interval effect for the PSE component on congestion scores. The applicant gained approval by conducting a further study, which demonstrated an end-of-dosing interval effect on congestion for the combination product when compared to loratadine as well as to placebo.

Table 3. Summary of single-dose and multiple-dose pharmacokinetics of pseudoephedrine in Clarinex-D® 24 HOUR compared to other formulations

PSE PK	PSE	
	Cmax ng/mL	AUC ng•hr/mL
Clarinex-D24 (240 mg extended release core) [1]		
Study P00439 (single-dose)	328	6780
Study P00884 (multiple-dose: 14 days)	523	8795 (AUC_{0-24})
PSE 240 mg extended release core with placebo Claritin overcoat [1]		
Study P00439 (single-dose)	349	6452
Claritin-D24 (240 mg extended release core) [1A]		
Single-dose	377	6867
Multiple-dose (8 days)	582	10161 (AUC_{0-24})
Clarinex-D12 (120 mg core PSE) [2]		
Single-dose	273	3309
Multiple-dose (BID x 14 days)	408	7667 (AUC_{0-24})
Afrinol (120 mg repetabs) [A]		
Multiple-dose (BID x 8 days)	571	9643
Allegra-D24 (Osmotic pump core release) [B]		
Single-dose	393	7988
Multiple-dose (7 days)	488	8490
[1] Clarinex D24 and Claritin D24 share the same core PSE [2] Clarinex D12 has half the dose of PSE as in Clarinex D24		

Sources: NDA 21-605: Hpbio, 6B: Study P00439, p2; Study P00884, p2;
[A] NDA 20-470 for Claritin D24
[B] NDA 21-764 for Allegra D24
Biopharm review of Dr. Al Habet, 2/23/2005

Study P00884

Study P00884 was a 14-day open-label multiple-dose study to characterize the steady-state pharmacokinetics of the to-be-marketed formulation of DL D-24. The study was conducted in 18 healthy subjects (15 males and 3 females) between 21 and 45 years of age (mean = 32.5 years). Fourteen were Caucasian and four were Black. Steady state conditions for DL and 3-OH DL were attained on Day 12. Steady-state conditions of PSE were attained by Day 10. Results for DL and 3-OH DL are shown in **Error! Reference source not found.**, and for PSE in Table 3.

Study P00441

Study P00441 was a bioavailability food-effect study that compared the to-be-marketed formulation of DL D-24 (5 mg / 240 mg) administered under both fasting and fed conditions. The study was an open-label, randomized, single dose, two-way crossover design, conducted in 38 healthy subjects (27 males and 11 females) between the ages of 19 and 44 years (mean = 29.5 years). Twenty-four subjects were Caucasian, 11 were Black, and three were Hispanic. In this study, the plasma profiles under fasted and fed conditions were similar for DL, 3-OH DL, and PSE, supporting a labeling claim that Clarinex-D24 Hour may be administered without regard to meals.

Clinical and Statistical

Two large clinical studies, P01875 and P01884, were performed to support the clinical efficacy (and safety) of Clarinex-D® 24 Hour tablets for the proposed indication of SAR (Table 4). The studies were essentially identical in design, and conducted in 2,852 patients with a 2-year history of SAR. The application is supported by a single-dose bioavailability study, a food-effect study (no food effect noted), and a multiple-dose steady-state pharmacokinetic study.

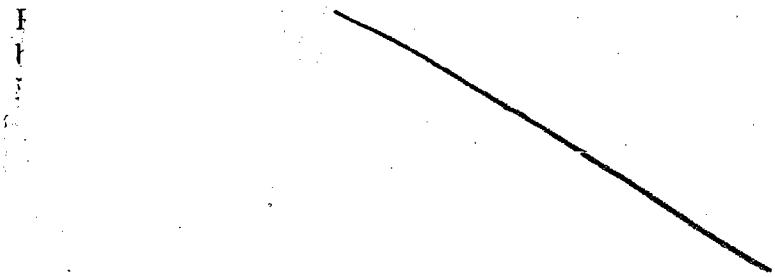
Table 4. Summary Clinical Studies

Study	Study Type / Design	Treatment Groups	Batch Number*	Ages	N (M, F)	Race
P01875	15 day, MC, R, DB, DD, AC, PG, Efficacy and Safety in SAR patients	DL D-24 (5 mg/PSE 240 mg) DL D-24 AF (5 mg/PSE 240 mg) DL 5 mg PSE 240 mg (extended release)	75882-056* 76466-073 0700032 75882-061	12-78	1495 527 M 968 F	1180 C 161 B 2 AI 29 A 112 H 11 O
P01884	15 day, MC, R, DB, DD, AC, PG, Efficacy and Safety in SAR patients	DL D-24 (5 mg/PSE 240 mg) DL D-24 AF (5 mg/PSE 240 mg) DL 5 mg PSE 240 mg (extended release)	75882-056* 76466-073 0700032 75882-061	11-78	1357 516 M 841 F	1080 C 120 B 2 AI 37 A 107 H 11 O

* In the CMC section for the investigational formulations used in Protocols P01875 and P01884 [Vol. 1.1, Section 3.D.2, p.36], Batch Number 76466-068, a formulation containing DL 6 mg/PSE 240 mg [Vol. 1.1, Section 3.D.2, p. 25-26] is listed as a formulation being used; however, the study report synopses for these two protocols [Vol. 1.1, Section 3.H., p.15 and 18] indicate that only formulations containing DL 5 mg/PSE 240 mg (Batch Numbers 75882-056 and 76466-073) were used [Vol. 1.1, Section 3.D.2, p. 17-18 and p. 27-28].

* Batch number 75882-056 is the proposed commercial formulation

Sources: Section 3H, page 9, summary.pdf; Section 4C, page 21, invest.pdf



Indication of Seasonal Allergic Rhinitis (SAR)

Protocol Summary of Clinical Studies

Studies P01875 and P01884 were large, multi-center, randomized, double-blind, double-dummy, 15-day safety and efficacy studies conducted in 2,852 patients, ages 12 to 78 years, with seasonal allergic rhinitis. Both were conducted in the US. The studies compared two formulations of Clarinex-D® 24 Hour extended-release tablets (called DL D-24 and DL D24 AF for Alternate Formulation) with Clarinex 5 mg tablets (DL) and pseudoephedrine 240 mg sustained release tablets (PSE), and were designed to satisfy the combination drug policy of superiority of the combination drug product to the individual component for a specific set of symptoms (i.e. added benefit from each ingredient). There was no placebo treatment group in these studies. The protocols were practically identical, including symptom scoring and all primary and secondary efficacy variables and endpoints, and are therefore discussed together. During the baseline and treatment periods, instantaneous (NOW) and reflective (PRIOR) nasal and non-nasal symptoms of SAR were scored twice daily. Scoring included evaluation of four nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and four non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate), each scored according to the following scale: 0=none, 1=mild, 2=moderate, and 3=severe. The total symptom score was the summation of the eight individual symptom scores.

For eligibility, patients were required to have a two-year documented history of fall SAR and a positive skin test to an appropriate fall seasonal allergen within the previous 12 months. In order to qualify for treatment, patients were required to have a minimum score of 42 for total nasal symptoms, a minimum score of 35 for total non-nasal symptoms, and a minimum score of 14 for each of the individual symptoms of nasal stuffiness/congestion and rhinorrhea, based on reflective (PRIOR 12 hours) scores for the 3 days prior to Baseline and the AM of the Baseline visit.

Patients were randomized 1:1:1:1 to 15 days of treatment with one of four treatment groups designated DL D-24, DL D-24 AF, DL 5mg, and sustained-release PSE 240 mg. The target enrollment was 350 patients per treatment group in each study. There was no placebo group. Each morning, patients took 2 tablets (one active, one placebo). On-treatment clinic visits were held on Day 8 and Day 15 (endpoint).

For the antihistamine component, the primary efficacy variable was the 12-hour reflective total symptom score excluding nasal stuffiness and congestion. For the decongestant component, the primary efficacy variable was the 12-hour reflective nasal

stuffiness/congestion score. For both primary variables, the primary endpoint was the change from baseline in average AM/PM 12-hour reflective scores over the 15 days of treatment. The primary comparisons for the antihistamine component were DL D-24 (and DL D-24 AF) versus PSE. The primary comparisons for the decongestant component were DL D-24 (and DL D-24 AF) versus DL. The primary variables were analyzed using a two-way analysis of variance (ANOVA), which extracted sources of variation due to treatment and center. All efficacy analyses were based on what the applicant termed a modified intent-to-treat (MITT) population of patients randomized who took at least one dose of study drug. Both studies used a two-tailed alpha level of 0.025 based on Bonferroni criteria to control for two pair of comparisons (for DL D-24 and DL D-24 AF with the mono-components) with an overall alpha level of 0.05. Since both primary comparisons (for the antihistamine and decongestant components) had to be statistically significant at an alpha level of 0.025, no adjustment of the significance level was performed for the individual comparisons.

Safety variables included a complete medical history and physical examination, 12-lead EKG, and clinical laboratory evaluations (chemistry, hematology, serum pregnancy test), prior to entering the screening period. Vital signs were taken at each visit. At the final visit at 15 days, the 12-lead EKG and clinical laboratory evaluations were repeated.

Enrollment and Demographics

A total of 2852 patients were randomized and received at least one dose of study drug, with 708 patients exposed to the to-be-marketed formulation. The two clinical studies were well-controlled and of adequate duration, 15 days, to assess the efficacy for the treatment of symptoms of seasonal allergic rhinitis. Treatment groups in each study were comparable at baseline with respect to demographics and disease characteristics and there was adequate representation of age groups.

Exposure to the to-be-marketed formulation of DL D-24 included 708 SAR patients, with a breakdown of: Males 39%, Females 61%, Caucasians 78%, Black 11%, Hispanic 8%, Other 3%. Only 8 patients ≥65 years of age were exposed to the to-be-marketed formulation in the clinical studies.

Safety

Review of the safety findings in this application revealed no new or unusual safety trends. Systemic exposure to desloratadine with this combination drug product was lower than when a 5 mg dose of Clarinex was taken. Therefore, the lack of bioequivalence to the mono-product does not result in any safety concerns, only potential efficacy concerns. Indeed, no new safety concerns were found during this review.

There were no deaths, and no serious and unexpected adverse events that were attributed by an investigator to study drug. The adverse event profile was similar to what might be expected from use of an antihistamine and a decongestant in combination, with the most common adverse events being dry mouth, headache, and insomnia. Of note, there was no placebo group to allow placement of the incidence of adverse events into perspective.

Efficacy

In both studies, Clarinex-D 24 Hour tablets (DL D-24) consistently demonstrated a statistically significant antihistaminic and decongestant effect over the individual mono-components, thereby satisfying the combination drug policy of added benefit (Table 5). However, in this application there were clinical issues arising from the lack of bioequivalence and from the results of the clinical studies, as discussed below.

For the primary comparison for the antihistaminic effect of DL D-24 vs PSE, p-values were 0.001 and 0.015 in studies P01875 and P01884, respectively. For this same comparison, the estimation of effect size (difference between treatment groups for change from baseline in symptoms scores) was 0.99 and 0.93 in studies P01875 and P01884, respectively. For the primary comparison for the decongestant effect of DL D-24 vs DL, p-values were 0.001 and <0.001 in studies P01875 and P01884, respectively. For this same comparison, the estimation of effect size (difference between treatment groups for change from baseline in symptoms scores) was 0.16 and 0.20 in studies P01875 and P01884, respectively. Response to treatment was examined by age, sex, and race, and was consistent with the primary efficacy results. The FDA statistical reviewer was able to confirm the sponsor's primary efficacy findings and the secondary findings related to end-of-dosing interval (see dosing and administration discussion below).

In both studies Clarinex-D 24 Hour tablets (DL D-24) also consistently demonstrated a statistically significant antihistaminic and decongestant effect over the individual mono-components for symptoms scores in the same drug class. In other words, the combination also beat PSE for the decongestant effect and DL for the antihistamine effect. This is an unexpected finding. In both studies there was an effect ordering for the decongestant effect, with DL-D24 superior (statistically significant) to both DL and PSE, and with only small numerical differences between DL and PSE, but with PSE numerically greater in the decongestant effect. For this reason, the systemic exposure to PSE was evaluated and compared to other formulations (see biopharm section) and found to be reasonable. While there was an effect ordering in both studies for the decongestant effect, this was not the case for the antihistaminic effect. In one study (P01875) the difference in effect size for the antihistaminic effect was so small as to be meaningless. In the other (P01884) the effect ordering was reversed. The interpretation of the primary reviewer was that there may be significant crossover in relief on patient reported symptoms by both drugs in the combination and the patient reported symptom scores for allergic rhinitis are simply not sensitive enough to elucidate these differences. While this may be true, it cannot be accepted at face value, as the implication could be a lack of therapeutic effect for the antihistamine component.

Therefore, the effect sizes for the antihistaminic and decongestant effects of other similar combination drug products were evaluated to try to place the results found in these studies into context and provide a frame of reference for interpretation. Since the NDA for Allegra-D24 was based on bioequivalence, there were no clinical studies to evaluate. However, there were studies available from the Claritin-D 24 Hour NDA. In pooled studies for Claritin-D 24, the change from baseline for total nasal symptoms excluding congestion over the duration of the study was -5.9 (-41.6%), -5.1 (-35.6%), -4.5 (-32.4%), and -3.9 (-25.8%) for Claritin-D 24, Claritin, PSE, and placebo, respectively. In the same pooled studies, the change from baseline for the nasal congestion score was -3.4 (-

37.5%), -2.6 (-27.4%), -3.0 (-32.7%), and -2.2 (-22.3%) for Claritin-D 24, Claritin, PSE, and placebo, respectively. Dose ordering was achieved, with numerical separation from placebo as well. Therefore, we are still left with a lack of dose ordering for the antihistaminic effect in the two studies in this application, which may potentially relate to the lower systemic exposure to desloratadine in the combination drug product.

Because of the lower systemic exposure to desloratadine in the combination drug product and because of the lack of dose ordering discussed above, there is a clinical concern that some patients who are switched from the mono-product to the combination product in order to add treatment with a decongestant may suffer from the loss of antihistamine exposure and not be adequately treated. This concern stems from results in this application and from the original dose-ranging study Clarinex, in which doses of 2.5 mg did not have a significant effect on symptom scores, but doses of 5 mg and above did. Because of the lower systemic exposure to desloratadine in the combination drug product, it is possible that some patients may be at the cusp of efficacy with this drug product. For those patients, it would be preferable to continue use of the Clarinex 5 mg mono-product and add an oral decongestant mono-product as needed. It should be noted that during the review of this drug product, an investigation of clinical outliers was not performed to evaluate whether this could be substantiated from the clinical data submitted. Nevertheless, without a placebo arm for comparison, it is very difficult to interpret the findings from these studies and make a firm conclusion regarding the differences in antihistaminic effects.

Despite the lack of bioequivalence and lower exposure to desloratadine, and despite the concerns regarding dose-ordering for the antihistamine symptoms, the results of these studies do satisfy the combination drug policy and support the efficacy of once daily Clarinex-D 24 Hour extended-release tablets for the treatment of symptoms of seasonal allergic rhinitis.

Table 5. Primary Efficacy: Mean AM/PM PRIOR 12 Hours, D 1-15, MITT*

Treatment Group	Baseline		Change from Baseline		Comparisons vs DL D-24	
	N[a]	LS Mean [b]	LS Mean [b]	%[c]	Δ [d]	P-value [e]
Total Symptom Score (Excluding Nasal Congestion)						
Study P01875						
DL D-24	372	15.01	-6.09	-38.8		
DL	369	14.71	-5.10	-33.5	-0.99	0.001
PSE	377	15.08	-5.08	-32.4	-1.01	**0.001**
Study P01884						
DL D-24	333	14.84	-5.71	-37.4		
DL	337	15.06	-4.78	-30.8	-0.93	0.003
PSE	337	15.03	-4.95	-32.0	-0.76	**0.015**
Nasal Stuffiness/Congestion						
Study P01875						
DL D-24	372	2.57	-0.90	-33.4		
DL	369	2.55	-0.74	-28.0	-0.16	**0.001**
PSE	377	2.56	-0.78	-28.6	-0.12	0.009
Study P01884						
DL D-24	333	2.56	-0.85	-32.3		
DL	337	2.57	-0.65	-24.8	-0.20	**<0.001**
PSE	337	2.54	-0.70	-27.1	-0.15	0.002

* The MITT population included all patients randomized (ITT pop) who had Baseline data plus at least one post-baseline efficacy assessment.
[a] Calculation of mean Baseline values included all patients with Baseline and Endpoint data; calculation of mean post Baseline values included all patients with both Baseline and post Baseline data at the specified time point(s).
[b] LS Means are obtained from the two-way ANOVA model with treatment and site effects.
[c] Mean percent changes are raw means.
[d] Delta is difference between treatments for change from baseline.
[e] Primary comparison of interest is **bolded**.
Note: Results for this set of analyses were verified by the Division's statistical reviewer, Dr. Ted Guo

Source: p01875.pdf, Table 1, p 226 ; Table 5, p 26 ; clinstat\p01884.pdf, Table 12, p 68 ; Table 13, p 71

Dosing Regimen and Administration

The applicant's proposed dosing regimen for Clarinex-D 24 Hour tablets is one tablet once daily, and once daily AM dosing was studied in both clinical trials. The applicant's data support the efficacy claim for once daily dosing. For the PSE component, Clarinex-D 24 Hour tablets was shown to have a statistical significant effect in both studies on the instantaneous end-of-dosing interval over the primary treatment period (AM NOW p-values: <0.001 in Study P01875, 0.001 in Study P01884). However, for the antihistamine component, a statistically significant effect was found in only one of the two studies, with a borderline effect in the second. The p values were <0.025 at all timepoints (Day 2, Day 3, Day 4, Days 2-8) except at Days 9-15 (p=0.193). This raised some concern that the effect may not last up to 24 hours after initial dosing, which is the proposed dosing regimen. This borderline effect in one of the two studies may be related to the lower systemic exposure to desloratadine from this drug product than from desloratadine 5 mg that was found in the clinical pharmacology studies. Nevertheless, the results of the applicant's data were felt to be clinically adequate to support the proposed dosing interval for a SAR indication.

Clinical pharmacology Study P00441 supported the statement in the DOSAGE AND ADMINISTRATION section that Clarinex-D 24 Hour tablets can be administered with or without a meal.

A major, previously identified, safety concern with desloratadine has been the issue of bioavailability of desloratadine in patients with liver or kidney impairment. For Clarinex 5 mg, the result is a labeling recommendation that patients with liver or kidney impairment be treated with every-other-day dosing. For patients with liver impairment, dosing in this manner is not practicable for Clarinex-D 24 Hour tablets, which contain a fixed-dose combination of desloratadine and pseudoephedrine in which the dosage of pseudoephedrine is not appropriate for every-other-day dosing. For patients with renal impairment, dosing in this manner is practicable for Clarinex-D 24 Hour tablets because PSE is also excreted by the kidneys. Therefore, every other day dosing is reasonable for both components of this combination drug product. In fact, the Claritin D24 product contains the same proposed labeling for both hepatic and renal impairment.

Abuse Considerations

There are no specific concerns for abuse of this drug product.

Data Quality, Integrity, and Financial Disclosure

During review of the studies, no ethical issues were noted. All studies were performed in accordance with accepted clinical standards.

Since both components in the combination product are approved and there is a significant amount of clinical experience with each, a DSI audit was not requested for the combination drug product.

A DSI audit for the clinical pharmacology studies was initially recommended at the filing and planning meeting on June 21, 2004 by the Biopharmaceutics team due to the questionable data integrity of Protocol P00439 in which two patients were noted to have measurable concentrations (14 ng/mL to 63 ng/mL) of PSE following the administration of DL. However, since Study P00439 was a failed study in that Clarinex-D 24 Hour tablets was found to lack bioequivalence to the desloratadine component in the combination product, the study is not crucial to support the approval of the drug product. Therefore, a DSI audit was not pursued.

A DSI audit for clinical Study P01875 was considered (but not pursued) at the mid-cycle review meeting due to protocol deviations for patient enrollment at study site P01875-07. A total of 4 (17%) out of 24 patients were randomized to treatments that were excluded from the final study protocol. Two patients received a DL D-24 formulation containing DL 6 mg and PSE 240 mg and two patients received placebo treatment. All four patients received 14 days out of 15 days of the full treatment duration even though they had visits at day 8 and the protocol deviation was not discovered and corrected at that time. A DSI audit was not pursued since only 4 out of the total 1495 patients enrolled at 47 sites for this study were involved, the 4 patients were excluded from the efficacy analyses, the efficacy results for the center were not significantly different from those for the rest of the study. Therefore, it was felt that any irregularities at this center would not impact upon the regulatory decision for the NDA.

The applicant provided adequate disclosure of financial interests of the clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. Only one investigator ( ) had a significant equity of interest in Schering Plough stock in the amount of approximately $403,500. Study center participated in and enrolled patients of the total randomized for from centers. Review of the primary efficacy as well as safety data for this study site indicated that patients at site did not have significantly different efficacy and safety results compared to the overall results of the clinical study that would raise questions about the integrity of the data.

Product Name

A trade name consult was not performed for this NDA. The registered name is Clarinex–D®. This is consistent with the Claritin and Allegra names and labels. The term '24 HOUR' further explains this product. While there is no Clarinex–D® 12 HOUR tablet, Schering is planning development of such a product in the next year. Therefore, the trade name for this product should include '24 HOUR' so that it may be distinguished from a 12 HOUR product when it becomes available. The term Extended Release Tablets is not considered to be part of the trade name.

Labeling

Labeling was submitted, reviewed, and compared with the latest Clarinex, Claritin-D 24 Hour (latest Rx PI, although Claritin-D 24 Hour is now OTC), Zyrtec-D 12 Hour, and Allegra-D 24 Hour package inserts. Several major areas of concern were identified and discussed with the sponsor. In particular, the labeling will carry clear wording in the Clinical Pharmacology section that bioequivalence was not achieved, necessitating clinical studies to support the SAR indication.

Summary and Recommendations

I recommend taking an Approval action of this drug product for the indication of seasonal allergic rhinitis.

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/s/

Peter Starke
3/2/05 02:50:14 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-605
Submission Number	N-000
Submission Code	
Letter Date	April 30, 2004
Stamp Date	May 3, 2004
PDUFA Goal Date	March 3, 2005
Reviewer Name	Katherine Szema, MD Review completed by Peter Starke, MD
Review Completion Date	February 1, 2005
Established Name	Desloratadine/pseudoephedrine sulfate
(Proposed) Trade Name	Clarinex–D® 24 HOUR Extended Release Tablet
Therapeutic Class	Antihistamine/decongestant combination
Applicant	Schering Corporation
Priority Designation	S
Formulation	Oral
Dosing Regimen	One tablet daily
(Proposed) Indications	Nasal and non-nasal symptoms of allergic rhinitis (seasonal [redacted])
Intended Population	12 years of age and older

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List of Abbreviations

AC	Active-controlled
AERS	Adverse Event Drug Reporting System
DB	Double-blind
DD	Double-dummy
DL	Desloratadine
DL D-24	The proposed long-acting formulation of Desloratadine/Pseudoephedrine in Clarinex-D® 24 HOUR Extended-Release Tablets
DL D-24 AF	Alternate long-acting formulation, not carried to the application
GRAE	Generally recognized as effective
GRAS	Generally recognized as safe
MC	Multi-center
MDI	Metered-dose inhaler
OL	Open-label
OTC	Over-the-Counter
PAR	Perennial Allergic Rhinitis
PC	Placebo-controlled
PG	Parallel group
PSE	Pseudoephedrine
QD	Once-daily dosing
R	Randomized
SAR	Seasonal Allergic Rhinitis

Population and Ethnic groups:

M	Male
F	Female
C	Caucasian
B	Black
H	Hispanic
AI	American Indian
A	Asian
O	Other

1 EXECUTIVE SUMMARY

This application from Schering Corporation is for a prescription combination antihistamine/decongestant tablet product containing desloratadine 5 mg in an immediate-release coating and pseudoephedrine sulfate 240 mg in a sustained-release matrix core for once daily dosing. The applicant refers to this product as DL D-24. The proposed a trade name is Clarinex-D® 24 HOUR Extended Release Tablets.

Clarinex-D® 24 HOUR tablets are proposed to be administered once daily to adults and children 12 years of age and older. The proposed indication is for the "relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal ———), including nasal congestion, in patients 12 years of age and older. CLARINEX-D 24 HOUR Extended Release Tablets can be administered when the antihistaminic properties of desloratadine and the nasal decongestant activity of pseudoephedrine are desired."

Reviewer's Note: A clinical program was performed because the combination drug product (5/240 mg) failed to show bioequivalence to the individual desloratadine 5 mg mono-product (i.e. the approved Clarinex 5 mg) in two bioequivalence studies. Systemic exposure to desloratadine with this combination was lower than with Clarinex 5 mg mono-product, leading to the suspicion that some patients who are switched from the mono-product to the combination product in order to add treatment with a decongestant may suffer from the loss of antihistamine exposure and not be adequately treated. For those patients, it would be preferable to continue use of the Clarinex 5 mg mono-product and add an oral decongestant mono-product as needed.

This review found adequate clinical data to support the efficacy claim for this combination drug product using once daily dosing for a seasonal allergic rhinitis (SAR) indication.

There were no safety issues found in the review of this application.

1.1 Recommendation on Regulatory Action

The clinical recommendation is for an Approval action for the indication of treatment of symptoms of seasonal allergic rhinitis.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific risk management activities are warranted for this product.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are recommended.

1.3 Summary of Clinical Findings

The Applicant initially planned a submission that would rely on data from previously approved desloratadine 5 mg tablets (NDA 21-165 and NDA 21-312), monographed pseudoephedrine, and five clinical pharmacology bioavailability and bioequivalence studies. However, Study P00439, a pilot open-label, single-dose, randomized, 3-way crossover study failed to demonstrate bioequivalence of desloratadine in the to-be marketed clinical formulation of Clarinex-D® 24 Hour to the individual component Clarinex 5 mg. Indeed, a separate study demonstrated that it would take a formulation of this drug product containing 6 mg of desloratadine and 240 mg of pseudoephedrine to produce systemic exposures of desloratadine comparable to the approved Clarinex 5 mg drug product. Because of the lack of bioequivalence, a clinical development program was required and was undertaken.

1.3.1 Brief Overview of Clinical Program

Two large clinical studies, P01875 and P01884, were performed to support the clinical efficacy (and safety) of Clarinex-D® 24 Hour tablets for the proposed indications. The studies were essentially identical in design, and conducted in 2,852 patients with a 2-year history of SAR. The applicant also performed a single-dose bioavailability study, a food-effect study (none found), and a multiple-dose steady-state pharmacokinetic study to support the application.

The two clinical studies support the proposed indication of seasonal allergic rhinitis. However, the lower clinical exposure to desloratadine with Clarinex-D® 24 Hour tablets has implications for the clinical program from an efficacy perspective. Only seasonal allergic rhinitis patients were studied, and the clinical studies were both of two weeks duration.

[redacted]

1.3.2 Efficacy

1.3.2.1 Indication of Seasonal Allergic Rhinitis (SAR)

Studies P01875 and P01884 were large, multi-center, randomized, double-blind, double-dummy, 15-day safety and efficacy studies conducted in 2,852 patients, ages 12 to 78 years, with seasonal allergic rhinitis. Both were conducted in the US. The studies compared two formulations of Clarinex-D® 24 Hour sustained-release tablets (called DL D-24) with Clarinex 5 mg tablets (DL) and pseudoephedrine 240 mg sustained release tablets (PSE), and were designed to satisfy the combination drug policy of superiority of the combination drug product to the individual component for a specific set of symptoms (i.e. added benefit from each ingredient). The protocols were practically identical, including symptom scoring and all primary and secondary efficacy variables and endpoints, and are therefore discussed together. During the baseline and treatment periods, instantaneous (NOW) and reflective (PRIOR) nasal and non-nasal symptoms of SAR were scored twice daily. Scoring included evaluation of four nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and four non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate), each scored according to the following scale: 0=none, 1=mild, 2=moderate, and 3=severe. The total symptom score was the summation of the eight individual symptom scores.

For eligibility, patients were required to have a two-year documented history of fall SAR and a positive skin test to an appropriate fall seasonal allergen within the previous 12 months. In order to qualify for treatment, patients were required to have a minimum score of 42 for total nasal symptoms, a minimum score of 35 for total non-nasal symptoms, and a minimum score of 14 for each of the individual symptoms of nasal stuffiness/congestion and rhinorrhea, based on reflective (PRIOR 12 hours) scores for the 3 days prior to Baseline and the AM of the Baseline visit.

Patients were randomized 1:1:1:1 to 15 days of treatment with one of four treatment groups designated DL D-24 (the to-be-marketed formulation), DL D-24 AF (an alternate formulation), DL 5gm, and sustained-release PSE 240 mg. The target enrollment was 350 patients per treatment group in each study. There was no placebo group. Each morning, patients took 2 tablets (one active, one placebo). On-treatment clinic visits were held on Day 8 and Day 15 (endpoint).

For the antihistamine component, the primary efficacy variable was the change from baseline in average AM/PM 12-hour reflective total symptom score excluding nasal stuffiness and congestion. For the decongestant component, the primary efficacy variable was the change from baseline in average AM/PM 12-hour reflective nasal stuffiness/congestion score. For both primary variables, the primary endpoint was the average over the 15 days of treatment. The primary comparisons for the antihistamine component were DL D-24 (and DL D-24 AF) versus PSE. The primary comparisons for the decongestant component were DL D-24 (and DL D-24 AF) versus DL. The primary

variables were analyzed using a two-way analysis of variance (ANOVA), which extracted sources of variation due to treatment and center. All efficacy analyses were based on what the applicant termed a modified intent-to-treat (MITT) population of patients randomized who took at least one dose of study drug. Both studies used a two-tailed alpha level of 0.025 based on Bonferroni criteria to control for two pair of comparisons (for DL D-24 and DL D-24 AF with the mono-components) with an overall alpha level of 0.05. Since both primary comparisons (for the antihistamine and decongestant components) had to be statistically significant at an alpha level of 0.025, no adjustment of the significance level was performed for the individual comparisons.

A total of 2852 patients were randomized and received at least one dose of study drug, with 708 patients exposed to the to-be-marketed formulation. The two clinical studies were well-controlled and of adequate duration, 15 days, to assess the efficacy for the treatment of symptoms of seasonal allergic rhinitis. Treatment groups in each study were comparable at baseline with respect to demographics and disease characteristics and there was adequate representation of age groups.

In both studies, Clarinex-D 24 Hour tablets (DL D-24) consistently demonstrated a statistically significant antihistaminic and decongestant effect over the individual mono-components, thereby satisfying the combination drug policy of added benefit. For the primary comparison for the antihistaminic effect of DL D-24 vs PSE, p-values were 0.001 in Study P01875 and 0.015 in Study P01884. For the primary comparison for the decongestant effect of DL D-24 vs DL, p-values were 0.001 in Study P01875 and <0.001 in Study P01884. Response to treatment was examined by age, sex, and race, and was consistent with the primary efficacy results.

It should be noted that while the combination beat PSE for the antihistamine effect and DL for the decongestant effect, the results are not at all pure. The combination also beat PSE for the decongestant effect and DL for the antihistamine effect. Reviewer's interpretation: there is significant crossover in relief on patient reported symptoms by both drugs in the combination and the patient reported symptom scores for allergic rhinitis are simply not sensitive enough to elucidate these differences.

When the end-of-dosing effect (the drug effect after 24 hours of taking the dose as evidenced by the 15-day mean AM NOW symptom scores) was examined, Clarinex-D 24 Hour tablets demonstrated a statistically significant decongestant effect throughout the treatment period for both studies (p-values: <0.001 in Study P01875, 0.001 in Study P01884), but did not consistently demonstrate superiority for the antihistamine component in the relief of total nasal/non-nasal symptoms, excluding nasal congestion (p-values: 0.001 in Study P01875, 0.028 in Study P01884). The p values were <0.025 at all timepoints (Day 2, Day 3, Day 4, Days 2-8) except at Days 9-15 (p=0.193). This raised some concern that the effect may not last up to 24 hours after initial dosing, which is the proposed dosing regimen. One may postulate that this finding may be related to the lower systemic exposure to desloratadine in the DL D24 formulation. While the clinical interpretation in this case is

that of a meaningful benefit to the patient with SAR

The FDA statistical reviewer was able to confirm the sponsor's primary efficacy findings and the secondary findings related to end-of-dosing interval.

Results support the efficacy of once daily Clarinex-D 24 Hour extended-release tablets for the treatment of symptoms of allergic rhinitis in patients with SAR. However, because of the lower systemic exposure to desloratadine in the combination drug product, some patients who are switched from the mono-product to the combination product in order to add treatment with a decongestant may suffer from the loss of antihistamine exposure and not be adequately treated. For those patients, it would be preferable to continue use of the Clarinex 5 mg mono-product and add an oral decongestant mono-product as needed.

1.3.3 Safety

As noted above, systemic exposure to desloratadine with this combination drug product was lower than when a 5 mg dose of Clarinex was taken. Therefore, the lack of bioequivalence to the mono-product does not result in any safety concerns, only efficacy concerns. Indeed, no new safety concerns were found during this review.

Safety variables in the clinical studies included a complete medical history and physical examination, 12-lead EKG, and clinical laboratory evaluations (chemistry, hematology, serum pregnancy test), prior to entering the screening period. Vital signs were taken at each visit. At the final visit at 15 days, the 12-lead EKG and clinical laboratory evaluations were repeated.

Exposure to the to-be-marketed formulation of DL D-24 during the clinical trials included 708 SAR patients, with a breakdown of: Males 39%, Females 61%, Caucasians 78%, Black 11%, Hispanic 8%, Other 3%. Only 8 patients ≥65 years of age were exposed to the to-be-marketed formulation in the clinical studies.

Review of the safety findings in this application revealed no new or unusual safety trends. There were no deaths, and no serious and unexpected adverse events that were attributed by an investigator to study drug. The adverse event profile was similar to what might be expected from use of an antihistamine and a decongestant in combination, with the most common adverse events being dry mouth, headache, and insomnia. Of note, there was no placebo group to allow placement of the incidence of adverse events into perspective.

1.3.4 Dosing Regimen and Administration

The applicant's proposed dosing regimen for Clarinex-D 24 Hour tablets is one tablet once daily. The results of the applicant's data supported the efficacy claim for once daily dosing for a SAR indication. Once daily AM dosing was studied in both clinical trials. For the PSE component, Clarinex-D 24 Hour tablets was shown to have a statistical significant effect in both studies on the instantaneous end-of-dosing interval over the primary treatment period. However, for the antihistamine component, a statistically significant effect was found in only one of the two studies, with a borderline effect in the second. This borderline effect may be related to the lower systemic exposure to desloratadine from this drug product than from desloratadine 5 mg that was found in the clinical pharmacology studies. Nevertheless, the results of the applicant's data were felt to be clinically adequate to support the proposed dosing interval for a SAR indication, [redacted]

Clinical pharmacology Study P00441 supported the statement in the DOSAGE AND ADMINISTRATION section that Clarinex-D 24 Hour tablets can be administered with or without a meal.

A major, previously identified, safety concern with desloratadine has been the issue of bioavailability of desloratadine in slow metabolizers or in patients with liver or kidney impairment who may have desloratadine levels up to nine times that seen in normal metabolizers. For Clarinex 5 mg, the result is a labeling recommendation that patients with liver or kidney impairment be treated with every-other-day dosing. Dosing in this manner is not practicable for Clarinex-D 24 Hour tablets, which contain a fixed-dose combination of desloratadine and pseudoephedrine in which the dosage of pseudoephedrine is not

appropriate for every-other-day dosing. Therefore, Clarinex-D 24 Hour tablets should be contraindicated in patients with renal or hepatic impairment.

1.3.5 Drug-Drug Interactions

There are no important drug-drug interactions that affect the product's clinical use.

1.3.6 Special Populations

No studies in special populations are needed. Because of the extended release nature and the PSE dose in this product, evaluation of this product in populations below 12 years of age is not indicated.

Note: This review was written by Katherine Szema, MD. However, she left the Agency prior to finalization of the review. Dr. Szema completed the reviews of the individual clinical trials and some of the background sections. The rest of the review was written by her Team Leader, Peter Starke, MD.

[Referential Notation: References to source material are provided in this review. Within text, the references are bracketed [] and follow a standard format: the module number within the NDA according to CTD format; the volume number; the section within the volume; and the page number(s) where the source material is located; for example, [M5, v 1.2, sec 5.3.5.1, p 499]. Unless otherwise noted, references refer to the original NDA submission. When referring to source material submitted after the date of the NDA submission, the stamp date is also noted. References within an electronically submitted document are based on navigation from the electronic TOC, with the pdf file name appended. However, it should be noted that the two reviewers used slightly different referential notations, which will be obvious to the reader.]

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor, Schering Corporation, submitted a 505(b)(1) NDA application for a prescription combination antihistamine/decongestant tablet product, referred to as DL D-24, containing desloratadine 5 mg in an immediate-release coating and pseudoephedrine sulfate 240 mg in a sustained-release matrix core for once daily dosing. The proposed a trade name is Clarinex-D® 24 HOUR extended-relief tablets.

A clinical program was performed because the combination drug product failed to show bioequivalence to the approved desloratadine 5 mg mono-product (Clarinex 5 mg) in two bioequivalence studies.

During the review process, the Division determined that the NDA application must be submitted as a 505(b)(2). The PSE extended release tablet cores used in this product are identical in composition and shape to the tablet cores used in Schering's Claritin-D® 24 Hour tablets, a technology which Schering owns. However, the sponsor refers to the OTC monograph for preclinical support of the pseudoephedrine ingredient contained in the combination product. Therefore, a 505(b)(2) [rather than a 505(b)(1)]application is appropriate.

Schering proposes that Clarinex-D® 24 Hour tablets be sold by prescription only. Currently, all of Schering's products containing Clarinex (desloratadine) are sold by prescription only. However, all of Schering's products containing Claritin (loratadine) are currently sold OTC. Note that this includes Claritin-D 24 Hour tablets, containing 10 mg loratadine and 240 mg pseudoephedrine. The pseudoephedrine sustained-release matrix core for both products are identical.

Clarinex-D® 24 Hour extended release tablets are proposed to be administered once daily to adults and children 12 years of age and older. The proposed indication is for the "relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal [redacted]), including nasal congestion, in patients 12 years of age and older. CLARINEX-D 24 HOUR Extended Release Tablets can be administered when the antihistaminic properties of desloratadine and the nasal decongestant activity of pseudoephedrine are desired."

2.2 Currently Available Treatment for Indications

Currently, there are many prescription and non-prescription products approved for the treatment of allergic rhinitis, nasal congestion, or both indications.

Various classes of drug products in different formulations are approved for the treatment of symptoms of allergic rhinitis. These include several prescription oral antihistamine tablets and capsules, approved for SAR (i.e. Allegra), or both SAR and PAR (i.e. Zyrtec). Several over-the-counter oral antihistamine tablets and syrups (Claritin, Alavert, Benadryl) are available for the treatment of symptoms due to hay fever or other respiratory allergies.

Furthermore, there are several classes of nasal sprays approved for symptoms of allergic rhinitis. These include: antihistamine nasal sprays (Astelin for SAR and vasomotor rhinitis), cromolyn nasal sprays (Nasalcrom for nasal allergies), anticholinergic nasal sprays (Atrovent 0.03% for allergic and nonallergic perennial rhinitis), and several prescription intranasal corticosteroid sprays. Beclomethasone dipropionate (Beconase AQ) is approved for the relief of the symptoms of seasonal, perennial, and nonallergic (vasomotor rhinitis) and fluticasone propionate (Flonase) is approved for the management of the nasal symptoms of seasonal, perennial, and nonallergic rhinitis. Mometasone (Nasonex), triamcinolone (Nasacort AQ), and budesonide (Rhinocort AQ) are approved for the management of nasal symptoms of seasonal or perennial allergic rhinitis.

There are several OTC products approved for the treatment of nasal congestion. These include oral decongestant tablets or syrups containing pseudoephedrine alone (i.e. Efidac, Sudafed 12 Hour, Afrinol). Several nasal decongestant sprays containing phenylephrine (i.e. Neosynephrine) or oxymetazoline are approved for the relief of nasal congestion.

There are several antihistamine/decongestant combination prescription and non-prescription products available for the treatment of both allergic rhinitis and nasal congestion in patients 12 years of age and older. Generally these products contain pseudoephedrine combined with and antihistamine. Prescription products approved for the relief of symptoms associated with SAR in patients 12 years of age and older include Allegra-D® (fexofenadine HCL 60 mg and pseudoephedrine 120mg) Extended Release Tablets one tablet twice daily and Semprex-D Capsules (Celltech) (acrivastine 8mg and pseudoephedrine HCl 60mg) one capsule every 4 to 6 hours four times a day. Zyrtec-D 12 HOUR® (cetirizine HCl 5 mg and pseudoephedrine 120 mg) Extended Release Tablets one tablet twice daily is also approved for SAR and PAR for the same patient population. There are many OTC products approved for the temporarily relief of symptoms due to hay fever or other respiratory allergies, reduction of swelling of

nasal passage, relief of sinus congestion and pressure, restoration of freer breathing through the nose. The more commonly used products include:

- Claritin-D Non-Drowsy 12 Hour Tablets (loratadine 5 mg and pseudoephedrine 120mg) one tablet twice daily
- Claritin-D Non-Drowsy 24 Hour Tablets (loratadine 10mg and pseudoephedrine 240 mg) one tablet daily
- Alavert Allergy & Sinus D-12 Hour Tablets (loratadine 5 mg and pseudoephedrine 120mg) one tablet twice daily
- Benadryl Allergy & Sinus (diphenhydramine HCl 25 mg and pseudoephedrine HCl 60mg) one tablet every 4 to 6 hours

2.3 Availability of Proposed Active Ingredient in the United States

Clarinex-D® 24 Hour contains desloratadine 5 mg and pseudoephedrine sulfate 240 mg and is not currently marketed in any country.

Desloratadine (DL, SCH 34117; formerly known as descarboethoxyloratadine or DCL), an active metabolite of loratadine (Claritin®), is a selective peripheral H1-receptor antagonist. Desloratadine is marketed under the trade name Clarinex® and is currently approved for the following indications and in the following age groups with the corresponding NDAs:

- NDA 21-165 (approved December 21, 2001) for Clarinex® Tablets 5 mg po QD in SAR in patients 12 years of age and older
- NDA 21-297 (approved February 8, 2002) for Clarinex® Tablets 5 mg po QD in CIU in patients 12 years of age and older
- NDA 21-363 (approved February 8, 2002) for Clarinex® Tablets 5 mg po QD in PAR in patients 12 years of age and older
- NDA 21-312 (approved June 26, 2002) for Clarinex® RediTabs® 5 mg po QD in SAR and CIU in patients 12 years of age and older

Since the sponsor submitted NDA 21-605 for Clarinex-D® 24 Hour tablets on April 30, 2004, the following NDAs for Clarinex® Syrup were approved after a second cycle review:

- NDA 21-300 and NDA 21-563 (both approved September 9, 2004) for Clarinex ® Syrup for the relief of the nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis, and the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria in patients 2 years of age and older.
    - NDA 21-300 was originally submitted on December 8, 2000, for Clarinex® Syrup 2.5 mg po QD in patients 6-11 years of age and 1.25 mg in patients 2 to 5 years of age for the treatment of SAR and CIU, was given an "Approvable" regulatory action on October 2, 2001. Deficiencies included CMC issues and lack of safety data in children who appear to be slow metabolizers of DL and the concerns regarding the extent of exposure from multiple dosing in this select population. It was also concluded that the issue of slow metabolizers in children would have implications on all desloratadine NDAs.

- NDA 21-563 was originally submitted on December 4, 2002 for SAR and CIU for use in children 6 months to 2 years of age received an "Approvable" regulatory action on May 14, 2003. Deficiencies included lack of sufficient evidence of safety associated with higher exposures in children who were poor metabolizers of desloratadine in addition to CMC deficiencies.

- On February 27, 2004, the sponsor submitted a complete response to the "Approvable" letters for NDA 21-300 and NDA 21-563 for the administration of Clarinex Syrup (desloratadine) to children 6 months-12 years of age. In the complete response, the sponsor adequately characterized the pharmacokinetics of repetitive dose administration in children who are poor metabolizers and demonstrated that the upper limit of exposure in pediatric and adult poor metabolizers is similar and 6-7 times higher than is seen in normal metabolizers. In terms of safety, the sponsor demonstrated in 6 multiple dose studies that there is no significant difference in adverse events, laboratory tests, or vital signs between pediatric poor metabolizers who receive desloratadine and pediatric normal metabolizers who receive desloratadine or children who receive placebo.

The following NDA for Clarinex-D® 12 HOUR extended-release tablets received an "Approvable" regulatory action:

- NDA 21-313 for Clarinex-D® 12 HOUR extended-release tablets (desloratadine 2.5 mg/pseudoephedrine 120 mg) to be administered BID was submitted on December 8, 2000 (and received on December 27, 2000), for the proposed indications for the treatment of seasonal allergic rhinitis in adults and children twelve years of age and older. The clinical development program contained five pharmacokinetic studies and two pivotal clinical trials comparing Clarinex-D® 12 Hour Extended-Release Tablets with pseudoephedrine 120 mg BID and desloratadine 5 mg QD. The NDA was given an "Approvable" regulatory action on October 26, 2001. Deficiencies included lack of pharmacokinetic data to establish the safety of the drug product in patients who poorly metabolized desloratadine. Poor metabolizers (approximately 6% in the population aged $\geq$ 12 years) were found to experience desloratadine exposures that were approximately 6 times those of normal metabolizers. According to page 14 of the Division Director's review, dated October 10, 2001, "to gain approval, the applicant will need to establish safety of DL in a large number of slow metabolizers dosed chronically for a long period of time. As an alternate, the applicant may take the route of establishing safety of DL in normal metabolizers given a large dose (at least 6-fold of the proposed does) to mimic the exposure level that can occur in slow metabolizers."

Therefore, the major safety concerns with desloratadine have been the issue of bioavailability of desloratadine in slow metabolizers or patients with liver or kidney impairment who may have desloratadine levels up to nine times that seen in normal metabolizers. The issue was resolved in that the labeling for Clarinex now carries a dosage adjustment for patients with liver or kidney impairment to every other day dosing. While the safety issue with regard to slow metabolizers is not an issue for this drug product, the use of a fixed-combination drug product in patients for whom a dosage adjustment must be made is an issue that is addressed in this review.

Pseudoephedrine is an established sympathomimetic nasal decongestant. Pseudoephedrine HCl is considered generally regarded as safe and effective (GRASE) for the treatment of nasal congestion due to hay fever or other respiratory allergies, the common cold, or associated with sinusitis. For adults and children ≥12 years, pseudoephedrine is approved at a dose of 60 mg Q 4 to 6 hours, not to exceed (NTE) 240 mg in 24 hours, under the Final Monograph for OTC Nasal Decongestant Drug Products [21 CFR 341.80].

Labeling changes for a few of the desloratadine products have occurred following their initial NDA approvals. A labeling change for NDA 21-165/S-001 (Clarinex 5 mg tablets) on February 8, 2002 approved a modification in the package insert to incorporate chronic idiopathic urticaria and perennial allergic rhinitis that were approved under NDA 21-297 and 21-363, respectively. A modification in the label for NDA 21-312/S-002 (Clarinex 5 mg orally-disintegrating tablet) was approved on February 6, 2003 for the addition of instructions for use for both the professional sample and 30 tablet unit-of-use packages. On January 29, 2004, NDA 21-312/S-004 (Clarinex 5 mg orally-disintegrating tablets) and NDA 21-165/S-006 (Clarinex 5 mg tablet) were granted approved for the addition of palpitations to the ADVERSE REACTIONS Section of the package insert and revision of the legal name of the manufacturer of Clarinex RediTabs.

There have been no changes in the monograph labeling for pseudoephedrine except the August 2, 2004 proposed rule to 21 CFR Parts 310 and 341 to remove the indication "for the temporary relief of nasal congestion associated with sinusitis" and to prohibit use of the terms "sinusitis" and "associated with sinusitis" elsewhere on the labeling. Final comments were due by November 2, 1004.

2.4 Important Issues With Pharmacologically Related Products

Desloratadine, the major metabolite of loratadine, is a tricyclic antihistamine with H_1 receptor antagonist activity. Desloratadine appears to have less extensive first-pass metabolism and a longer plasma elimination half-life than loratadine.

A concern with hypospadias and loratadine first arose after a 2002 Swedish study noted that the prevalence of hypospadias among male infants born to women who while pregnant had taken loratadine was twice that of the general population. However, there was insufficient data regarding the severity of the hypospadias and the study did not control confounding variables such as family history or maternal age. The CDC analyzed data from the National Birth Defects Prevention Study (NBDPS), a CDC-run database of selected birth defects regarding second or third-degree hypospadias in infants born to women who used loratadine early in pregnancy. The report did have a limitation because first-degree hypospadias was excluded and the potential association between this mildest form of hypospadias and loratadine could not be assessed.

On May 3, 2002, the FDA Division of Drug Risk Evaluation, HFD-430, conducted a review of congenital genitourinary anomalies associated with loratadine. The review included the data from the Swedish Medical Birth Registry (SMBR), Adverse Event Reporting System,

and the medical literature. Their review concluded that the data do not suggest that antihistamines in general are associated with congenital genitourinary malformations. The DDRE stated that these Swedish findings "may be due to chance and may not be generalizable to the US population; however, they represent a signal and warrant further study and observation."

AERS reported nine cases of infants with genitourinary anomalies who were exposed to antihistamines during gestation as a result of maternal intake. The following antihistamines were suspect and include hydroxyzine (2 cases), astemizole (1), diphenhydramine (1), azelastine (1), triprolicine (1), loratadine (1), promethazine (1), and both diphenhydramine and promethazine (1). Of these nine cases, only 3 occurred in the US and the suspect drugs were diphenhydramine, promethazine, and a combination of these two drugs. The infants had hypoplastic scrotum, epispadias and bifurcated clitoris, and ano-vulvar imperforation, respectively.

Within recent years, a few antihistamine products have been withdrawn due to adverse side effects, most specifically cardiac problems. The manufacturers Hoerscht Marion Roussel and Baker Norton Pharmaceuticals voluntarily discontinued distribution and marketing of their terfenadine containing products (Seldane and generic terfenadine) from the market on February 1, 1998 by because they were associated with rare, but serious heart problems (cardiac arrhythmias) when taken with certain other drugs, including certain antibiotics and antifungals. Janssen Pharmaceutica voluntarily discontinued the manufacturing, distribution, and marketing of Astemizole (Hismanal) on July 1999, due to fatal arrhythmias at high doses in combination with other medications.

2.5 Pre-submission Regulatory Activity

There have been many IND meetings and teleconferences related to the development program the desloratadine product line, which includes desloratadine single ingredient products in various formulations and combination products containing desloratadine and pseudoephedrine. Frequently, drug products submitted under different IND's were discussed during a single IND meeting. This section will focus on the regulatory history of Clarinex® D-24 Hour extended release tablets submitted under IND 58,545 on June 25, 1999, prior to the approval of NDA 21-165 for Clarinex® Tablets on December 21, 2001.

A pre-IND meeting for IND 55,364 (SCH 34117, desloratadine tablets) was held on January 12, 1998 in response to a meeting package submitted on November 10, 1997 to discuss the development of desloratadine tablets at dosages of 1.0, 2.5, 5.0, or 10.0 mg. for the treatment of SAR, PAR, and CIU. During the meeting, the Division informed the applicant that any plan to develop a combination product with DL and PSE must include a drug interaction study, food effect study, single-dose PK study, and possibly a multiple-dose PK study. If desloratadine were approved prior to the combination product, then no additional clinical studies would be needed. However, the Division stated that if bioequivalence of the combination product were not demonstrated to the reference products, then clinical data would be required.

Subsequently, the applicant developed Clarinex-D® 24 Hour extended release tablets, a combination product containing DL 5 mg / PSE 240 mg. The original IND 58,545 was submitted on June 25, 1999, and received on June 29, 1999. This submission included a proposal for Study P00439, a 3-way crossover study to determine the bioequivalence of DL, 3-OH DL, and PSE following single-dose administration of the combination product (DL 5 mg / PSE 240 mg), desloratadine 5 mg, and PSE 240 mg (extended-release cores from Claritin-D® 24 coated with placebo Claritin® coat). The applicant also proposed plans for a food effect study and a multiple-dose, steady state PK study.

On October 8, 1999, the Division sent comments regarding original IND 58,545 to the applicant which recommended that the combination product be tested in a bridging general toxicity study in an appropriate species for up to 90 days, and in a teratology study in one species. The Division also informed the applicant that if the combination product were not found to be bioequivalent to the reference products, the current study design would not provide information on whether the failure of the bioequivalence is due to the drug-drug interaction, or effect of formulation on the bioavailability of the combination product. Therefore, the Division recommended including a fourth arm in the study (containing simultaneous administration of single ingredient DL and single ingredient PSE).

The applicant submitted a letter [IND 55,364 N093, October 27, 1999] to the Agency requesting that that the Division consider not require a bridging toxicity and teratology study if desloratadine tablets were an approved product. The Division sent a fax to the applicant on November 12, 1999, confirming the applicant's request that these studies would not be necessary as long as NDA 21-165 for Clarinex® Tablets 5 mg is approved, and there is no substantial increase in the dose of DL in the combination product. Clarinex® Tablets were subsequently approved on December 21, 2001.

A pre-NDA meeting under IND 55,364 (Desloratadine tablets) was held with the applicant on January 18, 2000 [Meeting minutes, IND 55,364, February 24, 2000], in response to a meeting package [IND 55,364 N107 GC, December 22, 1999] to discuss the development program of the desloratadine product line, including DL D-24 tablets. The Division stated that answers provided in the meeting were based on the presumption that NDA 21-265 for Clarinex Tablets would be reviewed and approved within the first cycle. The Division agreed to the applicant cross-referencing NDA 21-165 for the drug substance. The Division requested separate dissolution studies for each formulation of the DL D-24 product. In addition, an integrated discussion of safety for all the indications proposed and a subanalysis of each condition concerning efficacy and safety would be necessary. Lastly, the Division also requested a rationale for not using a reference formulation for the DL D-24 multi-dose PK studies and asked the applicant to investigate the effect of gender on the PK of DL and PSE. Gender effects were subsequently evaluated in Studies P01813, P01875, and P01884.

A Type C meeting was held with the applicant on November 7, 2000 [Meeting minutes, IND 58,545, December 22, 2000] in response to a request on September 14, 2000, and submission of a meeting package [IND 58,545 N025 MR, October 10, 2000], to discuss the drug development plan of Clarinex-D® 24 Hour tablets concerning bioequivalence, chemistry, and

pediatric issues. At that time, a dose of desloratadine [redacted] was proposed to be used in the combination product as the commercial formulation since two combination products containing desloratadine 5 mg formulations failed to demonstrate bioequivalence to the individual product. The Division expressed concern with this since Schering was trying to develop a Clarinex-D 12 Hour Tablet which contains 2.5 mg of desloratadine while Clarinex-D 24 Hour extended release tablets would contain [redacted] of desloratadine. An adequate explanation would need to be provided in the labeling as to why the DL ingredient in the 24 hour extended release formulation was not bioequivalent at twice the dosage of the 12-hour formulation. In addition, recommendations were made to measure additional metabolites that could possibly arise with the [redacted] formulation. The applicant requested a waiver of pediatric studies below the age of 12 and certified that the drug product did not represent meaningful therapeutic benefit over existing treatments for children below the age of 12 years. The Agency agreed with the applicant's rationale for a pediatric waiver request and informed the applicant that the formal waiver process would be handled at the time of the NDA action.

A teleconference with the applicant was held on November 28, 2000 [Meeting minutes, IND 58,545, January 4, 2001], in response to a meeting request [IND 58,545 N024 MR, October 12, 2000] to discuss three clinical trials to establish the safety and efficacy of a formulation containing desloratadine 5 mg / pseudoephedrine 120mg for the proposed indication of SAR [redacted] in patients ≥12 years of age. Three issues of concern to the Division were: (1) the potential confusion associated with marketing three desloratadine/pseudoephedrine combination products (2.5 mg / 120mg BID, 5 mg / 120mg QD, [redacted]), (2) the medical rationale for a low-dose, shorter-duration pseudoephedrine product (5 mg / 120mg QD), and (3) the overall plan to assess safety and efficacy in the targeted patient population. The Division informed Schering that a statistical difference in efficacy and safety would need to be demonstrated in the studies. In addition, extrapolation of results from an SAR only patient study to [redacted] patients may be problematic. Schering responded that they would consider stratifying patients into [redacted] and SAR strata or conduct separate studies for each indication.

The applicant submitted a correspondence [IND 58,545 N05 GC, March 15, 2001], in which they informed the Division that they have decided to proceed with a formulation for Clarinex-D 24 Hour tablets that would contain 5 mg of desloratadine instead [redacted] as had been discussed at the meeting on November 7, 2000. Based on a change in the formulation, the Division informed Schering [Teleconference, IND 58,545, April 13, 2001], that the biopharmaceutics comments from the November 7, 2000 meeting would no longer apply. The Division subsequently informed Schering [Fax, IND 58,545, April 26, 2001], that they may not need to measure other metabolites of desloratadine in addition to the metabolites currently being measured after administration of Clarinex-D 24, provided the safety and efficacy of the product is established in clinical studies.

In the interim period, Desloratadine (Clarinex) which was developed for the treatment of symptoms of SAR, PAR, and CIU in adults and children 12 years of age and over was approved for marketing in the US as Clarinex® Tablets (NDA 21-165) on December 21, 2001

for SAR and on February 8, 2002 (NDA 21-297, NDA 21-363) for CIU and PAR [summary\summary.pdf, page 019].

The most recent approval to another drug product in the desloratadine product line was for Clarinex® Syrup for NDA 21-300 and NDA 21-563 (both approved September 9, 2004) for the relief of the nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis, and the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria in patients 2 years of age and older.

2.6 Other Relevant Background Information

Clarinex-D® 24 Hour (desloratadine 5 mg / pseudoephedrine 240 mg) extended-release tablets are not approved or marketed in any country. Desloratadine 5 mg tablets are approved for marketing for SAR in over 75 countries including the European Union (EU) and the USA, and for chronic idiopathic urticaria in 44 countries (including the EU and the USA). Desloratadine syrup was approved in the EU for treatment of SAR and CIU in children 2 years of age and older on April 25, 2002, and is approved in over 55 countries as of April 2004. Desloratadine 5 mg tablets were approved in the EU for PAR on May 17, 2002. Desloratadine rapidly-disintegrating tablets were approved for SAR and CIU in adults and children 12 years of age and older on May 17, 2002. [summary.pdf, Section 3.C., page 1-2]

Pseudoephedrine sulfate single ingredient products are marketed internationally by other manufacturers.

The applicant states that neither active ingredient has been withdrawn from foreign markets for reasons of safety or effectiveness.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

The findings stated here are based on preliminary discussions with the reviewers in the following disciplines: chemistry, manufacturing, and controls (CMC) and pharmacology/toxicology.

3.1 Chemistry, Manufacturing and Controls (CMC)

The proposed product, Clarinex-D 24 Hour extended release tablets, provide an immediate-release 5 mg dose of desloratadine and an extended-release 240 mg dose of pseudoephedrine sulfate. The product is formulated with desloratadine 5 mg in an immediate-release outer coating and pseudoephedrine sulfate 240 mg in a sustained-release matrix core for once daily dosing. The PSE extended release tablet cores used in Clarinex-D® 24 Hour Tablets are identical in composition and shape to the tablet cores used in the current commercial Claritin-D® 24 Hour tablets. The tablets are light blue, oval-shaped, with a trade name branded in black ink on one side.

The chemical name of the product is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine & benzenemethanol, a-[1-(methylamino)ethyl]-,[S-(R*,R*)]-,sulfate(2:1) (salt).

There are a number of CMC issues for this application, which are discussed in depth is Dr. Prasad's review. The two primary issues of concern are the lack of in-process controls for the application of the desloratadine 5 mg layer and poor stability of the drug product when exposed to heat.

Since these temperatures are common in everyday life, the result will likely be labeling limitations and requirements for storage of the drug product. However, the exact requirements have not been worked out as of the completion of this review.

3.2 Animal Pharmacology/Toxicology

The application contains no new, additional nonclinical information on either of the active ingredients, desloratadine or pseudoephedrine. The applicant refers to NDA 21-165 (desloratadine tablets) for the nonclinical developmental program of desloratadine. Under NDA 21-165 and as a phase-4 commitment, the sponsor has completed a 2-year carcinogenicity study of desloratadine in mice (Study #97255 that was submitted on November 13, 2003. The review team will complete the review of the study in the current review cycle of the NDA 21-605. The data from the above study is significant for the safety evaluation of the currently proposed drug product. The sponsor's currently proposed labeling for the Clarinex D-24 Hour did not mention the study and the sponsor was advised in the 75-day filing letter to update the labeling to include the study results. Please see Dr. Pei's review for further details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The applicant's submission contains five clinical pharmacology studies and 2 clinical studies. These studies are summarized in Table 4.2. Additional information obtained from the INDs and NDAs for other desloratadine products were used for this review. FDA sent a fax to the applicant on September 23, 2004 requesting a safety update including a literature review and review of worldwide postmarketing adverse event reports for single ingredients desloratadine and pseudoephedrine since the approval of Clarinex® tablets on December 21, 2001. The safety update was received via electronic document on December 2, 2004.

4.2 Tables of Clinical Studies

The following tables summarizes the two clinical studies (P01875 and P01884) (Table 1) as well as the five failed clinical pharmacology studies (Table 2) that Schering submitted to support the Approval of Clarinex-D® 24 Hour extended-relief tablets.

Of the five clinical pharmacology studies, three (P00439, P00441, and P00884) evaluated the pharmacokinetics (PK) and bioequivalence (BE) of the to-be-marketed 5 mg / PSE 240 mg formulation, and the remaining two clinical pharmacology studies evaluated a DL 6 mg / PSE 240 mg formulation. None of the clinical pharmacology studies were given an in-depth clinical review.

Table 1. Summary Clinical Studies

Study	Study Type / Design	Treatment Groups	Batch Number+	Ages	N (M, F)	Race
P01875	15 day, MC, R, DB, DD, AC, PG, Efficacy and Safety in SAR patients	DL D-24 (5 mg/PSE 240 mg) DL D-24 AF (5 mg/PSE 240 mg) DL 5 mg PSE 240 mg (extended release)	**75882-056*** 76466-073 0700032 75882-061	12-78	1495 527 M 968 F	1180 C 161 B 2 AI 29 A 112 H 11 O
P01884	15 day, MC, R, DB, DD, AC, PG, Efficacy and Safety in SAR patients	DL D-24 (5 mg/PSE 240 mg) DL D-24 AF (5 mg/PSE 240 mg) DL 5 mg PSE 240 mg (extended release)	**75882-056*** 76466-073 0700032 75882-061	11-78	1357 516 M 841 F	1080 C 120 B 2 AI 37 A 107 H 11 O

* In the CMC section for the investigational formulations used in Protocols P01875 and P01884 [Vol. 1.1, Section 3.D.2, p.36], Batch Number 76466-068, a formulation containing DL 6 mg/PSE 240 mg [Vol. 1.1, Section 3.D.2, p. 25-26] is listed as a formulation being used; however, the study report synopses for these two protocols [Vol. 1.1, Section 3.H., p.15 and 18] indicate that only formulations containing DL 5 mg/PSE 240 mg (Batch Numbers 75882-056 and 76466-073) were used [Vol. 1.1, Section 3.D.2, p. 17-18 and p. 27-28].

+ Batch number **75882-056** is the proposed commercial formulation

Sources: Section 3H, page 9, summary.pdf; Section 4C, page 21, invest.pdf

Table 2. Summary of Clinical Pharmacokinetic and Bioavailability Studies

Study	Study Type	Treatment Groups	Batch Number+	Ages	N (M, F)	Race
Studies using DL 5 mg / PSE 240 mg						
P00439	OL, SD, 3-way crossover BE of DL and PSE	DL D-24 (5 mg/PSE 240 mg) DL 5 mg PSE 240 mg (immed release)	**75882-056** 38833-142 75059-114	31-45	36 M	7 C 11 B
P00441	OL, SD, 2-way crossover BA, Food Effect	DL D-24 (fed state) DL D-24 (fasted state)	**75882-056** **75882-056**	19-44	27 M 11 F	24 C 11 B 3 H
P00884	14 day, OL, MD, steady-state PK	DL D-24 (5 mg/PSE 240 mg)	**75882-056**	21-45	15 M 3 F	14 C 4 B

Study	Study Type	Treatment Groups	Batch Number*	Ages	N (M, F)	Race
Studies using DL 6 mg / PSE 240 mg						
P01813	OL, 3-way crossover single dose BE	DL 6 mg/PSE 240 mg DL D-24 (5 mg/PSE 240 mg) DL 5 mg + PSE 240 mg (extended release)	76466-068 **75882-056** 38833-142 + 75882-061	19-45	21 M 21 F	37 C 4 B 1 H
P01981	OL, 4-way crossover single dose BA to evaluate PSE core with altered *in vitro* dissolution rates	DL 6 mg/PSE 240 mg DL 6 mg/PSE 240 mg DL 5 mg/PSE 240 mg DL 5 mg/PSE 240 mg	54039-143 54039-144 54039-138 **75882-056**	18-45	13 M 7F	5 C 1 B 14 H

*Batch number **75882-056** is the proposed commercial formulation
Sources: Section 3H, page7, summary.pdf; Section 4C, page 20, invest.pdf

4.3 Review Strategy

For both efficacy and safety, the clinical review focused on the two clinical studies, P01875 and P01884. Only three of the five clinical pharmacology studies utilized the to-be-marketed product and were reviewed clinically for supporting safety data. Please see Dr Al Habet's Clinical Pharmacology and Biopharmaceutics Review for further details of these studies. Safety data supporting this application was reviewed in depth. These data integrated safety data from the clinical studies, clinical pharmacology studies, postmarketing adverse event reports, an evaluation of information from the clinical literature, and a safety update.

4.4 Data Quality and Integrity

Since both components in the combination product are approved and there is a significant amount of clinical experience with each, a DSI audit was not requested for the combination drug product.

A DSI audit for the clinical pharmacology studies was initially recommended at the filing and planning meeting on June 21, 2004 by the Biopharmaceutics team due to the questionable data integrity of Protocol P00439 in which two patients were noted to have measurable concentrations (14 ng/mL to 63 ng/mL) of PSE following the administration of DL. However, since Study P00439 was a failed study in that Clarinex-D 24 Hour tablets was found to lack bioequivalence to the desloratadine component in the combination product, the study is not crucial to support the approval of the drug product. Therefore, a DSI audit was not pursued.

A DSI audit for clinical Study P01875 was considered (but not pursued) at the mid-cycle review meeting due to protocol deviations for patient enrollment at study site P01875-07. A total of 4 (17%) out of 24 patients were randomized to treatments that were excluded from the final study protocol. Two patients received a DL D-24 formulation containing DL 6 mg and PSE 240 mg and two patients received placebo treatment. All four patients received 14

days out of 15 days of the full treatment duration even though they had visits at day 8 and the protocol deviation was not discovered and corrected at that time. A DSI audit was not pursued since only 4 out of the total 1495 patients enrolled at 47 sites for this study were involved, the 4 patients were excluded from the efficacy analyses, the efficacy results for the center were not significantly different from those for the rest of the study, as shown in Table 3. Therefore, it was felt that any irregularities at this center would not impact upon the regulatory decision for the NDA.

Table 3. Site P01875-07 Efficacy Data (Protocol deviation in 4 of 24 patients)

Treatment Group	N	Baseline	Change from Baseline (Days 1-15)	Pairwise Comparisons v. DL D-24
			LS Mean* (%)	Difference
Total Symptom Score (Excluding Nasal Congestion) Mean AM/PM PRIOR 12 hours				
DL D-24	5	16.19	-4.97 (-30.6)	
DL	4	15.90	-1.52 (-8.7)	-3.45
PSE	5	17.18	-3.44 (-24.6)	-1.53
Nasal Stuffiness/Congestion Mean AM/PM PRIOR 12 Hours				
DL D-24	5	2.82	-0.42 (-14.7)	
DL	4	2.86	-0.15 (-5.2)	-2.71
PSE	5	2.85	-0.86 (-30.3)	-1.99

Source: Section 6 Clinical, Study P01875, Table 14.1.2, p 145-6, P01875.pdf

On November 5, 2004, the Division informed Joanne Rhoads of the Division of Special Investigations of our concerns regarding study site P01875-07. She informed us that the investigator, [redacted] had 27 INDs under various divisions. In addition, she noted that study site P01875-17 was investigated in April, 2004, in response to two routine PDUFA assignments, one for the Division of Special Pathogen and Immunologic Drug Products (HFD 590) and another for the Division of Pulmonary and Allergy Drug Products (HFD 570) for [redacted]). Both inspections were classified as No Action Indicated (NAI) and no 483s were issued.

4.5 Compliance with Good Clinical Practices

The Applicant states that the study was conducted in compliance with good clinical practices according to FDA regulations and in compliance with the institutional review board regulations under 21 CFR 56 and the informed-consent regulations under 21 CFR 50. Written informed consent was obtained from each subject prior to participation in the study. There were no major protocol violations noted in the clinical studies that would affect the outcome of the efficacy and safety results. [clinstat\8k.pdf, page 1-3]

4.6 Financial Disclosures

The following items were included in this submission:

- Form FDA 356h [Volume 1.1, page not numbered]
- Debarment certification [other.pdf, Section 16, page 1]
- Financial disclosure statement Form FDA 3455 for each clinical investigator [other.pdf, Section 19, pages 1-30]

The applicant provided adequate disclosure of financial interests of the clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. Only one investigator) had a significant equity of interest in Schering Plough stock in the amount of approximately $403,500. Study center participated in Study and enrolled patients of the total randomized for Study from centers. Review of the primary efficacy (Table 4) as well as safety data for this study site indicated that patients at site did not have significantly different efficacy and safety results compared to the overall results of the clinical study that would raise questions about the integrity of the data.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology program for DL D-24 (SCH 483) comprised five open-label studies in 154 healthy volunteers, as summarized in Table 2. Desloratadine is a long-acting tricyclic histamine antagonist with selective H_1-receptor histamine antagonist activity. It is the major active metabolite of loratadine. Desloratadine appears to exhibit less first-pass metabolism and a longer plasma elimination half-life than loratadine. Pseudoephedrine is a decongestant recognized and monographed as GRAS and GRAE.

5.1 Pharmacokinetics

A clinical development program was undertaken because bioequivalence study P00439 failed to demonstrate bioequivalence between the to-be-marketed DL D-24 (DL 5 mg / PSE 240 mg) formulation and the individual component desloratadine 5 mg. A second study (P01813) demonstrated that a DL 6 mg / PSE 240 mg formulation was in fact bioequivalent to the individual components using DL 5 mg plus extended-release PSE 240 mg. Pertinent bioequivalence studies are briefly discussed below. Please see Dr Al Habet's Clinical Pharmacology and Biopharmaceutics Review for further details of these studies.

5.1.1 Study P00439

Study P00439 was an open open-label, single-dose, randomized, 3-way crossover bioequivalence study comparing the to-be marketed DL D-24 (DL 5 mg / PSE 240 mg) formulation, DL 5 mg (Clarinex), and immediate release PSE 240 mg. The study was performed under fasted conditions. The study was conducted in 36 healthy men (12 Caucasians and 24 Blacks) between the ages of 21 and 45 years of age (mean = 39.3 years). Subjects were housed at the study site within 12 hours prior to each treatment (Day -1) until after their 120-hour sample was drawn. Blood samples (approximately 10 mL) were taken immediately before dosing (0 hours) 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 for plasma DL, 3-OH DL, and PSE levels. A minimum washout period of ten days separated each treatment period. Safety endpoints reported included adverse events. There were no withdrawals from the study. Eighteen of 36 subjects enrolled reported at least one AE. The most frequent AE was headache. There were no SAEs.

In this study, the desloratadine in the DL D-24 was not bioequivalent to desloratadine from Clarinex 5 mg: the 90% confidence intervals (CI) for DL and 3-OH did not meet the 80%-125% bioequivalence guidelines for both Cmax and AUC(tf) values. However, the CI (82%-92%) of 3-OH DL for AUC(I) did meet the 80%-125% bioequivalence guidelines. Following the administration of the DL D-24 tablet, the DL and 3-OH DL C_{max} and AUC values were approximately 15%-20% less than those observed following administration of the DL 5 mg tablet.

Despite this finding, the Applicant carried forward the DL-D-24 formulation (Batch 75882-056) used in this study, and conducted two Phase 3 clinical studies, P01875 and P01884, to support the efficacy of DL D-24 as the to-be-marketed formulation.

Of note, in this study two patients were noted to have measurable concentrations (14 ng/mL to 63 ng/mL) of PSE following the administration of DL. Since the Division felt that the data from these two patients would not affect the regulatory decision for this drug product, a DSI audit was not pursued.

5.1.2 Study P01813

Study P01813 was a bioequivalence study comparing the to-be-marketed DL D-24 (5 mg / 240 mg) formulation, a formulation of DL-D 24 containing DL 6 mg / PSE 240 mg, and DL 5 mg plus concomitantly administered PSE 240 mg extended-release tablets. The study was an open-label, randomized, single dose, three-way crossover design, conducted in 42 healthy male (21) and female (21) subjects between the ages of 19 and 45 years (mean = 35.8 years). Thirty-seven subjects were Caucasians, four were Black, and one was Hispanic. The study was performed under fasted conditions. Patients were housed at the study site within 12 hours prior to each treatment (Day -1) until after their 120-hour sample was drawn. Blood samples (approximately 10 mL) were taken immediately before dosing (0 hours) 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 for plasma DL, 3-OH DL, and PSE levels. A minimum washout period of 10 days separated each treatment period. There were no withdrawals from the study. Safety endpoints reported included adverse events. Twenty-one of 42 subjects reported at least one treatment-emergent AE. There were no SAEs.

Following the administration of the DL D-24 (5 mg / 240 mg) formulation, the DL and 3-OH DL C_{max} values were approximately 15% less than those observed following the administration of the DL 5 mg tablet. For the desloratadine component, the 6 mg / 240 mg formulation was bioequivalent to the DL 5 mg tablet based on both Cmax and AUC values. Relative to the PSE 240 mg tablet, both the 5 mg / 240 mg and the 6 mg / 240 mg formulations met the 80%-125% bioequivalence limit for both C_{max} and AUC values. Therefore, it was determined that a formulation of DL D-24 containing DL 6 mg and PSE 240 mg was bioequivalent to the approved DL 5 mg (Clarinex 5 mg tablet) based on both Cmax and AUC values. The DL-D-24 formulation containing DL 5 mg and 240 mg PSE used in this study was carried forward to the two Phase 3 clinical studies and is the to-be-marketed formulation.

5.1.3 Study P01981

Study P01981 was a bioavailability/bioequivalence study to evaluate the pseudoephedrine in the DL D-24 (5 mg/240 mg) formulation used in the clinical studies relative to pseudoephedrine sulfate from other DL D-24 formulations that were composed of cores modified to demonstrate in vitro dissolution rates that were either slow (5 mg / 240 mg), fast (6 mg / 240 mg), or very fast (6 mg / 240 mg) in comparison to the dissolution rate of the standard extended release core. The study was an open-label, randomized, single-dose, four-way crossover design, conducted in twenty healthy subjects (13 males and 7 females) between the ages of 18 and 45 years (mean = 36 years). Five subjects were Caucasian, one was black, and 14 were Hispanic. Subjects received one of four treatments containing a combination of either DL 5 mg/PSE 240 mg (standard or slow batch) or DL 6 mg/PSE 240 mg (fast or very fast batch). Blood samples (approximately 7 mL) were taken immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, and 48 hours post dose for plasma DL, 3-OH DL, and PSE levels. Subjects were confined to the study site until after their 48-hour blood sample was collected. A washout period of 7 days separated

each treatment period. Safety endpoints included adverse events. There were no withdrawals from the study. Ten of 20 subjects enrolled reported at least one AE. The most common AE was headache. There were no SAEs. [hpbio\bio\P01981.pdf]

The applicant states that relative to the reference standard (Treatment A containing the standard extended release PSE core), the slow and fast formulations met the 80%-125% bioequivalence guideline for C_{max}, AUC(tf), and AUC(I) values of PSE. The very fast formulation met the guidelines based on AUC, but not for Cmax values of PSE. One of the experimental DL-D-24 5 mg / PSE 240 mg formulations (Batch 75882-056) used in this study was carried forward to the two Phase 3 clinical studies and is the to-be-marketed formulation.

5.1.4 Study P00441

Study P00441 was a bioavailability food-effect study that compared the to-be-marketed formulation of DL D-24 (5 mg / 240 mg) administered under both fasting and fed conditions. The study was an open-label, randomized, single dose, two-way crossover design, conducted in 38 healthy subjects (27 males and 11 females) between the ages of 19 and 44 years (mean = 29.5 years). Twenty-four subjects were Caucasian, 11 were Black, and three were Hispanic. Subjects were fasted overnight for 10 hours and then randomized to either (Treatment A) receive study drug in the fasted state and continue fasting for 4 hours or (Treatment B) receive study drug after a standardized high-fat, high-caloric breakfast. Blood samples (approximately 10 mL) were taken immediately before dosing (0 hours) 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 for plasma DL, 3-OH DL, and PSE levels. Subjects were housed at the study site within 12 hours prior to each treatment (Day -1) until after their 120-hour sample was drawn. A minimum washout period of 10 days separated each treatment period. Safety endpoints included adverse events. There were two withdrawals from the study after treatment Period 1 for reasons unrelated to study drug. Four of 37 subjects reported at least one AE. There were no SAEs. [hpbio\bio\P00441.pdf]

The applicant states that the plasma profiles under fasted and fed conditions were similar for DL, 3-OH DL, and PSE. The 90% CIs of AUC(I) and C_{max} values for DL, 3-OH DL, and pseudoephedrine under a fed condition relative to a fasted condition met the 80%-125% bioequivalence guideline. Based on these data, the applicant concluded that a high-fat meal had no effect on the bioavailability of DL, 3-OH DL, or PSE levels. The DL-D-24 formulation (Batch 75882-056) used in this study was carried forward to the two Phase 3 clinical studies and is the to-be-marketed formulation.

5.1.5 Study P00884

Study P00884 was a 14-day open-label multiple-dose study to characterize the steady-state pharmacokinetics of the to-be-marketed formulation of DL D-24. The study was conducted in 18 healthy subjects (15 males and 3 females) between 21 and 45 years of age (mean = 32.5 years). Fourteen were Caucasian and four were Black. Subjects received study drug each

morning (8 AM) for 14 days. An overnight fast (approximately 10 hours) was required prior to the AM dose only on the morning of Day 14 and no food was allowed for four hours after this dose. Samples were taken immediately before dosing (0 hours) on Days 1, 10, 11, 12, and 13, and then on Day 14 at the following times: 0 (pre-dose) 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours post dose. Subjects were confined at the study site until the 24-hour post-Day-14 study-related procedures were obtained. A minimum washout period of 10 days separated each treatment period. Subject 2 withdrew from the study on Day 5 for reasons unrelated to study treatment. Safety endpoints included adverse events. Eight of 18 subjects enrolled reported at least one AE. The most common AEs were dizziness and somnolence. There were no SAEs. [hpbio\hupharm\P00884.pdf]

The applicant states that steady state conditions of DL and 3-OH DL were attained on Day 12 following repeated administration of DL D-24. After reaching steady-state, the average C_{max} of DL was 2.44 ng/mL at a mean T_{max} of 3.68 hours. The average C_{min} was 0.788 ng/mL. The mean steady-state $AUC_{(0\text{-}24\ hr)}$ value was 34.8 ng/mL. For 3-OH DL, the mean C_{max} value of 1.56 ng/mL was reached at a mean T_{max} of 4.65 hours, close to that of the parent compound. The average C_{min} was 0.689 ng/mL. The mean steady-state $AUC_{(0\text{-}24\ hr)}$ value was 25.7 ng/mL. Steady-state conditions of PSE were attained by Day 10 of multiple-dose administration of DL D-24 tablets. The mean PSE C_{max} value of 523 ng/mL was reached at 6.65 hours. The average C_{min} was 1.61 ng/mL. The mean steady-state $AUC_{(0\text{-}24\ hr)}$ value was 8795 ng/mL. The DL-D-24 formulation (Batch 75882-056) used in this study was carried forward to the two Phase 3 clinical studies and is the to-be-marketed formulation.

5.2 Pharmacodynamics

No pharmacodynamic studies were performed for this NDA.

5.3 Exposure-Response Relationships

Please see above Clinical Pharmacology discussion of the propose drug product.

6 INTEGRATED REVIEW OF EFFICACY

The proposed indications for Clarinex-D® 24 Hour extended-release tablets are for the relief of the nasal and non-nasal symptoms of seasonal [redacted] allergic rhinitis, including nasal congestion.

The Applicant initially planned a 505(b)(2) submission, relying on data from previously approved desloratadine 5 mg tablets (NDA 21-165 and NDA 21-312), monographed pseudoephedrine, and five clinical pharmacology studies conducted in a total of 154 healthy subjects. However, Study P00439, a pilot open-label, single-dose, randomized, 3-way crossover study failed to demonstrate bioequivalence of desloratadine in the to-be marketed clinical formulation of Clarinex-D® 24 Hour to the individual component Clarinex 5 mg. A separate study (Study P01813) demonstrated that it would take a formulation of this drug product containing 6 mg of desloratadine and 240 mg of pseudoephedrine to produce

systemic exposures of desloratadine comparable to the approved Clarinex 5 mg drug product. Because of the lack of bioequivalence, a clinical development program was required and was undertaken.

Two clinical studies, P01875 and P01884, were performed to support the clinical efficacy (and safety) of Clarinex-D® 24 Hour tablets for the proposed indications. These two studies do provide clinical support for the indication of seasonal allergic rhinitis. However, systemic exposure with 5 mg desloratadine in this long-acting combination was less than with approved desloratadine 5 mg formulations. The lower clinical exposure with the long-acting formulation has implications for the clinical program from an efficacy perspective. Only seasonal allergic rhinitis patients were studied, and the clinical studies were both of two weeks duration.

The FDA statistical reviewer, Ted Guo, was able to confirm the sponsor's primary efficacy findings.

Of note, a second formulation was included in these studies, a so-called DL D-24 AF formulation. This formulation was not found to be statistically significant for relieving the overall nasal/non-nasal symptoms, will not be marketed, and is therefore not discussed in this section of the review.

6.1 Indication for the treatment of Seasonal Allergic Rhinitis

6.1.1 Methods

Clinical data from two clinical efficacy and safety studies, Studies P01875 and P01884 were used in the efficacy review to support the proposed indication. These two studies were conducted because the clinical pharmacology program failed to demonstrate bioequivalence of the drug product to the individual reference components. Refer to Section 4.1 for sources of clinical data.

6.1.2 General Discussion of Endpoints

Symptom scoring and all primary and secondary efficacy variables, endpoints, and comparisons were the same in both studies. In both studies, nasal and non-nasal symptoms of SAR, overall condition of SAR, and response to treatment were scored for efficacy assessment. Patients (or caregivers) scored symptoms of SAR twice daily throughout the study. Scoring was based on the patient's status over the previous 12 hours and also at instantaneous time points before dosing and 12 hours after dosing. Overall condition of SAR was scored by physicians and by patients at each screening and each treatment visit.

Instantaneous (NOW) and reflective (PRIOR) symptom scoring included evaluation of four nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and four non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate), each scored according to the following scale: 0=none, 1=mild, 2=moderate, and 3=severe. The total symptom score was the summation of the eight individual symptom scores.

For the antihistamine component, the primary efficacy variable was the change from baseline in average AM/PM 12-hour reflective total symptom score excluding nasal stuffiness and congestion. For the decongestant component, the primary efficacy variable was the change from baseline in average AM/PM 12-hour reflective nasal stuffiness/congestion score. For both primary variables, primary time point was the average over the 15 days of treatment. The primary comparisons for the antihistamine component were DL D-24 (and DL D-24 AF) versus PSE. The primary comparisons for the decongestant component were DL D-24 (and DL D-24 AF) versus DL. The primary variables were analyzed using a two-way analysis of variance (ANOVA), which extracted sources of variation due to treatment and center. All efficacy analyses were based on what the applicant termed an "All Randomized Subject" population, which in fact was a modified intent-to-treat (MITT) population that included all patients randomized (ITT) who had Baseline data plus some post-baseline efficacy data for the variable analyzed [3H, p 168, summary.pfd], later defined in the applicant's ISE as any patient randomized who had at least one dose of study drug. Since there were two independent sets of comparisons (DL D-24 versus its components, and DL D-24 AF versus its components), the alpha level was set to 0.025 for each pair of comparisons based on Bonferroni criteria to control the overall alpha level of 0.05. Since both primary comparisons (for the antihistamine and decongestant components) had to be statistically significant at an alpha level of 0.025, no adjustment of the significance level was performed for each of these individual comparisons [3H, p 160, summary.pfd]. For the secondary comparison of interest, the end-of-dosing interval AM instantaneous score, the Division arbitrarily applied the same 0.025 alpha level of significance.

For each study, efficacy variables were also analyzed for each of the first 4 days of treatment and the average over each of Week 1 and Week 2. Secondary variables included: total (with nasal congestion), total nasal (with and without nasal stuffiness/congestion), total non-nasal, and individual mean AM/PM PRIOR 12-hour symptom scores expressed as a change from baseline. The total, total nasal, total non-nasal, and individual symptoms scores were also analyzed for the following: average AM/PM NOW, AM and PM PRIOR 12 hours, and AM and PM NOW.

The variables and endpoints chosen by this applicant are typical for allergic rhinitis studies and have been used by other applicants previously to provide a reasonable assessment of clinical benefit. More frequently the total nasal symptom score has been used as a primary endpoint in previously approved NDAs for seasonal and perennial allergic rhinitis. In this case, non-nasal symptoms were also included. Based on the combination drug policy, it is reasonable for the applicant to have separated out the nasal stuffiness/congestion score for evaluation of the contribution of the decongestant component of the drug combination.

However, the Division does not specifically separate symptom scores into nasal and non-nasal categories, as did the Applicant. A drug approved for allergic rhinitis is expected to improve a wide variety of symptoms of the disease.

6.1.3 Study Design

Both clinical studies were 15-day, multi-center, randomized, double-blind, double-dummy, active-controlled, parallel-group, multiple-dose, efficacy and safety studies of 2 formulations of DL D-24 versus its individual components (5 mg DL and 240 mg PSE). The studies were originally designed with four treatment arms, including DL D-24 QD, DL D-24 6/240 mg QD, DL 5 mg QD, PSE 240 mg QD. However, the DL D-24 6/240 mg (tablet composed of 6 mg DL and 240 mg PSE) and placebo dose groups deleted in the final protocol, and the DL D-24 alternate formulation was substituted.

Reviewer's Note: In several locations within the application, the applicant states that there were six arms, including a placebo arm. This is simply incorrect, as a careful review of the protocols and protocol amendments will show. While a placebo was used in the studies, it was used to provide a double-dummy for the various treatment arms.

A total of 2852 patients, ages 11 to 78 years of age, with SAR were randomized at multiple sites in the United States. In both studies, patients were screened for enrollment eligibility, including a two-year documented history of fall SAR and a positive skin test to an appropriate fall seasonal allergen within the previous 12 months. Patients had a complete medical history and physical examination, 12-lead EKG, and clinical laboratory evaluations (chemistry, hematology, serum pregnancy test), and skin test (if appropriate) prior to entering a screening period. In addition to recording twice-daily (AM and PM) instantaneous (NOW) and reflective (PRIOR) scores for nasal and non-nasal symptom scores throughout the baseline and treatment periods, patients recorded dosing information, concomitant medication use, and adverse events on a diary card. Patients were required to have symptoms at screening and during the baseline period. In order to qualify for treatment, patients were required to have a minimum score of 42 for total nasal symptoms, a minimum score of 35 for total non-nasal symptoms, and a minimum score of 14 for each of the individual symptoms of nasal stuffiness/congestion and rhinorrhea, based on reflective (PRIOR 12 hours) scores for the 3 days prior to Baseline and the AM of the Baseline visit. On-treatment clinic visits were held on Day 8 and Day 15 (endpoint). Diary cards were evaluated at all clinic visits. Joint physician-patient assessments for the overall condition of seasonal allergic rhinitis were assessed at Screening and Day 8 and Day 15, and the response to therapy was evaluated at Day 8 and Day 15.

Patients were appropriately blinded to minimize bias and the clinical studies included a prospective statistical analytic plan with proposed endpoints. There were no placebo or control groups in the two clinical studies; however, the study design provided for an adequate comparison of Clarinex-D 24-HOUR tablets compared to the individual components. Both studies were designed to have a power of 90% to detect a clinically meaningful difference

between DL D-24 and the other treatment groups (DL D-24 AF, DL, PSE) for the primary efficacy variable, using a two-tailed α-level of 0.025. (See Section 6.1.2 above)
The target enrollment was 350 patients per treatment group in each study. Actual enrollment was higher is Study P01875 (Table 21) and slightly lower in Study P01884 (Table 30). The study design was adequate and well-controlled and was able to provide a reasonable assessment of clinical benefit to patients and to support the efficacy for the treatment of nasal and non-nasal symptoms of seasonal allergic rhinitis. Details of the study procedures may be found in Appendix 10 of this review.

6.1.4 Efficacy Findings

A total of 2852 patients were randomized and received at least one dose of study drug, with 708 patients exposed to the to-be-marketed formulation. The two clinical studies were well-controlled and of adequate duration, 15 days, to assess the efficacy for the treatment of symptoms of seasonal allergic rhinitis. Results of the primary efficacy variable are shown in the table below. In both studies, Clarinex-D 24 Hour Tablets (DL D-24) consistently demonstrated a statistically significant antihistaminic and decongestant effect over the individual mono-components (Table 5), thereby satisfying the combination drug policy of added benefit. The FDA statistical reviewer was able to confirm the sponsor's primary efficacy findings and the secondary findings related to end-of-dosing interval, as shown in Table 5 and Table 6.

It should be noted that while the combination beat PSE for the antihistamine effect and DL for the decongestant effect, the results are not at all pure. The combination also beat PSE for the decongestant effect and DL for the antihistamine effect. Reviewer's interpretation: there is significant crossover in relief on patient reported symptoms by both drugs in the combination and the patient reported symptom scores for allergic rhinitis are simply not sensitive enough to elucidate these differences.

Response to treatment was examined by age, sex, and race. Overall in both studies, DL D-24 was numerically more effective than PSE in reducing mean AM/PM PRIOR 12 hour total symptom scores excluding nasal congestion in both sexes. Similar results were seen among age and race subgroups for both studies. Due to small numbers of patients in the Asian, American Indian, and other ethnic subgroups, it is not possible to draw meaningful conclusions from these differences. Only 8 patients ≥65 years of age were exposed to the to-be-marketed formulation in the clinical studies.

When the end-of-dosing effect (the drug effect after 24 hours of taking the dose as evidenced by the 15-day mean AM NOW symptom scores) was examined (Table 6), Clarinex-D 24 Hour Tablets demonstrated a statistically significant decongestant effect throughout the treatment period for both studies (p-values: <0.001 in Study P01875, 0.001 in Study P01884), but did not consistently demonstrate superiority for the antihistamine component in the relief of total nasal/non-nasal symptoms, excluding nasal congestion (p-values: 0.001 in Study P01875, 0.028 in Study P01884). At all other timepoints (Day 2, Day 3, Day 4, Days 2-8) except at Days 9-15 (p=0.193), the p values were <0.025. This raised some concern that

the effect may not last up to 24 hours after initial dosing, which is the proposed dosing regimen. One may postulate that this finding may be related to the lower systemic exposure to desloratadine in the DL D24 formulation. While the clinical interpretation in this case is that of a meaningful benefit to the patient with SAR, [redacted]

[redacted]

Table 5. ISE: Primary Efficacy: Mean AM/PM PRIOR 12 Hours, D 1-15, MITT*

Treatment Group	Baseline		Change from Baseline		Pairwise Comparisons vs. DL D-24	
	N[a]	LS Mean[b]	LS Mean[b]	%[c]	Δ	P-value[d]
Total Symptom Score (Excluding Nasal Congestion)						
Study P01875						
DL D-24	372	15.01	-6.09	-38.8		
DL	369	14.71	-5.10	-33.5	-0.99	0.001
PSE	377	15.08	-5.08	-32.4	-1.01	**0.001**
Study P01884						
DL D-24	333	14.84	-5.71	-37.4		
DL	337	15.06	-4.78	-30.8	-0.93	0.003
PSE	337	15.03	-4.95	-32.0	-0.76	**0.015**
Nasal Stuffiness/Congestion						
Study P01875						
DL D-24	372	2.57	-0.90	-33.4		
DL	369	2.55	-0.74	-28.0	-0.16	**0.001**
PSE	377	2.56	-0.78	-28.6	-0.12	0.009
Study P01884						
DL D-24	333	2.56	-0.85	-32.3		
DL	337	2.57	-0.65	-24.8	-0.20	**<0.001**
PSE	337	2.54	-0.70	-27.1	-0.15	0.002

* The MITT population included all patients randomized (ITT pop) who had Baseline data plus some post-baseline efficacy data for the variable analyzed (i.e. at least one dose of study drug). [3H, p 168, summary.pfd]

[a] Calculation of mean Baseline values included all patients with Baseline and Endpoint data; calculation of mean post Baseline values included all patients with both Baseline and post Baseline data at the specified time point(s).

[b] LS Means are obtained from the two-way ANOVA model with treatment and site effects

[c] Mean percent changes are raw means

[d] Primary comparison of interest is **bolded**.

Note: Results for this set of analyses were verified by the Division's statistical reviewer, Dr. Ted Guo

Source: p01875.pdf, Table 1, page 226 ; Table 5, page 26 ; clinstat\p01884.pdf, Table 12, page 68 ; Table 13, page 71

Table 6. ISE: Secondary Efficacy: End-of-Dosing Mean AM NOW, D 2-15, MITT*

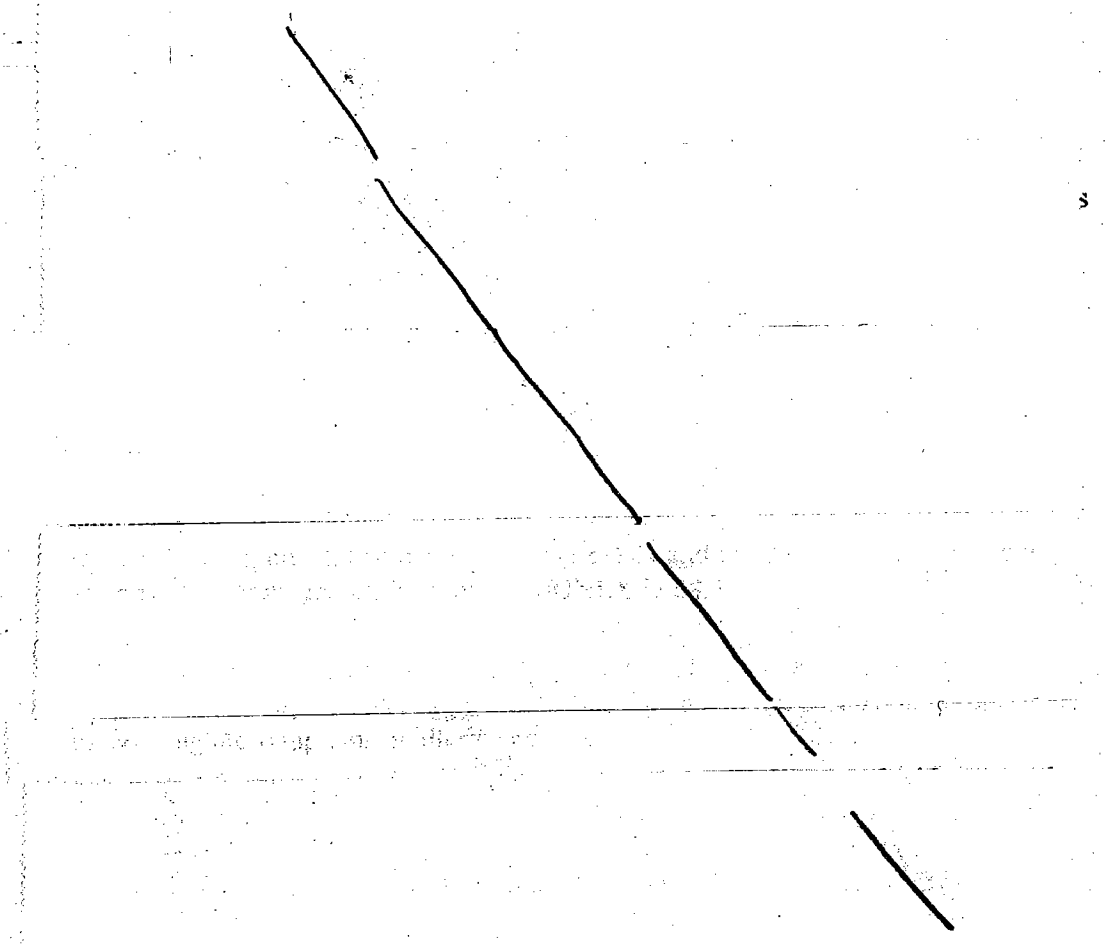
Treatment Group	Baseline		Change from Baseline		Pairwise Comparisons vs. DL D-24	
	N	LS Mean	LS Mean	%	Δ	P-value
Total Symptom Score (Excluding Nasal Congestion)						
Study P01875						
DL D-24	372	14.65	-5.57	-36.6		
DL	367	14.61	-4.61	-30.2	-0.97	
PSE	371	14.79	-4.56	-29.2	-1.01	0.001
Study P01884						
DL D-24	333	14.76	-5.34	-34.4		

Treatment Group	Baseline		Change from Baseline		Pairwise Comparisons vs. DL D-24	
	N	LS Mean	LS Mean	%	Δ	P-value
DL	337	14.93	-4.48	-27.8	-0.86	
PSE	335	15.14	-4.65	-29.2	-0.69	0.029
Nasal Stuffiness/Congestion						
Study P01875						
DL D-24	372	2.55	-0.80	-30.0		
DL	367	2.57	-0.63	-22.6	-0.17	<0.001
PSE	371	2.58	-0.69	-25.0	-0.11	
Study P01884						
DL D-24	333	2.56	-0.75	-27.6		
DL	337	2.57	-0.59	-21.1	-0.16	0.001
PSE	335	2.58	-0.61	-22.3	-0.14	

* The MITT population included all patients randomized (ITT pop) who had Baseline data and at least one dose of study drug.
Note: Results for this secondary set of analyses were verified by the Division's statistical reviewer, Dr. Ted Guo

Source : Section 3H, Table 6, p 176 ; Table 7, p 178, summary.pdf; Section 8.G.3.4, Table 7, ise.pdf

6.2



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6.3 Clinical Microbiology

Because there was no need for a clinical microbiology review, a clinical microbiology review was not conducted for this NDA application.

6.4 Efficacy Conclusions

A clinical program was performed because the desloratadine in Clarinex-D 24 Hour extended release tablets failed to show bioequivalence to the individual desloratadine 5 mg mono-product (i.e. Clarinex 5 mg) in two bioequivalence studies. Study P00439 failed to demonstrate bioequivalence of desloratadine in the DL D-24 (desloratadine 5 mg / pseudoephedrine 240 mg) combination to Clarinex 5 mg, with lower systemic exposure to desloratadine with this combination than with Clarinex. Study P01813 subsequently determined that a formulation of DL D-24 containing DL 6 mg (and PSE 240 mg) was bioequivalent to Clarinex 5 mg based on both Cmax and AUC values. The clinical implication is that some patients who are switched from the mono-product to the combination product in order to add treatment with a decongestant may suffer from the loss of antihistamine exposure and not be adequately treated. For those patients, it would be preferable to continue use of the Clarinex 5 mg mono-product and add an oral decongestant mono-product as needed.

Nevertheless, this review found that the clinical data are adequate to support the efficacy claim for Clarinex-D 24 Hour tablets QD for the treatment of SAR in patients 12 years of age and older. Studies P01875 and P01884 were adequately performed, with adequate representation of age groups and sex. The DL D-24 to-be-marketed formulation satisfied the combination drug policy by demonstrating a consistent statistically significant effect on relieving total nasal and non-nasal symptoms, excluding nasal stuffiness/congestion compared to PSE for antihistamine component, and a statistically significant effect on relieving nasal stuffiness/congestion compared to DL alone for the decongestant component.

While instantaneous AM scoring at the end of the dosing interval supported use of the PSE extended release core, the scores for the DL component were marginal for one of the two studies. This adds to the suspicion that the DL in this formulation is at the lower end of the clinically effective dose range but still adequate to support the proposed once-daily dosing for SAR patients.

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