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APPLICATION NUMBER:

21-313

MEDICAL REVIEW(S)

CLINICAL REVIEW

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

Executive Summary Section

Clinical Review for NDA 21-313

Executive Summary

I. RECOMMENDATIONS

A. Recommendation on Approvability

The Division generally recognizes that antihistamines and decongestants provide complementary benefits in the treatment of seasonal allergic rhinitis (SAR). Clarinex-D 12 HOUR Extended Release Tablet (DL D-12) is composed of an antihistamine (desloratadine) and a decongestant (pseudoephedrine). Pseudoephedrine is an accepted decongestant at the proposed dose (120mg BID). The data submitted with this application demonstrate that desloratadine, at the proposed dose (2.5mg BID), is effective in the relief of the symptoms of SAR, excluding nasal congestion. The treatment effect size is small, but statistically significant. The data also demonstrated efficacy of the pseudoephedrine component in the treatment of nasal congestion associated with SAR. The safety of DL D-12, including the adverse event profile, is comparable to that of its components.

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

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The Applicant must submit data that demonstrates the safety of the desloratadine exposures exhibited by subjects who are poor metabolizers. Once this data is submitted, the Division will determine whether approval is supported. No Phase 4 Studies or specific risk management steps would then be necessary.

II. SUMMARY OF CLINICAL FINDINGS

A. Brief Overview of Clinical Program

Clarinex-D 12 HOUR (DL D-12) is a bilayer tablet consisting of immediate release desloratadine 2.5mg and pseudoephedrine 120mg in a sustained release matrix. Desloratadine is an H₁

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receptor antagonist. Pseudoephedrine is an established sympathomimetic nasal decongestant. The proposed indication is for the relief of symptoms of seasonal allergic rhinitis (SAR) in adults and children 12 years of age and older. The proposed dose is 1 tablet by mouth BID.

In general, antihistamines are useful for treating many of the symptoms of seasonal allergic rhinitis with the exception of nasal congestion. Decongestants (e.g. pseudoephedrine) are useful for treating the nasal congestion component. The Division has previously recognized that, because antihistamines and decongestants offer complementary beneficial effects in the treatment of SAR, combination products consisting of an effective antihistamine and an effective decongestant are intrinsically rational. Therefore, in order to support approval of a combination product consisting of an antihistamine and a decongestant, it would be sufficient to establish the efficacy of the individual components and the absence of pharmacokinetic interaction between the components. The requirements of the Agency's combination drug policy (21 CFR 300.50) are not relevant for these specific combination products.

Pseudoephedrine 120mg BID is an established decongestant whose safety and efficacy are accepted. Pseudoephedrine 120mg BID is approved for the treatment of allergic rhinitis, both alone, and in combination with antihistamines. Therefore, the development program for DL D-12 was not required to establish the safety and efficacy of pseudoephedrine.

Desloratadine is not currently approved for use in the US. In addition to this NDA, the Applicant has submitted five other NDAs for the drug substance desloratadine. These NDAs are for Clarinex 5mg tablets (NDA 21-265; once-daily dosing for SAR), Clarinex 5mg tablets (NDA 21-297, once-daily dosing for chronic idiopathic urticaria), Clarinex 5mg tablets (NDA 21-363; once-daily dosing for allergic rhinitis, including perennial allergic rhinitis), Clarinex Syrup (NDA 21-300; pediatric indication), and Clarinex RediTabs (NDA 21-312). These NDAs are currently under review. NDA 21-165 has been determined to be approvable from the clinical perspective. Because desloratadine 2.5mg BID has not been approved for the treatment of SAR, the development program for DL D-12 must establish the efficacy of desloratadine 2.5mg BID in the treatment of SAR.

The clinical development program for DL D-12 consisted of five pharmacokinetic and bioavailability studies and two pivotal clinical safety and efficacy studies. The pharmacokinetic and bioavailability studies were performed to determine the appropriate formulation for the PSE core of the combination product, to determine the effect of food on the pharmacokinetics of DL and PSE, to examine for interactions between the components, and to examine the pharmacokinetics of DL and PSE after multiple dose administration. The two pivotal clinical trials were randomized, multicenter, double-blind, active-controlled, parallel group studies, which were conducted under identical protocols. In these 15-day studies, DL D-12 BID was compared to pseudoephedrine 120mg BID (PSE) and desloratadine 5mg QD (DL) in patients with SAR. The primary outcome variables were symptom assessments. A total of 1248 subjects were randomized and treated to one of the three treatment arms. This included 414 subjects treated with DL D-12, 412 subjects treated with DL, and 422 subjects treated with PSE. As

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mentioned above, desloratadine is the subject of five additional NDAs, including NDA 21-165, desloratadine 5mg tablets. In NDA 21-165, a total of 2346 subjects received desloratadine and 1044 subjects received placebo.

B. Efficacy

The clinical program for Clarinex-D 12 HOUR Extended Release Tablets (DL D-12) was designed to support a single indication, the relief of symptoms of SAR in adults and children 12 years of age and older. The two pivotal clinical trials submitted with this NDA support the use of DL D-12 for this indication. The program consisted of two pivotal Phase 3 studies that were performed under identical protocols (Study P00355 and Study P00362). The design and results of these studies are discussed in detail in Section XI, B of this review and an integrated discussion of the efficacy aspects of these studies is located in Section VI of this Review. These studies were randomized, double-blind, active-controlled, parallel group studies, each performed at 20 centers in the US. The three treatment groups were: desloratadine 5mg (DL) QD, pseudoephedrine (PSE) 120mg BID, and DL D-12 BID. A total of 598 subjects and 650 subjects were randomized in Study P00355 and Study P00362, respectively. In these studies, subjects 12 years of age and older, with at least a 2-year history of SAR, positive skin test to appropriate seasonal allergen, and clinical symptoms were enrolled. During the screening period (3-14 days) and throughout the 15-day treatment period, subjects recorded SAR symptoms (reflective and instantaneous) twice daily. The following eight symptoms were assessed: rhinorrhea, nasal congestion, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate. The first four were considered to be the nasal symptoms, and the latter four were considered the non-nasal symptoms. Symptoms were scored on a scale of 0-3 (0=none, 1=mild, 2=moderate, 3=severe). The primary efficacy variables were: 1) change from Baseline in mean AM+PM reflective symptom score excluding nasal congestion (for the antihistamine component) and, 2) change from baseline in mean AM+PM reflective nasal congestion score (for the decongestant component). The primary time point for both variables was the average over the 15-day treatment period. The primary comparison for the antihistamine component was DL D-12 versus PSE. The primary comparison for the decongestant component was DL D-12 versus DL. Instantaneous symptom scores were analyzed as secondary efficacy variables. Numerous other secondary efficacy variables were also assessed, including assessments of the "overall condition of SAR" and "response to test drug treatment," performed jointly by the subject and investigator. The studies were powered to detect a difference of 1.6 between study groups for the primary antihistamine efficacy comparison (DL D-12 vs. PSE). The ITT population was used in the efficacy analyses. The definitions of the ITT population provided in the protocol and study report differed slightly, but this difference is unlikely to have affected the interpretation of the study results (See section XI, B).

The rationale for the absence of a placebo group and for the choice of the primary efficacy comparisons is discussed in detail in Section VI of this Review. In brief, Division of Pulmonary and Allergy Drug Products has been willing to assume that antihistamines and decongestants provide complementary salutary effects in patients with allergic rhinitis. Therefore, approval of a proposed combination product comprised of an approved antihistamine and an approved

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decongestant would require only pharmacokinetic data establishing that the exposures for each component are equivalent when given separately and in combination. However, clinical data was required for this NDA because the Applicant has not demonstrated the efficacy of desloratadine at a dose of 2.5mg BID. Therefore, in order to support approval, the clinical studies submitted with this Application must establish that desloratadine 2.5mg BID is effective for allergic rhinitis. Thus, while the stated primary objective of these studies was to compare the efficacy of DL D-12 with that of its components, for the purposes of approval, the most important data from the studies is that which provides evidence of the efficacy desloratadine 2.5mg BID component of the combination product. The comparison intended to establish this is that of DL D-12 versus PSE, using the endpoint of the histamine-related symptoms of allergic rhinitis (total symptoms, excluding nasal congestion). Superiority on this endpoint would demonstrate that the desloratadine component of the combination product is effective. The second primary analysis, addressing the efficacy of the decongestant component (PSE) (DL D-12 versus DL, using the endpoint of nasal congestion) is less critical for the purposes of approval because PSE120 mg BID has previously been demonstrated to be effective in the treatment of nasal congestion. For this reason, the decongestant component comparisons will be discussed only briefly in this section. Further details regarding the decongestant comparisons are included in Section XI, B of this review.

(1) Clinical Trials: Primary Efficacy Results

In both studies, the demographic and baseline characteristics of the study subjects were similar across the three treatment groups. The majority of the subjects were female (61% -69%) and the majority were caucasian (79%-86%). Very few patients at either end of the age spectrum (<18yrs and ≥65yrs) were studied.

As shown in the table below, in both studies, DL D-12 was statistically more effective than PSE on the change from baseline average AM+PM reflective total symptom score, excluding nasal congestion. It should be noted that the differences that were demonstrated between the two groups (1.47 in Study P00355, and 1.37 in Study P00362) did not reach the magnitude that the study was powered to detect (1.6).

Antihistamine Comparison							
Total symptom score, excluding nasal congestion (reflective, AM+PM): Change from Baseline to Days 1-15							
	DL D-12			PSE			p-value
	N	Mean	%change	N	Mean	%change	
Study P00355	199	-6.54	-46.0%	197	-5.07	-35.9%	<0.001
Study P00362	213	-6.65	-43.0%	221	-5.28	-35.4%	<0.001

The results from both studies regarding the primary decongestant comparison (change from Baseline reflective nasal congestion score, DL D-12 vs. DL5) demonstrated that DL D-12 was superior to DL5.

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(2) Clinical Trials: Secondary Efficacy Results

The secondary reflective antihistamine comparisons of DL D-12 versus PSE included the change from Baseline in the reflective total symptom score, excluding nasal congestion, at Days 1-4 individually, Days 1-8, and Days 9-15. With the exception of the Day 1 comparison in Study P00355, DL D-12 was statistically superior to PSE at each of the time points in both studies.

Instantaneous symptom scores were collected as a means of assessing the end of dosing interval efficacy. The endpoint used to assess end of dosing interval antihistamine efficacy was the change from baseline to Days 1-15 AM+PM instantaneous total symptom score, excluding nasal congestion, comparing DL D-12 with PSE. As shown in the table below, in both studies, DL D-12 was statistically superior to PSE on this endpoint. These data support the proposed dosing interval.

End of Dosing Interval, Antihistamine Comparison							
Total symptom score, excluding nasal congestion (instantaneous, AM+PM): Change from Baseline to Days 1-15							
	DL D-12			PSE			p-value
	N	Mean	%change	N	Mean	%change	
Study P00355	199	-6.27	-45.1%	197	-4.92	-35.6%	0.001
Study P00362	213	-6.30	-42.1%	221	-5.28	-35.7%	0.010

Other secondary endpoints included numerous analyses of the subject-evaluated symptom scores. These included reflective and instantaneous assessments of total symptom scores, total symptom scores, excluding nasal congestion, and nasal congestion, which were recorded in the AM, the PM, and the AM+PM, at Days 1-4 individually, Days 1-8, Days 9-15, and Days 1-15. In addition, the joint subject/investigator evaluations of the overall condition of SAR and the therapeutic response were included among the secondary efficacy analyses. In both studies, the results of these secondary analyses support the conclusion that DL D-12 had statistically superior anti-histamine effects as compared with PSE, and statistically superior decongestant effects as compared with DL5. In regard to both the subject evaluated "overall condition of SAR," and the subject/investigator joint assessment of the "therapeutic response," DL D-12 was statistically superior to both DL5 and PSE in Study P00362. The differences between groups were not statistically significant in Study P00355.

(3) Efficacy Conclusions

The results of the two pivotal clinical studies support the conclusion that DL D-12 is effective in the treatment of SAR. As discussed above, the primary endpoints in the two pivotal studies were designed to demonstrate that DL D-12 was superior to PSE regarding antihistamine activity, and

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that DL D-12 was superior to DL5 regarding decongestant activity. Further, based on the Division's experience and assumptions regarding the clinical effects of antihistamines and decongestants, the critical comparison for this product was the antihistamine comparison. The primary endpoint for the antihistamine comparison was the change from Baseline to Days 1-15 in the reflective AM+PM total symptom score, excluding nasal congestion.

The results of the two studies were similar. The studies demonstrated that DL D-12 is statistically superior to PSE in regard to antihistamine activity. This was supported by the primary analyses as well as the numerous secondary analyses. Of note, the magnitude of the benefit of DL D-12 over PSE did not reach the magnitude for which the study was powered, suggesting that the treatment effect size was lower than expected. However, the Division has not previously insisted upon a treatment effect size of a specific magnitude. Treatment effect sizes likely vary according to the severity of the baseline symptoms. Also, it is difficult to identify what treatment effect size correlates with a meaningful clinical effect.

The two studies also demonstrated that DL D-12 was superior to DL5 in regard to decongestant activity. This result was expected because DL D-12 contains pseudoephedrine, a drug that is known to have decongestant effect.

C. Safety

The majority of the safety information in this application is derived from the two pivotal Phase 3 studies, in which a total of 1248 subjects were treated, with a total of 414 subjects receiving DL D-12, 412 subjects receiving DL, and 422 subjects receiving PSE. The safety testing, duration of exposure, and follow-up in these studies was in keeping with the standard expectations for this class of agent. Additionally, a total of 126 healthy volunteers were enrolled in the pharmacokinetic studies. Finally, although not submitted with this NDA, and not reviewed in this Medical Officer Review, a substantial safety experience with desloratadine has been reported in the several additional NDAs for desloratadine products that have been submitted for review. NDA 21-165, desloratadine 5mg tablets, has been reviewed and found to be approvable from a clinical standpoint, indicating an acceptable safety profile for that product.

The safety data arising out of the two pivotal Phase 3 studies do not suggest a safety concern for DL D-12. The adverse event profile of DL D-12 was similar to that of PSE. The studies did not include a placebo group for comparison. There was one serious adverse event in these trials, an ECG abnormality in a subject being treated with PSE. There were no deaths. The incidence of subject withdrawal from the protocol due to adverse event (AE) was highest in the PSE group (5%), followed by the DL D-12 group (3.6%), and the DL group (2.2%). The most frequent events associated with discontinuation were dizziness and somnolence in the DL D-12 group (1% for each), and insomnia and sinusitis in the PSE group (1.4% and 1.2%, respectively). The overall incidence of treatment emergent AEs was greater in the DL D-12 and PSE groups (44.0% and 44.8%, respectively) compared with the DL group (37.9%). The incidence of severe AEs was also greater in the DL D-12 and PSE groups (7.7% and 9.2%, respectively) compared with

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the DL group (4.9%). The most frequently reported treatment emergent adverse events were insomnia, headache, and dry mouth. Insomnia and dry mouth occurred with greater frequency among subjects treated with DL D-12 (9.7% and 7.5%, respectively) and PSE (12.6% and 7.8%, respectively) compared with subjects treated with DL (2.7% and 2.4%, respectively). Headache occurred with similar frequency in all treatment groups (7.5%, 7.5%, and 8.8% in the DL D-12, DL, and PSE groups, respectively). There were three treatment emergent adverse events occurring with a frequency greater than 2%, and more frequently in the DL D-12 group than in the DL and PSE groups. These were fatigue (3.9% vs. 2.2 and 2.4%, respectively), dizziness (3.4% vs. 2.4% and 2.1%, respectively), and pharyngitis (3.4% vs. 2.7% and 2.6%, respectively).

The vital signs, ECGs, and laboratory testing did not suggest a safety concern, with the possible exception of the liver function testing. The observation that five subjects, all in either the DL D-12 group or the DL group, exhibited a rise to a “clinically meaningful” liver function test value, raises the possibility of an effect of desloratadine on liver function tests.

The most important safety issue arising from the review of this NDA was identified in the pharmacokinetic studies, and is discussed in detail in Section III of this Review. The pharmacokinetic studies indicate that there exists a “poor metabolizer” phenotype in the population. These poor metabolizers exhibit very high exposure to desloratadine, and very low exposure to the major metabolite, 3-OH desloratadine. The specific impairment in the metabolic pathway in these subjects has not been elucidated. The frequency of this poor metabolizer phenotype in the general population is approximately 6% in adults and children aged 12 years and older, and 15% in children younger than 12 years of age. Poor metabolizers exhibit exposures to desloratadine (AUC) that are approximately six fold higher than those of normal metabolizers. [The estimates of the frequency of the poor metabolizer phenotype and the relative exposures are based upon data submitted to NDAs for the various desloratadine formulations. For details regarding these estimations, the reader is referred to the Medical Team Leader Secondary Review of this NDA, dated October 10, 2001.

The identification of this poor metabolizer phenotype raises several important safety issues. This NDA submission contains no specific data demonstrating the safety of chronic dosing with: 1) DL D-12 at the proposed dose, in poor metabolizers; or 2) DL D-12 in normal metabolizers at doses high enough to achieve exposures that are equal to or greater than the exposures expected in poor metabolizers after chronic dosing at the proposed dose (Note: As discussed above, this value has not been established). Although some poor metabolizers were presumably included in the pivotal safety and efficacy studies in proportion to their prevalence in the general population, the number of such patients is likely low. There may be some relevant safety data submitted to other NDAs, such as data from a high dose desloratadine cardiac safety study (submitted to NDA 21-165), the numbers of subjects is likely small, it is not clear that the exposures were sufficient, and the data was not submitted to this NDA for review. Also, because the metabolic impairment that results in the poor metabolizer phenotype and any alternative metabolic pathways that may occur in poor metabolizers have not been elucidated, it is not known whether drug interactions could either impair metabolism in otherwise normal metabolizers, or impair alternative metabolic

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pathways utilized by poor metabolizers. Such drug interactions could then increase the effective prevalence of poor metabolizers in the population (intrinsically poor metabolizers plus drug interaction-induced poor metabolizers), or increase the exposure to desloratadine in poor metabolizers (by impairing alternative metabolic pathways).

Given the presumed prevalence of the poor metabolizer phenotype (approximately 3%, based on the data available in this NDA), the magnitude of the increased exposure (five to six times, following single dose), and the absence of safety data at these higher exposures, this NDA should not be approved. The Applicant should first document the desloratadine exposures that occur with multiple dosing at the proposed dose in poor metabolizers, then justify the safety of such exposures based on studies already performed or new studies designed to assess safety.

D. Dosing

The proposed dose of Clarinex-D 12 HOUR Extended Release Tablet (desloratadine 2.5mg/pseudoephedrine 120mg), one tablet BID, is acceptable. This dose of pseudoephedrine (120mg BID) is the accepted, approved dose for the treatment of nasal congestion. Although dose-ranging studies with desloratadine (DL) were not included in this NDA, the dose of the desloratadine component (2.5mg) is based on the approved dose of the parent drug (5mg BID, as a component of Claritin D-12 [loratadine 5mg/ pseudoephedrine 120mg]), and pharmacokinetic studies demonstrating that administration of DL 5mg gives the same systemic exposure (plasma AUC) as administration of 10 mg of loratadine. The dosing interval is justified based on the accepted dosing interval of pseudoephedrine (BID) and the data from the two pivotal studies indicating that the antihistamine effect of DL D-12 is still present at the end of the dosing interval. The endpoint used to assess the end of dosing interval antihistamine efficacy was the change from baseline to Days 1-15 AM+PM instantaneous total symptom score, excluding nasal congestion. In both studies DL D-12 was statistically superior to PSE on this endpoint. The safety profile established in the two pivotal studies support the safety of the proposed dose. In the pivotal trials, the treatment effect was small. It is possible that a higher dose of desloratadine might be more effective in treating the histamine-related symptoms of SAR. This possibility was not examined in the studies submitted to this NDA.

E. Special Populations

The NDA includes an adequate assessment of gender differences in safety and efficacy. In the two pivotal clinical studies, approximately 64% of the subjects were women. In these studies, there were no differences in the patterns of overall AEs and treatment-related AEs among the treatment groups based on gender. The overall incidence of AEs was slightly greater in females than males, across treatment groups. In regard to efficacy, the Applicant examined the response to treatment, by gender, for both clinical studies. In both studies, DL D-12 was numerically more effective than PSE on the antihistamine comparison and numerically superior to DL on the decongestant comparison for both men and women. The Biometrics reviewer (Dr. Zhou) found that in Study P00355, DL D-12 was statistically superior to the appropriate comparator on both primary endpoints in both men and women. In Study P00362, DL D-12 was statistically superior

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on the antihistamine component in both men and women, and was statistically superior on the decongestant component in women and approached statistical significance in men ($p=0.0553$). Finally, the Applicant states that no clinically important differences between males and females were observed in regard to the mean DL, 3-OH DL, and pseudoephedrine pharmacokinetic parameters.

The Applicant provided summaries of the effects of age and race on the incidence of adverse events, treatment-related AEs, and SAEs in the two pivotal clinical studies. However, there were too few subjects in the age groups 12 to <18, and ≥ 65 years (the subgroup definitions in regard to age was 12 to <18 years, 18 to <65 years, and ≥ 65 years), or who were non-Caucasians to allow meaningful comparisons with respect to age or race. The same concern applies to subgroup analyses based on age or race with regard to efficacy. Previous studies, which have been submitted to other NDAs, have evaluated the pharmacokinetics of DL in the elderly (Study P00275) as well as patients with renal (Study C98-355) and hepatic impairment (Study C98-354). According to the Applicant, based on these data there was no alteration in the safety profile and no dosage adjustment was recommended.

This application did not contain a pediatric program. The Applicant has requested a waiver of the "Pediatric Use Information" requirements (21 CFR 314.55(a)) for the pediatric age groups below 12 years [S20/peduse/page 1]. The Applicant asserts that DL D-12 does not represent a meaningful therapeutic benefit over existing treatments and is not likely to be used in a substantial number of patients below the age of 12 years because the dose of pseudoephedrine (120mg BID) is not recommended for such patients. The request for a waiver of the pediatric use information requirement is appropriate.

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

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CLINICAL REVIEW

Introduction and Background

Clinical Review

I. INTRODUCTION AND BACKGROUND

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

This NDA is submitted in support of CLARINEX-D™ 12 HOUR Extended Release Tablet. This product is a bilayer tablet consisting of immediate-release desloratadine 2.5mg and pseudoephedrine 120mg in a sustained release matrix. Desloratadine is an H₁ receptor antagonist. Pseudoephedrine is an established sympathomimetic nasal decongestant. The proposed indication is for the relief of symptoms of seasonal allergic rhinitis (SAR). The proposed dose is 1 tablet BID. The proposed population is adults and children 12 years of age and older.

B. State of Armamentarium for Indication

Several classes of drugs are currently indicated for the treatment of allergic rhinitis (seasonal and/or perennial). These include: antihistamines, nasally inhaled corticosteroids, nasally inhaled cromones, nasally inhaled anticholinergics, and sympathomimetics. Of these, nasally inhaled steroids are possibly the most effective. Antihistamines are available over-the-counter (OTC) and by prescription-only. The OTC antihistamines are the earlier generation antihistamines, which are associated with central nervous system sedation. The prescription-only antihistamines have a more favorable safety profile. Among the prescription-only antihistamines, Schering's Claritin (loratadine) is a market leader. Desloratadine is a major metabolite of loratadine. Several antihistamines, both OTC and prescription-only, are available as combination formulations with the decongestant pseudoephedrine. Pseudoephedrine is considered to be effective for the relief of the nasal congestion that is a component of the symptoms of allergic rhinitis.

C. Important Milestones in Product Development

Desloratadine is a metabolite of loratadine (Claritin®), which was approved for marketing in the US in 1993. On January 12, 1998, a pre-IND meeting for desloratadine tablet was held. During that meeting, the possibility of developing a combination product (desloratadine and pseudoephedrine) was discussed. On June 18, 1999, the Applicant submitted an IND for such a combination product (Clarinx-D; IND 58,506). A telephone conference was held on August 9, 1999, to discuss design issues of various proposed studies, including the studies submitted to this NDA. According to the minutes of this telephone conversation, the Division stated that the proposed dose of desloratadine and the proposal to include no placebo arm in these studies would be acceptable. On January 18, 2000 a "pre-NDA style meeting" was held to discuss Clarinx-D. In addition to the information conveyed to the Applicant at these meetings, the Division has

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also developed a Guidance for Industry addressing issues in development of drug products for allergic rhinitis ("Allergic Rhinitis: Clinical Development Programs for Drug Products").

D. Other Relevant Information

This NDA is one of six NDAs submitted by the Applicant that contain desloratadine. These NDAs are summarized in the following table.

NDAs containing the drug substance desloratadine			
NDA #	Formulation	Indication	Status
21-165	5mg tablets	SAR	Clinically approvable
21-297	5mg tablets	Chronic Idiopathic Urticaria	Under review
21-300	Syrup	Pediatric SAR and CIU	Under review
21-312	5mg "RediTabs"	SAR	Under review
21-313	Combination tablet (desloratadine and pseudoephedrine)	SAR	Current Application
21-363	5mg tablets	PAR	Under review

DL D-12 is a combination product containing an antihistamine (desloratadine) and a decongestant (pseudoephedrine). Based on the current understanding of the pathophysiology of the various symptoms of allergic rhinitis, as well as extensive experience with other antihistamine/decongestant combination products, the Division has been willing to assume that antihistamines and decongestants provide complementary salutary effects in patients with allergic rhinitis. As such, approval of a proposed combination product comprised of an approved antihistamine and an approved decongestant would not require clinical data demonstrating superiority of the combination product over each of its components. In that circumstance, approval could be based upon pharmacokinetic data establishing that the exposures for each component are equivalent when given separately and in combination. However, clinical data was required for this NDA because the Applicant has not demonstrated the efficacy of desloratadine at a dose of 2.5mg BID. Therefore, the clinical studies submitted with this Application must establish that desloratadine 2.5mg BID is effective for allergic rhinitis.

Desloratadine is a metabolite of loratadine, which has been marketed internationally since 1988 and in the US since 1993 for the treatment of allergic rhinitis and allergic skin disorders. The Applicant states that pharmacokinetic studies have shown that administration of 5mg desloratadine gives the same systemic exposure as administration of the marketed dose of 10mg loratadine [S8/summary/23]. The Applicant estimates the total patient exposure to loratadine (tablet and syrup formulations) was _____ patient days as of April 2000 [S8/summary/26]. No approved dose of loratadine formulation has been withdrawn from any market. Pseudoephedrine 120mg BID is an

CLINICAL REVIEW

Introduction and Background

approved and accepted daily dose for a decongestant regimen. Pseudoephedrine 120mg in combination with loratadine 5mg BID (Claritin® D-12) is approved for relief of symptoms of SAR. At the time of submission, desloratadine had not yet been approved for marketing in any country [S8/summary/26].

E. Important Issues with Pharmacologically Related Agents

Prolongation of the electrocardiographic QT interval has been noted with certain of the antihistamines. The Applicant has performed a high dose cardiac safety study with desloratadine. This study, which was submitted to NDA 21-165, was designed to specifically address the possibility of an effect on the QT interval. No effect on the corrected QT interval was seen at doses that were nine times the recommended dose. For a detailed review of this study the reader is referred to the Medical Officer Review of NDA 21-165.

APPEARS THIS WAY ON ORIGINAL

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

Clinically Relevant Findings from Other Disciplines

II. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

There are no important CMC issues with regard to the drug substances (See CMC Review by Dr. Peri). The drug substance desloratadine has been previously reviewed by the CMC reviewer and has been deemed adequate (NDA 21-165). The Applicant has been asked to respond to the fact that the desloratadine drug particle specification in this NDA differs from the specification in NDA 21-165. The drug substance pseudoephedrine sulfate was found to be inadequate in a previous review and the Applicant has been asked to respond to issues identified in that review. Clinically important CMC issues regarding the drug product relate to stability issues. The CMC reviewer has determined that the proposed ~~unit-dose~~ packaging is not appropriate due to the accumulation of degradants, as well as issues of hardness, moisture, and friability of the tablets that occurs with this form of packaging. The proposal to package the product in HDPE bottles is acceptable. Also, the data provided by the Applicant does not support the proposed expiry period. The Applicant has been informed of these findings and a response from the Applicant is expected. An EER was submitted for the drug product manufacturing and testing facilities (Kenilworth and Union, New Jersey). These drug product manufacturing/testing facilities are under OAI Alert status.

In regard to the Pharm/Tox perspective, the preclinical evaluation of desloratadine has been reviewed under NDA 21-165 and has been determined to be acceptable. Pseudoephedrine is an established drug substance. The Pharm/Tox group is currently reviewing the specifications regarding ~~DL D-12~~ impurities of DL D-12. Because there are structural alerts for some of these impurities and because the preclinical evaluation may be incomplete for some, it is possible that the Pharm/Tox reviewer may determine that the preclinical data do not support the proposed specifications. In that case, the Applicant would either need to tighten the specifications, or to perform additional preclinical studies.

Clinically relevant findings related to biopharmaceutics are discussed in Section III of this Clinical Review (Human Pharmacokinetics and Pharmacodynamics). No consultations were requested for this application.

**CLINICAL REVIEW: Clarinex-D 12-Hour ER Tablets
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Human Pharmacokinetics and Pharmacodynamics

III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The clinical pharmacology program for DL D-12 comprised 5 completed pharmacokinetic and bioavailability studies in a total of 126 healthy volunteers. Of these 126 subjects, 73 received only DL D-12, 36 received each DL D-12, 2.5mg DL, and 120mg PSE, and 17 received only PSE [S8/ISS/68]. The table below summarizes these studies. Three of the five studies involved dosing with DL D-12 (P00440, P00446, and P00883). One of the five studies involved multiple dosing (P00883).

Overview of the DL D-12 Tablet Clinical Pharmacology Program								[S8/ISS/69]
Study No.	Primary Objective or Variable	Design	DL D-12 Dose	Comparator(s) and dose (mg)	Sex	Age	Race	
P01352	Bioavailability of Pseudoephedrine/ Controlled-release formulations	Open-label 4-way crossover	2.5 mg DL + 120 mg PSE in standard, fast, slow, and very fast-release formulations	none	11F/8M	19-42	11C/5B/2A/1O	
P00230	Bioavailability of Pseudoephedrine Extended-release formulations	Open label 4-way crossover	none	120 mg PSE bilayer tablet formula 3525 3526 and; 120 mg PSE Drixoral tablet; 30 mg PSE solution administered 4 times daily,	17M	20-39	16C/1B	
P00446	Bioequivalence of DL and PSE	Open label 3-way crossover	2.5 mg DL + 120 mg PSE	120 mg PSE 2.5 mg DL	19M/17F	19-45	31H/4B/1O	
P00440	Bioavailability of Pseudoephedrine Food Effect	Open label 2-way crossover	2.5 mg DL + 120 mg PSE (w/wo breakfast)	none	24M/12F	18-44	25C/10B/1O	
P00883	Multiple Dose Pharmacokinetics D-12	Open label, multiple dose, 14 days	2.5 mg DL + 120 mg PSE BID	none	9M/9F	21-43	2C/2B/14H	

DL = desloratadine, SCH 34117; BID = twice daily; w/wo = with or without..

Race: C = Caucasian; B = Black; A = Asian; H = Hispanic; O = Other, not indicated as either Caucasian, Black Asian, or Hispanic on the CRF.

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Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

(4) Background

DL D-12 is a bilayer combination of immediate release desloratadine 2.5mg and pseudoephedrine sulfate 120mg in a sustained release matrix. DL D-12 is designed for twice-daily dosing. The PK studies submitted in this application are summarized in the table above. Safety information from these studies is discussed in the Overview of Safety in this Review.

Detailed analyses of these studies may be found in a separate review document created by the Office of Clinical Biopharmaceutics (OCPB) reviewer, Dr. Suarez. Study P00230 was a formulation selection study. This study was performed to determine the appropriate formulation for the PSE core of the combination product, based on bioequivalence to a single-dose administration of Drixoral® nasal decongestant (pseudoephedrine 120mg) and a pseudoephedrine 30mg solution administered QID. Study P00440 was a food effect study. It demonstrated that the bioavailability of DL D-12 is not effected by a high-fat, high-calorie meal. Study P00446 was a component interaction study. This study showed no interaction between the DL and the PSE in the DL D-12 combination product. Study P00883 was a multiple dose study. Steady state concentrations of desloratadine, 3-hydroxy desloratadine, and pseudoephedrine were obtained following twice daily dosing of DL D-12 for 14 days. Study P01352 was a study performed to evaluate the bioequivalence of pseudoephedrine from several extended release formulations. This study demonstrated that DL D-12 formulations with pseudoephedrine dissolution rate profiles that were faster and slower than the to-be-marketed formulation were bioequivalent in vivo.

(5) Poor Metabolizers

Review of the individual data from the PK studies indicates that a fraction of the population metabolize desloratadine poorly. Of the PK studies submitted to this NDA, two single-dose PK studies involved dosing with desloratadine, alone and/or as a component of the combination product (Study P00440 and Study P00446), and one multiple-dose study involved dosing with DL D-12 (Study P00883). One patient out of 35 in Study 00440 and one patient out of 35 in Study 00446 were poor metabolizers of desloratadine. The data from these two patients are summarized below. There were no poor metabolizers in the multiple-dose study. In this NDA, the Applicant has not specifically addressed important issues raised by the observation that a population of poor metabolizers exists. Such issues would relate to the mechanisms involved, the predicted prevalence of the poor metabolizer phenotype in the general population, and safety and efficacy implications related to the high exposures expected in poor metabolizers.

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Study P00440 was a randomized, open-label, two-way crossover, PK study in which subjects received a single dose of DL D-12 in the fed state and in the fasting state. Blood samples were collected for 120 hours post-dose. A two-week washout period separated the two treatments. In this study, Subject 33 exhibited exposure to DL that was approximately five to six times the overall median exposure. In the fed state, the AUC_{0-tf}^1 was 100.21, and in the fasting state the AUC_{0-tf} was 118.99. This compares with a median AUC_{0-tf} value of 19.195 for this study. In this patient, the Time 0 blood sample for Period 2 contained measurable DL, despite a two-week washout period. Although the Applicant states that "the reason for this is unknown," [Electronic Submission Dated: August 22, 2001, hupharm/P00440.pdf, page 325/1182], it is quite likely that the continued presence of DL in this subjects blood is due to the very prolonged $T_{1/2}$. Subject 33 was a 20 year-old, black female [Submission Dated 8/22/01, hupharm/P00440.pdf, page 38/1182]. The following figures illustrate the plasma concentration-time curves for Subject 33 and for the group as a whole (mean).

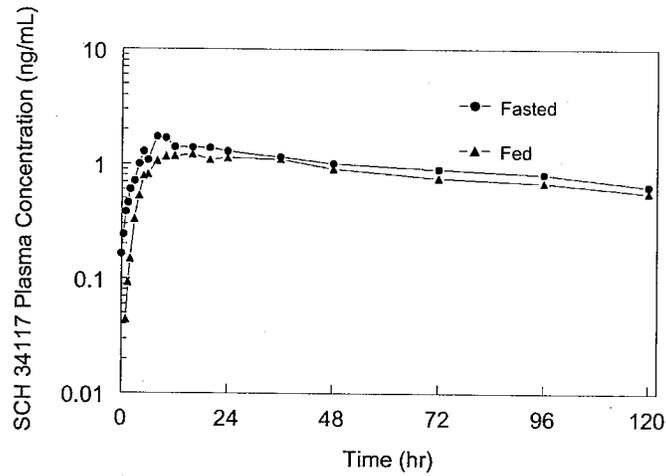
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¹ tf=time of final quantifiable sample in terminal phase

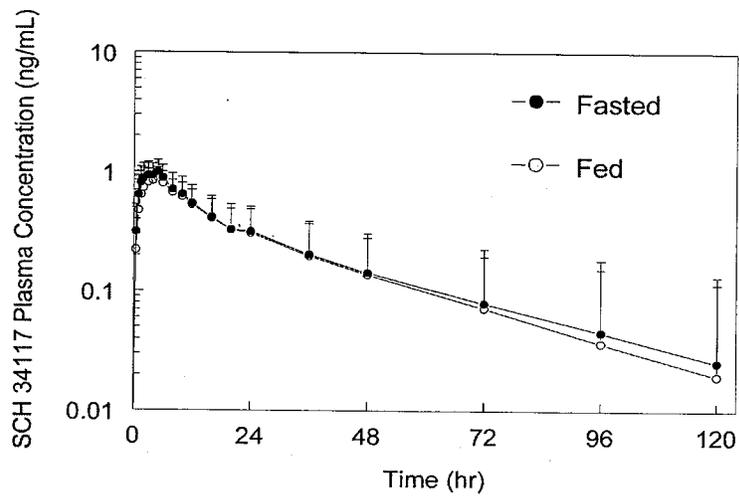
**CLINICAL REVIEW: Clarinex-D 12-Hour ER Tablets
(NDA 21-313)**

Human Pharmacokinetics and Pharmacodynamics

**Plasma Concentration-Time Curve: Subject 33
(SCH 34117 = DL)**



**Mean Plasma Concentration-Time Curve: Study 00440
(SCH 34117 = DL)**



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Human Pharmacokinetics and Pharmacodynamics

A review of the safety data for Subject 33 reveals the following. This subject reported one adverse event: mild dyspepsia (stomach ache), that began and ended on Day 16 [Submission Dated 8/22/01, hupharm/P00440.pdf, page 1044/1182]. Her ECGs were normal, with the exception of a notation of a new finding of RSR' in V1 or V2 on Day 20, interpreted as not clinically significant [Submission Dated 8/22/01, hupharm/P00440.pdf, page 1064-5/1182]. Her laboratory testing was normal, with the exception of a HCT that was normal (37.8) at baseline, and declined to 32.9 by Day 20, and bacteria, RBCs and WBCs in the urinalysis [Submission Dated 8/22/01, hupharm/P00440.pdf, pages 1092-1134/1182]. Her vital signs were unremarkable [Submission Dated 8/22/01, hupharm/P00440.pdf, page 1164-5/1182].

Study P00446 was a randomized, open-label, three-way crossover study intended to determine the bioequivalence of desloratadine, 3-OH desloratadine, and pseudoephedrine following single dose administration of DL D-12. Blood samples were collected for 120 hours post-dose. In this study, Subject 19 exhibited exposure to DL that was approximately 4.6 to 4.9 times the median exposure. After administration of DL D-12, the AUC_{0-tf} for DL was 102.1, and after administration of DL alone, the AUC_{0-tf} for DL was 107.53. This compares with a median AUC_{0-tf} value of 22.03 for this study. After administration of both DL D-12 and DL, the levels of the major metabolite, 3-hydroxy desloratadine were 0 in this subject,. Despite a washout period of at least 14 days, this subject had measurable serum desloratadine levels at the start of Period 2 [Submission dated 8/22/01, hupharm/P00446.pdf, page 28]. Subject 19 was a 27 year-old Hispanic female. Review of the safety data for Subject 19 revealed the following. This subject reported one adverse event: mild headache, that began on Day 33 and ended on Day 35. Her ECGs, laboratory studies, and vital signs were unremarkable.

The data above provide information regarding the exposures exhibited by two patients who are apparently "poor metabolizers," after single dosing . The only possible safety signal arising out of the experience with these two patients in the decline in Hct demonstrated by the subject in study P00440.

Because none of the subjects in the multiple dose PK study (Study P00883) were poor metabolizers, the study does not provide data regarding the exposures that are generated in poor metabolizers with multiple dosing. The OCPB reviewer, Dr. Suarez, performed a statistical simulation of multiple dosing, based upon the single dose data from Subject 33 in Study 00440. According to her calculations, dosing with 2.5mg of desloratadine BID for 20 days would result in an AUC of 170 ng·hr/mL. Using data submitted to several of the desloratadine NDAs, Dr. Chowdhury has determined that poor metabolizers exhibit desloratadine exposures that are approximately six times those of normal metabolizers [see the Medical Team Leader Secondary Review of this Application, dated October 10, 2001].

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Human Pharmacokinetics and Pharmacodynamics

The original NDA submission (NDA 21-313) did not contain multiple dose safety data for subjects with exposures that would be expected among patients who are slow metabolizers who use DL D-12 as proposed (multiple dose, BID). The safety of desloratadine in poor metabolizers is discussed in the four-month safety update submitted to NDA 21-300 (dated 4/6/01), and cross-referenced to this submission. Dr. Chowdhury, in his Medical Team Leader secondary review, has reviewed the data on poor metabolizers from clinical and clinical pharmacology studies submitted to the various desloratadine NDAs [secondary medical review, dated October 10, 2001]. The total safety database in slow metabolizers includes 75 subjects from the clinical pharmacology studies, most of whom received single dose, and 21 subjects from a clinical study (P01434). Additional relevant safety data may be derived from high dose desloratadine studies in subjects with unknown metabolizer status. These include dosing of 24 subjects with desloratadine 45mg daily for 10 days, dosing of 10 subjects with desloratadine 20mg, and dosing of 169 subjects with 20mg daily for 2 weeks. Although no safety signals were detected in these studies, the database is small.

Summary

The PK data suggest that approximately 6% of the population aged 12 years and older metabolize desloratadine poorly. These patients exhibit a very long $T_{1/2}$ and have very low to unmeasurable levels of the major metabolite, 3-OH desloratadine. The specific impairment in the metabolic pathway in these subjects has not been elucidated. Based on the data submitted to the various desloratadine NDAs, poor metabolizers exhibit exposures to desloratadine ($AUC_{0-\infty}$) that are approximately six fold higher than those of normal metabolizers.

The identification of this poor metabolizer phenotype raises two important safety issues. First, this NDA submission contains no specific data demonstrating the safety of DL D-12 in poor metabolizers. Such data would include chronic dosing with: 1) DL D-12 at the proposed dose, in poor metabolizers; or 2) DL in normal metabolizers at doses high enough to achieve exposures that are equal to or greater than the exposures expected in poor metabolizers after chronic dosing at the proposed dose. Although some poor metabolizers were presumably included in the pivotal safety and efficacy studies in proportion to their prevalence in the general population, the number of such patients is likely low. Some relevant safety data addressing this issue has been submitted to other NDAs. This data has been reviewed by Dr. Chowdhury, in his Medical Team Leader secondary review of this NDA, dated October 10, 2001. However, the safety database is small, and in many cases the exposures were not sufficient in terms of dose and duration. Second, because the metabolic impairment that results in the poor metabolizer phenotype, and any alternative metabolic pathways that may occur in poor metabolizers have not been elucidated, it is not known whether drug interactions could either impair metabolism in otherwise normal metabolizers, or impair alternative metabolic pathways utilized by poor metabolizers. Such drug interactions could then increase the effective prevalence of poor metabolizers in the population (intrinsicly poor metabolizers plus drug interaction-

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induced poor metabolizers), or increase the exposure to desloratadine in poor metabolizers (by impairing alternative metabolic pathways).

Reviewer's Comment: Given the presumed prevalence of the poor metabolizer phenotype (approximately 6%), the magnitude of the increased exposure (approximately six times the exposure in normal metabolizers), and the absence of safety data at these higher exposures, this NDA should not be approved. The Applicant should justify the short- and long-term safety of these elevated exposures.

B. Pharmacodynamics

Pharmacodynamic variables were not assessed in this program [Submission dated 4/2/01, 8c.pdf, page 51/51]. NDA 21-165, desloratadine 5mg QD for SAR, included a high dose cardiac safety study designed to address cardiac safety concerns, including QTc effects. This study was reviewed by the Medical Officer assigned to NDA 21-165, and was found to support the cardiac safety of desloratadine.

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Description of Clinical Data and Sources

IV. DESCRIPTION OF CLINICAL DATA AND SOURCES

A. Overall Data

This NDA is based upon trials conducted by the Applicant. Two clinical safety and efficacy trials performed under identical protocols were submitted. In addition, five pharmacokinetic trials were submitted. The pivotal safety and efficacy trials are outlined in the table below. The pharmacokinetic trials are outlined in Section III of this Medical Officer Review.

B. Tables Listing the Clinical Trials

Table of Pivotal Studies						
Study Number / Sites / Location/ Dates	Study Design/ Population	Treatment Period	Ages	Treatment Groups	Number of Subjects	Population breakdown (N)
P00355 20 centers US Aug-Dec, 1999	R, DB, PG, double-dummy, active-control, safety and efficacy in subjects with SAR	15 days	12-76	DL D-12 BID	200	Male 224
				DL 5mg QD	198	Female 374
				PSE 120mg BID	200	
				Total	598	
P00362 20 centers US Aug-Nov, 1999	(same as above)	(same as above)	12-78	DL D-12 BID	214	Male 221
				DL 5mg QD	214	Female 429
				PSE 120mg BID	222	
				Total	650	

Source: [S3/Clinical Data]

C. Postmarketing Experience

Desloratadine has not been approved for marketing in the US or elsewhere. Therefore, no postmarketing data for desloratadine was submitted. Desloratadine is a metabolite of loratadine, which is a market leader in the US, with extensive worldwide distribution. The Applicant estimates the total patient exposure to loratadine (tablet and syrup formulations) was _____ patient days as of April 2000 [S8/summary/26]. The submission did not include specific post-marketing data on loratadine. However, the Division has recently reviewed the post-marketing data on loratadine in response to a citizen petition regarding the possibility of shifting loratadine from prescription-only status to over-the-counter status. The Division's conclusion was that post-marketing safety of loratadine is favorable.

D. Literature Review

A literature review was not performed by the Applicant or the Medical Reviewer.

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Clinical Review Methods

V. CLINICAL REVIEW METHODS

How the Review was Conducted

The two pivotal safety and efficacy trials were first reviewed in-depth individually. Efficacy conclusions were drawn individually for each of the two studies, then synthesized into an overall discussion of efficacy in the Integrated Review of Efficacy. Safety issues were examined based upon the combined data from the two studies. Following the in-depth review of the two pivotal studies, three of the pharmacokinetic studies were reviewed, with specific attention to the issue of poor metabolizers. CMC and Pharm/Tox data were not reviewed in depth by this reviewer. The 120-Day Safety Update was reviewed for pertinent additional information not included in the original submission.

Overview of Materials Consulted in Review

This NDA, including the original submission and all additional submissions, was submitted electronically. This following submissions were reviewed: December 8, 2000 (original submission), April 2, 2001 (general correspondence), April 6, 2001 (120-Day Safety Update), and August 22, 2001 (response to request for information).

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audits were performed for this NDA. Independent statistical analyses were performed by the Biometrics reviewer. The Applicant states that in the course of monitoring the clinical studies, the original patient records were reviewed by Quintiles monitoring personnel to verify the accuracy of the case report forms.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were conducted in accordance with accepted ethical standards, including regulations regarding appropriate IRB approval and informed consent [S8/8k/ page 2].

E. Evaluation of Financial Disclosure

The Applicant submitted a completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form [S19/page 1]. In this form the Applicant certified that it had not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2a. This form was signed by Dr.

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Clinical Review Methods

Staudinger, Vice-President, Clinical Research, Allergy/Resp. Diseases/Clinical Immunology, Schering-Plough Research Institute. Four investigators involved in Study P00355 did not return a financial disclosure statement [S19/page 8]. One investigator involved in Study P00362 did not return a financial disclosure statement (S19/10). Attempts to obtain these statements were made by express mail and telephone contact. The Applicant states that a review of internal records showed no significant payments of "other sorts" to these investigators [S19/pages 8 and 10]. The table below provides information on five investigators who disclosed specific financial interest or arrangements with the Applicant.

Specific Financial Disclosures		
Investigator Address	Study/ Site Number of Subjects Enrolled	Disclosure
[REDACTED]	[REDACTED]	Received consultation fees in the amount of \$100,000 per year
[REDACTED]	[REDACTED]	Schering-Plough stock in the amount greater than \$50,000, but less than \$100,000
[REDACTED]	[REDACTED]	Schering-Plough stock in the amount greater than 1,500 shares (common stock)
[REDACTED]	[REDACTED]	Schering-Plough stock in the amount of 3,527 shares or \$140,000
[REDACTED]	[REDACTED]	Schering-Plough stock in the amount greater than \$74,000 (common stock)

Because of these potential financial conflicts, the Biometrics reviewer analyzed the data for treatment-by-center effect. No such effect was detected. Based on this fact, and because the two pivotal studies were large, multicenter, double-blind, placebo-controlled studies, these potential conflicts are unlikely to have affected the results.

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

Integrated Review of Efficacy

VI. INTEGRATED REVIEW OF EFFICACY

A. Brief Statement of Conclusions

The two pivotal clinical trials submitted with this NDA support the proposed labeling claim that CLARINEX-D 12 HOUR (DL D-12) is effective for the relief of symptoms of SAR in adults and children 12 years of age and older. Specific comments regarding the Applicant's proposed labeling language appear in Section X of this review.

B. General Approach to Review of the Efficacy of the Drug

The efficacy database for this NDA consisted of two large, randomized, double-blind, double-dummy studies, P00355 and P00362. The protocols for these two studies were identical. Each of these studies was reviewed in detail. This section of the NDA Review contains an integrated summary of the efficacy findings from these two studies. The in-depth reviews of the design and efficacy results from these two studies can be found in Section XI, B of this NDA Review.

C. Detailed Review of Trials by Indication

(6) Clinical Trials: Design Issues

The clinical program for Clarinex-D 12-Hour ER Tablets (DL D-12) was designed to support a single indication, the relief of symptoms of SAR in adults and children 12 years of age and older. The program consisted of two pivotal Phase 3 studies that were performed under identical protocols (Study P00355 and Study P00362) [S3/Clinical Data/149-153]. The design and results of these studies are discussed in detail in Section XI, B of this review. These studies were randomized, double-blind, active-controlled, parallel group studies, each performed at 20 centers in the US. The three treatment groups were: desloratadine 5mg (DL5) QD, pseudoephedrine (PSE) 120mg BID, and DL D-12 BID. A total of 598 subjects and 650 subjects were randomized in Study P00355 and Study P00362, respectively. In these studies, subjects 12 years of age and older, with at least a 2-year history of SAR, positive skin test to appropriate seasonal allergen, and clinical symptoms were enrolled. During the screening period (3-14 days) and throughout the 15-day treatment period, subjects recorded SAR symptoms (reflective and instantaneous) twice daily. The following eight symptoms were assessed: rhinorrhea, nasal congestion, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate. The first four were considered to be the nasal symptoms, and the latter four were considered the non-nasal symptoms. Symptoms were scored on a scale of 0-3 (0=none, 1=mild, 2=moderate, 3=severe). The primary efficacy variables were: 1) change from Baseline in mean AM+PM reflective symptom score excluding nasal congestion (for the antihistamine component) and, 2) change from baseline in mean AM+PM reflective nasal congestion score (for the decongestant

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

Integrated Review of Efficacy

component). The primary time point for both variables was the average over the 15-day treatment period. The primary comparison for the antihistamine component was DL D-12 versus PSE. The primary comparison for the decongestant component was DL D-12 versus DL. Instantaneous symptom scores were analyzed as secondary efficacy variables. Numerous other secondary efficacy variables were also assessed, including assessments of the "overall condition of SAR" and "response to test drug treatment," performed jointly by the subject and investigator. The studies were powered to detect a difference of 1.6 between study groups for the primary antihistamine efficacy comparison (DL D-12 vs. PSE). The ITT population was used in the efficacy analyses. The definitions of the ITT population provided in the protocol and study report differed slightly, but this difference is unlikely to have affected the interpretation of the study results (See section XI, B).

The rationale for the absence of a placebo group and for the choice of the primary efficacy comparisons merits further discussion. Based on the current understanding of the pathophysiology of the various symptoms of allergic rhinitis, as well as extensive experience with other antihistamine/decongestant combination products, the Division has been willing to assume that antihistamines and decongestants provide complementary salutary effects in patients with allergic rhinitis. This assumption is based on the fact that antihistamines have been shown to treat many nasal and non-nasal symptoms of SAR felt to be mediated, at least in part, by histamine. However, the antihistamines have not been shown to ameliorate the symptom of nasal congestion associated with SAR. Given these assumptions, approval of a proposed combination product comprised of an approved antihistamine and an approved decongestant would not require clinical data demonstrating superiority of the combination product over each of its components. In that circumstance, approval could be based upon pharmacokinetic data establishing that the exposures for each component are equivalent when given separately and in combination. However, clinical data was required for this NDA because the Applicant has not demonstrated the efficacy of desloratadine at a dose of 2.5mg BID. Therefore, in order to support approval, the clinical studies submitted with this Application must establish that desloratadine 2.5mg BID is effective for allergic rhinitis. Thus, while the stated primary objective of these studies was to compare the efficacy of DL D-12 with that of its components, for the purposes of approval, the most important data from the studies is that which provides evidence of the efficacy desloratadine 2.5mg BID component of the combination product. The comparison intended to establish this is that of DL D-12 versus PSE, using the endpoint of the histamine-related symptoms of allergic rhinitis (sneezing, itching, and rhinorrhea). Superiority on this endpoint would demonstrate that the desloratadine component of the combination product is effective. The second primary analysis, addressing the efficacy of the decongestant component (PSE) (DL D-12 versus DL, using the endpoint of nasal congestion) is less critical for the purposes of approval because PSE 120 mg BID has previously been demonstrated to be effective in the treatment of nasal congestion. For this reason, the decongestant

**CLINICAL REVIEW: Clarinex-D 12-Hour ER Tablets
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Integrated Review of Efficacy

component comparisons will be discussed only briefly in this section. Further details regarding the decongestant comparisons are included in Section XI, B of this review.

(7) Clinical Trials: Primary Efficacy Results

In both studies, the demographic and baseline characteristics of the study subjects were similar across the three treatment groups. The majority of the subjects were female (61%-69%) and the majority were caucasian (79%-86%). Very few patients at either end of the age spectrum (<18yrs and ≥65yrs) were studied.

As discussed above, for the purposes of approval, the most important endpoint was the antihistamine comparison, which was the comparison of DL D-12 versus PSE on the change from baseline average AM+PM reflective total symptom score, excluding nasal congestion. As shown in the table below, in both studies, DL D-12 was statistically more effective than PSE on this endpoint. It should be noted that the differences that were demonstrated between the two groups (1.47 in Study P00355, and 1.37 in Study P00362) did not reach the magnitude that the study was powered to detect (1.6). Interestingly, in both studies the DL5 treatment did not appear to be effective on this variable, despite the fact that this variable is intended to demonstrate antihistamine efficacy (data provided in Section XI, B of this review).

Antihistamine Comparison							
Total symptom score, excluding nasal congestion (reflective, AM+PM): Change from Baseline to Days 1-15							
	DL D-12			PSE			p-value
	N	Mean	%change	N	Mean	%change	
Study P00355	199	-6.54	-46.0%	197	-5.07	-35.9%	<0.001
Study P00362	213	-6.65	-43.0%	221	-5.28	-35.4%	<0.001

The results from both studies regarding the primary decongestant comparison (change from Baseline reflective nasal congestion score, DL D-12 vs. DL5) demonstrated that DL D-12 was superior to DL5. Interestingly, in these studies DL5 had a greater effect on nasal congestion than did PSE. The difference reached statistical significance in Study P00355. This is an unexpected finding and may suggest that patients have difficulty separating the congestion and non-congestion symptoms.

(8) Clinical Trials: Secondary Efficacy Results

The secondary reflective antihistamine comparisons of DL D-12 versus PSE included the change from Baseline in the reflective total symptom score, excluding nasal congestion, at Days 1-4 individually, Days 1-8, and Days 9-15. With the exception of the Day 1

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comparison in Study P00355, DL D-12 was statistically superior to PSE at each of the time points in both studies.

In these studies instantaneous symptom scores were collected as a means of assessing the end of dosing interval efficacy. The endpoint used to assess end of dosing interval antihistamine efficacy was the change from baseline to Days 1-15 AM+PM instantaneous total symptom score, excluding nasal congestion, comparing DL D-12 with PSE. As shown in the table below, in both studies, DL D-12 was statistically superior to PSE on this endpoint.

End of Dosing Interval, Antihistamine Comparison							
Total symptom score, excluding nasal congestion (instantaneous, AM+PM): Change from Baseline to Days 1-15							
	DL D-12			PSE			p-value
	N	Mean	%change	N	Mean	%change	
Study P00355	199	-6.27	-45.1%	197	-4.92	-35.6%	0.001
Study P00362	213	-6.30	-42.1%	221	-5.28	-35.7%	0.010

The secondary endpoints included numerous analyses of the subject evaluated symptom scores. These included reflective and instantaneous assessments of total symptom scores, total symptom scores, excluding nasal congestion, and nasal congestion, which were recorded in the AM, the PM, and the AM+PM, at Days 1-4 individually, Days 1-8, Days 9-15, and Days 1-15. In addition, the joint subject/investigator evaluations of the overall condition of SAR and the therapeutic response were included among the secondary efficacy analyses. In both studies, the results of these secondary analyses support the conclusion that DL D-12 had statistically superior anti-histamine effects as compared with PSE, and statistically superior decongestant effects as compared with DL5. In regard to both the subject evaluated "overall condition of SAR," and the subject/investigator joint assessment of the "therapeutic response," DL D-12 was statistically superior to both DL5 and PSE in Study P00362. The differences between groups were not statistically significant in Study P00355.

D. Efficacy Conclusions

The results of the two pivotal clinical studies support the conclusion that DL D-12 is effective in the treatment of SAR. As discussed in Section VI, C, the primary endpoints in the two pivotal studies were designed to demonstrate that DL D-12 was superior to PSE regarding antihistamine activity, and that DL D-12 was superior to DL5 regarding decongestant activity. Further, based on the Division's experience and assumptions regarding the clinical effects of antihistamines and decongestants, the critical comparison for this product was the antihistamine comparison. The primary endpoint for the

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antihistamine comparison was the change from Baseline to Days 1-15 in the reflective AM+PM total symptom score, excluding nasal congestion.

The results of the two studies were similar. The studies demonstrated that DL D-12 is statistically superior to PSE in regard to antihistamine activity. This was supported by the primary analyses as well as the numerous secondary analyses. Of note, the magnitude of the benefit of DL D-12 over PSE did not reach the magnitude for which the study was powered, suggesting that the treatment effect size was lower than expected. However, the Division has not previously insisted upon a treatment effect size of a specific magnitude. Treatment effect sizes likely vary according to the severity of the baseline symptoms. Also, it is difficult to identify what treatment effect size correlates with a meaningful clinical effect.

The two studies also demonstrated that DL D-12 was superior to DL5 in regard to decongestant activity. This result was expected because DL D-12 contains pseudoephedrine, a drug that is known to have decongestant effect.

Interestingly, the two studies failed to demonstrate the efficacy of desloratadine 5mg QD (DL) as an antihistamine. This might indicate that dosing of desloratadine at 2.5mg BID is superior to dosing at 5mg QD. However, a separate NDA (#21,165) has been submitted in support of desloratadine 5mg QD for the treatment of seasonal allergic rhinitis. That NDA has been reviewed and has been found to be sufficient for approval, from a clinical standpoint. The clinical and pharmacokinetic studies submitted to NDA 21,165 were supportive of QD dosing.

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VII. INTEGRATED REVIEW OF SAFETY

A. Brief Statement of Conclusions

The data submitted with this NDA demonstrate that the combination product, DL D-12, has a safety profile similar to each of its components. The more common adverse effects of the combination product (insomnia and dry mouth) are likely attributable to the PSE component. Because the studies that were performed to support approval of DL D-12 did not include a placebo group, they do not serve well to distinguish drug-related adverse events from non drug-related adverse events.

In addition to the safety data from the Phase 3 development of DL D-12, there are several sources of supportive safety evidence. For instance, there is extensive experience with both of the individual components of the DL D-12 combination product.

Pseudoephedrine is already approved for use for this indication and is contained in numerous prescription and non-prescription drug products. Desloratadine is the subject of NDA 21-165, submitted to support the approval of desloratadine 5mg QD for SAR. In the development program for NDA 21-165 a total of 2346 subjects received desloratadine and 1044 subjects received placebo. In that program, daily doses of 5mg and 7.5mg were administered for up to 4 weeks. NDA 21-165 is currently under review. Of note, the proposed dosing schedule for DL in NDA 21-165 (5mg QD) differs from the dosing schedule proposed in this NDA (2.5mg BID as part of the combination product). Finally, further supportive safety information can be derived from the experience with the parent drug (loratadine) as a single agent and as the combination drug product Claritin-D® 12 Hour Extended Release Tablets (5.0mg loratadine and 120mg pseudoephedrine sulfate), both of which are currently approved for SAR.

B. Description of Patient Exposure

(1) Primary Studies

The Integrated Summary of Safety (ISS) submitted by the Applicant provides pooled safety data from the two pivotal, Phase 3, randomized, multicenter, double-blind, active-controlled, parallel group studies, which were conducted under identical protocols (P00355 and P00362) [S8/ISS]. These studies are discussed in detail in the Integrated Review of Efficacy and in the Appendix to this Medical Review document. The table below summarizes the studies briefly.

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Phase 3 Clinical Trials		[S8/ISS/10]
Study Number	Study Design	Total Number of Subjects (randomized/treated)
Study Dates		Age Range (years)
Investigators		Sex Distribution
P00355	Double-Blind, Active-controlled, Parallel-group, Efficacy and Safety Study: DL D-12 BID versus DL 5.0 mg QD and PSE 120 mg BID for 15 days	598/598
Aug 1999 to Dec 1999 20 centers in the United States		12-76 224 M, 374 F
P00362	Double-Blind, Active-controlled, Parallel-group, Efficacy and Safety Study: DL D-12 BID versus DL 5.0 mg QD and PSE 120 mg BID for 15 days	650/650
Aug 1999 to Nov 1999 20 centers in United States		12-78 221 M, 429 F

(2) Secondary studies/supplemental information

In addition to the pooled safety information from the two Phase 3 studies, the Applicant has submitted safety data from five Phase 1 studies: four bioavailability studies and one multiple-dose pharmacokinetic study. The designs of these studies are summarized in Section III of this Review. One study did not include DL D-12 (Study P00230), and one study included only DL D-12 (fed versus fasted state, in Study P00440). A total of 126 healthy volunteers participated in these single- and multiple-dose Phase 1 studies. Of these 126 volunteers, 73 received only DL D-12, 36 received each DL D-12, 2.5mg DL, and 120mg PSE, and 17 received only PSE. Safety evaluations in these studies included assessments of clinical adverse events, clinical laboratory tests, vital signs, and ECGs. These secondary studies did not raise a significant safety concern. Details of the safety findings from these studies are included in the paragraph below.

The Applicant states that there were no changes in the clinical laboratory test results, vital signs, or ECGs that were of clinical significance [S8/ISS/69]. This reviewer could not locate this data in the submission. Section 8/8c of the submission included summaries of the Phase 1 Studies. These summaries included discussions of the adverse events experienced in the studies. One subject in the multiple dose PK study (P00883) developed mild elevations in serum liver enzymes on Day 15 (one day post-treatment). The abnormalities (ALT 133 U/L; normal range 21-72U/L; AST 56 U/L; normal range 15-50 U/L) resolved within one week [S8/8c/42]. One subject discontinued treatment due to an adverse event (moderate rash) that was considered by the investigator to be probably related to treatment with PSE (Study P00230). The frequency of adverse events in the single-dose studies ranged from 11% (food-effect study, P00440) to 42% (bioavailability study, P001352). Adverse events were reported in 39% of patients in the multiple-dose PK study (P00883). The most common AE was headache (6%-28% of those who received DL D-12). In the absence of a placebo control, it is difficult to

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interpret the safety data from these studies. The remaining discussion in this Integrated Review of Safety will refer to the safety data from the Phase 3 clinical program.

(3) Exposure/Demographics/Disposition of Patients

A total of 1248 subjects were randomized in the two Phase 3 studies and received at least one dose of study drug. Of these, 414 subjects received DL D-12, 412 subjects received DL, and 422 subjects received PSE. The majority of the randomized patients received treatment for 13-16 days. The table below provides the data on the extent of the exposure for the pooled population.

Extent of Exposure by Treatment Group: Studies P00355 and P00362, All Randomized Subjects [S8/ISS/20]			
Day Interval	Number (%) of Subjects		
	DL D-12 (N = 414)	DL (N = 412)	PSE (N = 422)
1 - 4	412 (99.5)	412 (100)	420 (99.5)
5 - 8	403 (97.3)	408 (99.0)	410 (97.2)
9 - 12	396 (95.7)	398 (96.6)	395 (93.6)
13 - 16	389 (94.0)	391 (94.9)	385 (91.2)
17 - 20	57 (13.8)	57 (13.8)	52 (12.3)
21 - 24	2 (< 1)	3 (< 1)	2 (< 1)
Missing	2 (< 1)	0	2 (< 1)
Mean (days)	14.9	15.0	14.6
Median	15	15	15
Range (Min - Max)	1 - 21	2 - 23	1 - 23

Of the 1248 subjects, a total of 83 discontinued the study prior to completion. Forty-four of these discontinuations were due to adverse events (6.0% in the DL D-12 group, 5.1% in the DL group, and 8.8% in the PSE group).

The treatment groups were similar at baseline in terms of age, gender, race, weight, height, and duration of disease (mean = approximately 18 years, range = 2-69 years) [S8/ISS/19].

C. Methods and Specific Findings of Safety Review

(1) Safety Evaluations Performed

The Phase 3 studies evaluated the safety of the study drugs using the following assessments: clinical adverse events, electrocardiograms (ECGs), vital signs, and clinical laboratory results. The adverse events reported in the NDA were all events that were considered to be "treatment emergent." Treatment emergent adverse events were defined as any adverse event that began on or after the first day of treatment through 30 days after the last day the subject participated in the study, and any adverse event that was observed

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before the first day of treatment but was later reported with a greater severity during study participation after the first day of treatment. Clinical laboratory testing was performed at Screening and at the Final Visit (Visit 4). A physical examination was performed at the Screening visit. Vital signs (blood pressure, pulse, and respiratory rate) were performed at all visits. A 12-lead ECG was recorded (after the subject had been supine for at least 3 minutes) at Screening and at the Final visit, approximately 1-3 hours after the last dose of study drug. Analysis of the ECGs included measurement of the standard intervals, ventricular rate, and the calculated QTc using both the Fredericia and the Bazett corrections.

(2) Significant/Potentially Significant Events (Deaths, Serious Adverse Events, and Study Discontinuation Due to AEs)

There were no deaths in either of the two studies.

The only serious adverse event was an ECG abnormality (sinus bradycardia and antero/lateral ischemia) that developed on the Day 15 ECG in a patient in the PSE group. The investigator indicated this was of moderate severity and was unlikely to be treatment related. This subject was a 45-year-old Caucasian male with a history of hypertension that was being treated with amlodipine. He was also taking pain medication for arthritis and back pain. His baseline ECG showed sinus bradycardia. At the final visit (Day 15) it was discovered that he had experienced chest pain during the study on Day 8. On Day 8 he had gone to see a non-study physician who prescribed prednisone and rofecoxib. He continued to take his study medication. On Day 15 the ECG changes were noted but the patient refused referral to a cardiologist or further work-up [S8/ISS/34].

A total of 45 of the 1248 (3.6%) subjects discontinued from the studies as a result of adverse events. The incidence of discontinuation due to AE was greatest in the PSE group (5.0%), followed by the DL D-12 group (3.6%), and the DL group (2.2%) [S8/ISS/35]. None of these events were considered serious. The most frequent events associated with discontinuation were dizziness and somnolence in the DL D-12 group (1% and 1%, respectively), and insomnia and sinusitis in the PSE group (1.4% and 1.2%, respectively). All other AEs leading to discontinuation occurred in $\leq 1\%$ of subjects in any treatment group [S8/ISS/39].

Six subjects discontinued the study due to adverse events characterized as General Cardiovascular Disorders, or Heart Rate and Rhythm Disorders. This included two subjects in the DL D-12 group (1 for hypertension [BP 165/120], and 1 for tachycardia), and four subjects in the PSE group (3 for palpitations, and 1 for tachycardia). Two additional subjects in the DL group discontinued due to chest pain. For all of these subjects, with the exception of the subject with hypertension, all vital signs and ECG data were normal both at Screening and at study discontinuation.

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A total of six subjects temporarily interrupted treatment due to an AE. This included 1 subject in the DL D-12 group (dizziness and dyspepsia), 1 subject in the DL group (somnolence), and 4 subjects in the PSE group (dizziness/nausea, mouth dry/sleep deprivation, vertigo, and insomnia). Of these, the only events categorized as severe were the dizziness/nausea experienced by a subject in the PSE group [S8/ISS/40].

(3) Other safety findings: Adverse Events, Lab findings, Vital Signs, and ECGs

(a) Adverse Events

The majority of the adverse events that occurred following treatment with DL D-12 were similar in type and frequency to those observed with PSE. The overall incidence of adverse events was greater in the DL D-12 and PSE treatment groups (44.0% and 44.8%, respectively) compared with the DL group (37.9%) [S8/ISS/21]. The incidence of severe adverse events was also greater in the DL D-12 and PSE treatment groups (7.7% and 9.2%, respectively) compared with the DL group (4.9%). The table below summarizes the occurrences of the following adverse events: all AEs; all AEs deemed treatment-related; severe AEs; and severe AEs deemed treatment-related).

Number (%) of Subjects Reporting Adverse Events: Studies P00355 and P00362, All Randomized Subjects						
[Number(%) of Subjects]	<u>DL D-12</u>		<u>DL</u>		<u>PSE</u>	
	(N = 414)		(N = 412)		(N = 422)	
Any Adverse Event	182	(44.0)	156	(37.9)	189	(44.8)
Any Treatment-Related Adverse Event	110	(26.6)	62	(15.0)	110	(26.1)
Any Severe Adverse Event	32	(7.7)	20	(4.9)	39	(9.2)
Any Severe Treatment-Related Adverse Event	17	(4.1)	5	(1.2)	19	(4.5)

The most frequently reported adverse events were insomnia, headache, and dry mouth. Insomnia and dry mouth occurred with greater frequency among subjects treated with DL D-12 (9.7% and 7.5%, respectively) and PSE (12.6% and 7.8%, respectively) compared with subjects treated with DL (2.7% and 2.4%, respectively). Headache occurred with similar frequency in all treatment groups (7.5%, 7.5%, and 8.8% in the DL D-12, DL, and PSE groups, respectively). The table below summarizes all of the adverse events that were reported by at least 2% of subjects in any treatment group. The table below includes only AEs that were "treatment-emergent." Treatment emergent AEs were those that began on or after the treatment start date up to 30 days after the treatment stop date, or began prior to the treatment start date and worsened in severity while on treatment. Adverse events that did not have a start date were considered treatment emergent. Any adverse event that began prior to the treatment start date and did not increase in severity during treatment or began more than 30 days after the treatment stop date was not considered treatment emergent. **Reviewer's Note: While this is a reasonable definition**

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of types of AEs that would be of interest in a safety analysis, it appears from the data that there may have been some variability in its application. The reported overall incidence of headache was notably higher than the reported incidence of treatment emergent headache. Overall, headache occurred in 12%, 10.7%, and 12.3% of patients in the DL D-12, DL, and PSE groups, respectively [reference: Biometrics Review]. This is in contrast to the incidences of treatment emergent headache, which were 7.5%, 7.5%, and 8.8% (see table below). However, the differences between the overall incidences and treatment emergent incidences of the other AEs were much smaller. Nonetheless, because there is some question about the application of the “treatment emergent” standard, the product label should include the overall incidences of the adverse events. A table of the overall incidences of AEs occurring at a rate $\geq 1\%$ in any treatment group may be found in the Biometrics Review written by Dr. Zhou. The adverse events that were reported more frequently in the DL D-12 group than either of the other groups are shaded. These events were fatigue, dizziness, and pharyngitis.

Incidence of Treatment Emergent Adverse Events Reported by $\geq 2\%$ of Subjects in Any Treatment Group, by Body System/Organ Class (Studies P00355/P00362, All Randomized Subjects)						
[Number (%) of subjects]						
Body System/Organ Class Preferred Term	DL D-12 (N = 414)		DL (N = 412)		PSE (N = 422)	
Any Adverse Event	182	(44.0)	156	(37.9)	189	(44.8)
Autonomic Nervous System Disorders	34	(8.2)	11	(2.7)	33	(7.8)
Mouth Dry	31	(7.5)	10	(2.4)	33	(7.8)
Body As a Whole - General Disorders	54	(13.0)	50	(12.1)	56	(13.3)
Fatigue	16	(3.9)	9	(2.2)	10	(2.4)
Headache	31	(7.5)	31	(7.5)	37	(8.8)
Central and Peripheral Nervous System Disorders	24	(5.8)	13	(3.2)	17	(4.0)
Dizziness	14	(3.4)	10	(2.4)	9	(2.1)
Gastrointestinal System Disorders	35	(8.5)	27	(6.6)	37	(8.8)
Anorexia	8	(1.9)	0		9	(2.1)
Nausea	9	(2.2)	5	(1.2)	13	(3.1)
Musculoskeletal System Disorders	11	(2.7)	14	(3.4)	12	(2.8)
Myalgia	6	(1.4)	9	(2.2)	6	(1.4)
Psychiatric Disorders	66	(15.9)	31	(7.5)	73	(17.3)
Insomnia	40	(9.7)	11	(2.7)	53	(12.6)
Nervousness	6	(1.4)	0		11	(2.6)
Somnolence	13	(3.1)	16	(3.9)	7	(1.7)
Resistance Mechanism Disorders	10	(2.4)	12	(2.9)	13	(3.1)
Infection Viral	9	(2.2)	8	(1.9)	10	(2.4)
Respiratory System Disorders	32	(7.7)	33	(8.0)	38	(9.0)
Pharyngitis	14	(3.4)	11	(2.7)	11	(2.6)
Sinusitis	3	(< 1)	4	(1.0)	11	(2.6)

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The incidence of adverse events that were deemed treatment-related by the investigator was greater in the DL D-12 and PSE treatment groups compared with the DL treatment group (26.6% and 26.1%, versus 15.0%, respectively) [S8/ISS/25]. Insomnia was the most frequently reported treatment-related AE among subjects treated with DL D-12 and PSE (8.9% and 12.1%, respectively) and the incidence in these two groups was significantly greater than in the DL group (2.2%). The next most frequently reported treatment-related AE among subjects in the DL D-12 and PSE group was dry mouth (7.2% and 7.8%, respectively). Treatment-related dry mouth was less common in the DL group (2.4%). The majority of adverse events were mild to moderate in severity. The incidence of severe adverse events was 7.7% in the DL D-12 group, 4.9% in the DL group, and 9.2% in the PSE group [S8/ISS/22]. The table below summarizes the incidence of treatment-related adverse events reported by $\geq 2\%$ of subjects. The treatment related adverse events that were more frequent in the DL D-12 group than in the other two groups are shaded. These events were fatigue, headache, and dizziness.

Incidence of Treatment-Related Adverse Events Reported by $\geq 2\%$ of Subjects in Any Treatment Group, by Body System/Organ Class (Studies P00355/P00362, All Randomized Subjects)						
(Number (%) of Subjects)						
Body System/Organ Class Preferred Term	DL D-12 (N = 414)		DL (N = 412)		PSE (N = 422)	
Any Treatment-Related Adverse Event	110	(26.6)	62	(15.0)	110	(26.1)
Autonomic Nervous System Disorders	33	(8.0)	11	(2.7)	33	(7.8)
Mouth Dry	30	(7.2)	10	(2.4)	33	(7.8)
Body As a Whole - General Disorders	24	(5.8)	14	(3.4)	19	(4.5)
Fatigue	11	(2.7)	6	(1.5)	6	(1.4)
Headache	13	(3.1)	6	(1.5)	11	(2.6)
Central and Peripheral Nervous System Disorders	17	(4.1)	7	(1.7)	11	(2.6)
Dizziness	10	(2.4)	4	(1.0)	3	(<1)
Gastrointestinal System Disorders	20	(4.8)	8	(1.9)	22	(5.2)
Anorexia	8	(1.9)	0		9	(2.1)
Psychiatric Disorders	59	(14.3)	26	(6.3)	71	(16.8)
Insomnia	37	(8.9)	9	(2.2)	51	(12.1)
Nervousness	5	(1.2)	0		11	(2.6)
Somnolence	11	(2.7)	14	(3.4)	6	(1.4)

The incidence of severe adverse events (SAEs) was greater in the DL D-12 (7.7%) and PSE (9.2%) groups compared to the DL group (4.9%). The table below shows the incidence of SAEs that were reported by >1 subject, by treatment group. The most frequent severe adverse events were insomnia, headache, and dry mouth. The two SAEs that were more frequent in the DL D-12 group than in the other two groups are shaded. These SAEs were headache and dry mouth (1.9% and 1.0% in the DL D-12 group; $<1\%$ and $<1\%$ in the PSE group; and $<1\%$ and 0 in the DL group) [S8/ISS/27]. Severe

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insomnia was reported in 1.4% of subjects in the DL D-12 group, 2.4% of subjects in the PSE group, and <1% of subjects in the DL group.

Incidence of Severe Adverse Events Reported by > 1 Subject in Any Treatment Group, by Body System/Organ Class (Studies P00355 and P00362 , All Randomized Subjects) [S8/ISS/27]				
Body System/Organ Class Preferred Term	Number (%) of Subjects			
	DL D-12 (N = 414)	DL (N = 412)	PSE (N = 422)	
Any Severe Adverse Event	32	(7.7)	20	(4.9)
Autonomic Nervous System Disorders	4	(1.0)	0	4 (< 1)
Mouth Dry	4	(1.0)	0	4 (< 1)
Body As a Whole - General Disorders	10	(2.4)	4	(1.0)
Headache	8	(1.9)	3	(< 1)
Central and Peripheral Nervous System Disorders	3	(< 1)	0	3 (< 1)
Dizziness	2	(< 1)	0	1 (< 1)
Gastrointestinal System Disorders	4	(1.0)	3	(< 1)
Anorexia	1	(< 1)	0	2 (< 1)
Nausea	1	(< 1)	1	(< 1)
Vomiting	0	(< 1)	2	(< 1)
Musculoskeletal System Disorders	2	(< 1)	2	(< 1)
Arthralgia	2	(< 1)	0	0
Psychiatric Disorders	10	(2.4)	2	(< 1)
Insomnia	6	(1.4)	1	(< 1)
Somnolence	3	(< 1)	0	0
Respiratory System Disorders	2	(< 1)	6	(1.5)
Pharyngitis	0	(< 1)	2	(< 1)
Sinusitis	0	(< 1)	1	(< 1)
Vision Disorders	0	(< 1)	2	(< 1)
Eyes, Dry	0	(< 1)	2	(< 1)

(b) Laboratory Findings

Blood chemistry, hematology, and urinalysis were performed at Baseline and at the end of treatment. The median percent change from baseline to end of treatment was not significant for any of these variables in any treatment group, and there were no important differences between groups [S8/ISS/42]. In addition to the analyses of median values, the Applicant provided data on the percentages of patients in each treatment group that exhibited a change relative to the normal range (low, normal, or high) from Baseline to endpoint for each laboratory variable [S8/ISS/44-47]. In this data, the only change of possible significance was the percentage of patients who had a normal eosinophil count at Baseline and a high count at the endpoint (8% in the DL D-12 group, 5% in the DL group, and 3% in the PSE group).

The Applicant defined the following laboratory values as being “clinically meaningful”: blood chemistry value ≥ 2.6 times the upper limit of normal, hemoglobin concentration \leq

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9.4g/dL, platelet count $\leq 74,000 \mu\text{L}$, or WBC $\leq 2,900/\mu\text{L}$. **Reviewer's Comment:** Although these cut-off values are reasonable, it is not clear whether these definitions were pre-specified or if they were applied post-hoc. Using these definitions, 17 subjects had clinically meaningful laboratory values (6 in the DL D-12 group, 9 in the DL group, and 2 in the PSE group) [S8/ISS/47].

Seven subjects had liver function test abnormalities (1 in the DL D-12 group, 5 in the DL group, and 1 in the PSE group) [S8/ISS/47]. Three of these seven were abnormal at Screening and either remained outside the upper limit of normal or normalized. Two of the seven subjects (1 in the DL D-12 group, 1 in the DL group) had values that were at or above the upper limit of normal at Screening and that were ≥ 2.6 times the upper limit of normal at Endpoint. The remaining two subjects, both of whom were in the DL group, had normal values at Screening and values at endpoint that were ≥ 2.6 times the upper limit of normal. The table below summarizes the subjects with "clinically meaningful" values for liver function tests. Values that increased between Screening and endpoint are shaded. **Reviewer's Comment:** The fact that all of the subjects exhibiting a rise to a "clinically meaningful" value for a liver function test were in either the DL D-12 or the DL group, raises the possibility that the liver function abnormalities could be attributed desloratadine. However, it is difficult to draw any conclusions based on these few patients.

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Subjects with "clinically meaningful" liver function test values (Studies P00355 and P00362) [S8/ISS/49]				
Subject No.	Lab Parameter	Screening Value	Endpoint Value	Reference Range
DL D-12 Group				
P00355-03/056	ALT (SGPT)	185 U/L	269 U/L	0-45 U/L
	AST (SGOT)	74 U/L	123 U/L	0-41 U/L
DL Group				
P00362-04/171	ALT (SGPT)	146 U/L	120 U/L	0-45 U/L
P00362-06/243	AST (SGOT)	22 U/L	123 U/L (36 U/L) ^a	0-41 U/L
P00362-09/781	AST (SGOT)	41 U/L	132 U/L (48 U/L) ^a	0-41 U/L
P00362-12/747	ALT (SGPT)	39 U/L	269 U/L (150 U/L) ^b (72 U/L) ^a	0-45 U/L 0-41 U/L
	AST (SGOT)	30 U/L	135 U/L (35 U/L) ^b (29 U/L) ^a	
P00362-19/599	AST (SGOT)	136 U/L	14 U/L	0-41 U/L
P00362-20/015	LDH	185 U/L	663 U/L (173 U/L) ^a	100-220 U/L
PSE Group				
P00355-15/311	ALT (SGPT)	130 U/L	66 U/L	0-45 U/L

(a) repeat value approximately 1-2 weeks later

(b) repeat value approximately 2 days later

(c) Vital Signs

Vital signs were evaluated at each visit. The mean change from Baseline was examined for diastolic and systolic blood pressure, heart rate, and respiration rate. Analyses of systolic and diastolic blood pressure and respiratory rate using both mean values [S8/ISS/51] and distribution of subjects among percentiles of change [S8/ISS/52] did not suggest a treatment effect. Changes in heart rate were noted in the DL D-12 and PSE groups. At endpoint, an increase of 3.8 bpm in mean heart rate was noted for both the DL D-12 and the PSE groups, compared with 2.3 bpm in the DL group. The percentage of patients exhibiting a $\geq 30\%$ increase in heart rate between baseline and endpoint were 5.4% in the DL D-12 group, 5.7% in the PSE group, and 2.7% in the DL group.

(d) ECG Results

Twelve-lead ECGs were obtained at Baseline and at Visit 4. The majority of the ECGs were normal at both time points. Of the 1248 randomized subjects who had both Baseline and Endpoint ECGs, only 3 had clinically significant abnormal ECGs at Endpoint: one subject (DL D-12 group) had a normal ECG at Baseline and mild tachycardia at Endpoint; two subjects had Baseline ECGs that were abnormal but not clinically significant at Baseline, and clinically significant abnormal ECGs at Endpoint.

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

Integrated Review of Safety

The clinically significant abnormalities were mild premature atrial contractions (DL D-12 group) and sinus bradycardia with anterolateral ischemia (PSE group). The table below summarizes the classifications of the Baseline and Endpoint ECGs by treatment group.

Summary of ECG Evaluations at Baseline and Endpoint:							
(Studies P00355 and P00362, All Randomized Subjects)							
[Number (%) of Subjects]						[S8/ISS/53]	
		<u>DL D-12</u>		<u>DL</u>		<u>PSE</u>	
Baseline Evaluation	Endpoint Evaluation	(N = 414)		(N = 412)		(N = 422)	
Normal	Normal	213	(51)	247	(60)	214	(51)
	Abnormal, NCS	29	(7)	37	(9)	58	(14)
	Abnormal, CS	1	(< 1)	0		0	
	Not Done	0		0		0	
	Missing	3	(1)	2	(< 1)	3	(1)
Abnormal, NCS	Normal	71	(17)	42	(10)	61	(14)
	Abnormal, NCS	95	(23)	83	(20)	84	(20)
	Abnormal, CS	1	(< 1)	0		1	(< 1)
	Not Done	0		0		0	
	Missing	0		1	(< 1)	1	(< 1)
Abnormal, CS	Normal	1	(< 1)	0		0	

Note: NCS = Not clinically significant. CS = Clinically significant.

The mean ventricular rate increased by 7.1 bpm in the DL D-12 group, and 6.4 bpm in the PSE group, compared to an increase of 3.2 bpm in the DL group. Among subjects who received DL D-12, the increase from Baseline in ventricular rate was slightly greater among females than males (8.0 bpm versus 5.8 bpm). The percentage of patients exhibiting an increase in ventricular rate $\geq 20\%$ was greater in the DL D-12 group (26%) and the PSE group (22%), than in the DL group (13%) [S8/ISS/59].

The mean change in QT was -14msec in the DL D-12 group, -6.3msec in the DL group, and -14.5msec in the PSE group [S8/ISS/55]. The mean change in QTc using the Fredericia formula was -1.2msec in the DL D-12 group, -0.1msec in the DL group, and -3sec in the PSE group [S8/ISS/55]. The mean change in QTc using the Bazett formula was +5.7 in the DL D-12 group, +3.2 in the DL group, and +3.2 in the PSE group [S8/ISS/380]. QTc outliers (using the Fredericia formula) were assessed by presenting the percentage of patients with changes in QTc of <0, 0-30, 31-60 and ≥ 61 milliseconds. A total of 26 patients had a change in QTc of 31-60 milliseconds: 8 (2%) in the DL D-12 group, 11 (3%) in the DL group, and 7 (2%) in the PSE group. Two subjects each in the DL D-12 and DL groups had a change from baseline that was >60 milliseconds [S8/ISS/60].