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RESEARCH**

*APPLICATION NUMBER:*

**21-300**

**MEDICAL REVIEW**

## CLINICAL REVIEW

Application Type NDA  
Submission Number 21-300 and 21-563  
Submission Code N000 (B2)

Letter Date 27 February 2004  
Stamp Date 2 March 2004  
PDUFA Goal Date 27 August 2004

Reviewer Name Richard Nicklas MD  
Review Completion Date 31 August 2004

Established Name desloratadine  
(Proposed) Trade Name Clarinex syrup  
Therapeutic Class antihistamine  
Applicant Schering Corporation

Priority Designation 1S

Formulation syrup  
Dosing Regimen 2.5 mg once daily (6-11 years); 1.25 mg once daily (2-5 years); 1.25 mg once daily (12-23 months) and 1 mg once daily (6-11 months)  
Indication allergic rhinitis, chronic idiopathic urticaria  
Intended Population patients 6 months-11 years of age with allergic rhinitis or chronic idiopathic urticaria

\* The sponsor submitted a response to the Division's Pediatric Written Request for Clarinex syrup on 6 June 2000. Studies 302 and 303 of the Written Request were submitted under NDA 21-300 on 8 December 2000. A supplemental NDA for patients 6 months to 2 years of age was submitted on 4 December 2002 (see MOR of 14 May 2003). It was given the NDA number 21-563 because NDA 21-300 was in approvable status and therefore a response to the Division's Pediatric Written Request could not be submitted to that NDA. There are, therefore, three submissions by the sponsor on 27 February 2004: 1) a complete response to the NDA 21-300 approvable letter; 2) a response to the NDA 21-300 CMC DRL; and 3) complete response to the NDA 21-563 approvable letter. The supplemental NDA submitted under NDA 21-563 references the data submitted under NDA 21-300 to support the safety of desloratadine in poor metabolizers 6-23 months of age. Therefore, this review of the data submitted under NDA 21-300 applies to NDA 21-563 as well.

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## 1 Executive Summary

### 1.1 Recommendation on Regulatory Action:

The safety of Clarinex for the treatment of allergic rhinitis and chronic idiopathic urticaria in patients 2-11 years of age was demonstrated in the SNDA (NDA 21-300) of 8 December 2000 which led to the Approvable Letter of 2 October 2001. As indicated in the Approvable Letter, additional data was needed to assess the safety in patients who were poor metabolizers of desloratadine. In addition, in response to the Division's Pediatric Written Request, a SNDA for patients 6 months to 2 years of age was submitted on 4 December 2002 under NDA 21-563 and found to be approvable (see MOR of 14 May 2003 under NDA 21-563). In terms of safety, this decision was based on the safety of Clarinex syrup in patients 6-23 months of age that was demonstrated in the studies submitted by the sponsor. In addition, the efficacy of Clarinex was demonstrated by extrapolation of data from adults to patients 6-23 months of age because there was no reason to believe that either the clinical condition being studied nor the pharmacokinetics or pharmacodynamics would be different in this age group than in adults. However, approval of Clarinex syrup for patients 6-23 months of age was also dependent on the resolution of issues related to the safety in this age group of poor metabolizers of desloratadine.

On 27 February 2004, the sponsor submitted a Complete Response to the Approvable Letters for NDA 21-300 and NDA 21-563 for the administration of Clarinex Syrup (desloratadine) to children 6 months-12 years of age. From a clinical standpoint, the Approvable Letter requested data characterizing the pharmacokinetics of repetitive dose administration in children who are poor metabolizers of desloratadine that would establish an upper limit of exposure in poor metabolizers and provide data to support the safety of this level of exposure. In addition, the sponsor was encouraged to determine the mechanism for higher levels of desloratadine exposure in poor metabolizers. The sponsor, in this submission, has adequately characterized the pharmacokinetics of repetitive dose administration in children who are poor metabolizers and shown that the upper limit of exposure in pediatric and adult poor metabolizers is similar and 6-7 times higher than is seen in normal metabolizers. In terms of safety, the sponsor has shown in 6 multiple dose studies, that there is no significant difference in adverse events, laboratory tests or vital signs between pediatric poor metabolizers who receive desloratadine and pediatric normal metabolizers who receive desloratadine or children who receive placebo. Under NDA 21-165, the tablet formulation for Clarinex, a dose of 45 mg of desloratadine (9 times the recommended dose) (study 357 – see MOR for Clarinex tablets) was given to healthy volunteers for 10 days without any clinically significant prolongation of the QTc interval compared with placebo, based on machine reading of the QTc interval and maximum QTc from serial ECGs. Although the sponsor has submitted no ECG data on children 6 months to 2 years of age who are poor metabolizers, there is not reason to believe that this age group would be more likely to develop prolongation of the QTc interval after administration of desloratadine. The sponsor has provided data to support the proposed dosing of Clarinex, dosing that in the initial review of this NDA and the supplement for patients 6-23 months of age was found to be safe and effective, and in this complete response to the approvable letter has been shown to be safe in children who are poor metabolizers of desloratadine. Therefore, Clarinex syrup should be approved for administration to children 6 months to 12 years of age.

## 1.2 Recommendation on Postmarketing Actions

There are no recommendations for post-marketing action at this time.

### 1.2.1 Risk Management Activity

No Risk Management Activity is necessary for this drug product.

### 1.2.2 Required Phase 4 Commitments

No Phase 4 Commitment is necessary for this drug product.

### 1.2.3 Other Phase 4 Requests

There are no Phase 4 Requests.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Desloratadine (Clarinx) is an antihistamine that is a metabolite of loratadine, an OTC antihistamine and has been approved for treatment of allergic rhinitis and chronic idiopathic urticaria for patients 12 years of age and older. In evaluating the data submitted for approval of the syrup formulation in patients 2-11 years of age, it was found that a subset of patients were poor metabolizers of desloratadine. In order to evaluate the clinical significance of this finding in patients 2-11 years of age, the following studies were performed and submitted in this complete response to the Division's Approvable Letter of 2 October 2001.

Overall, in the three key studies evaluating the safety of desloratadine in patients 2-11 years of age (2798, 3016 and 2994) there were 2554 patients of whom 158 were poor metabolizers.

The sponsor performed a single dose screening study in children 2-11 years of age with allergic rhinitis to identify patients who were poor metabolizers of desloratadine syrup (study 2818) for prospective evaluation in repetitive dose studies (studies 2798 and 3016). In addition, the sponsor did another single dose screening study in patients 2-11 years of age with allergic rhinitis (study 3031) to identify poor metabolizers for enrollment in a subsequent multicenter study with sites in the United States and Latin America (study 2994). The sponsor also did a retrospective review of data from studies 302, 303 and C98-566, which had been performed previously (see table and discussion of clinical studies below). From these screening studies, 106 poor metabolizers were evaluated in regard to safety parameters after receiving repetitive doses of desloratadine or loratadine at a dose of 1.25 mg (2-5 years) or 2.5 mg (6-11 years) of desloratadine or 5 mg of loratadine.

There were 359 patients enrolled in study 2818 who were 2-11 years of age with allergic rhinitis. They received a single dose of 10 mg of loratadine and were phenotyped for poor metabolizer status. There were 53 poor metabolizers, of whom 16 were 2-5 years and 37 were 6-11 years. From this study, 17 poor metabolizers were entered into study 2798 and 15 poor metabolizers were entered into study 3016. Study 2798 was a repetitive dose, randomized, placebo controlled, double-blind, parallel group study in patients 2-11 years of age with allergic rhinitis who received either 1.25 mg (2-5 years) or 2.5 mg (6-11 years) per day of desloratadine for 17 days.

In addition to the 17 poor metabolizers, there were 21 patients who were normal metabolizers and 10 placebo patients. Study 3016 was a repetitive dose, randomized, double-blind, placebo-controlled, parallel group study in patients 2-11 years of age with allergic rhinitis who received either 1.25 mg (2-5 years) or 2.5 mg (6-11 years) per day of desloratadine for 29 days. In addition to the 15 poor metabolizers, there were 5 patients who were normal metabolizers and 22 placebo patients. Safety evaluation in studies 2798 and 3016 included adverse events, vital signs, laboratory tests, and ECGs. In study 3016, ECGs were performed at baseline and 3 hours after drug administration on selected study days during drug administration while in study 2798, ECGs were performed at baseline and on selected study days 2, 4, 8, 12 and 24 hours after drug administration.

There were 162 patients in study 2781, an analysis of patients from studies previously performed in patients 2-11 years of age, for the purpose of identifying patients who were poor metabolizers. These included study 302, a randomized, double-blind, placebo-controlled, parallel group study in 120 patients 6-11 years of age with allergic rhinitis or idiopathic chronic urticaria who received 2.5 mg of desloratadine per day for a period of 15 days. In this study there were 8 poor metabolizers identified, as well as 52 patients who were normal metabolizers and had received desloratadine and 60 patients who received placebo. In study 303, there were 107 patients 2-5 years of age who received 1.25 mg of desloratadine per day for a period of 15 days in a randomized, repetitive dose, double-blind, placebo-controlled, parallel group study. Included in this study were 8 poor metabolizers, 43 normal metabolizers who received desloratadine and 56 patients who received placebo. There were 112 patients from study C98-566 – 41 normal metabolizers, 10 poor metabolizers and 61 patients who received placebo who were included in study 2781 as well. C98-566 was a repetitive dose, randomized, placebo controlled, double-blind, parallel group study in patients 2-5 years of age with either allergic rhinitis or chronic idiopathic urticaria who received loratadine 5 mg per day for 14 days.

Study 3031 was a single dose screening study in 2075 patients 2-11 years of age with a history of atopy or chronic idiopathic urticaria who received 10 mg of loratadine. From this study, 79 poor metabolizers were identified. Of these, 27 were 2-5 years of age and 52 were 6-11 years of age. Study 2994 was a repetitive dose, multicenter, double-blind, placebo-controlled, parallel group study in 97 patients 2-11 years of age who received either 1.25 mg (2-5 years) or 2.5 mg (6-11 years) per day for 36 days. There were 97 patients in this study, including 58 poor metabolizers who received desloratadine and 49 patients who received placebo.

### 1.3.2 Efficacy

There was no efficacy evaluation in this submission. Studies were performed to assess the safety of desloratadine when administered to patients who had been identified as poor metabolizers.

### 1.3.3 Safety

Safety of desloratadine administration in patients 2-11 years of age who were poor metabolizers was assessed by adverse events, vital signs, laboratory studies, and ECGs in studies 2798, 3016 and 2994 prospectively and studies 302, 303 and C98-566 retrospectively. These repetitive dose studies included 96 poor metabolizers who received desloratadine, 10 poor metabolizers who received loratadine, 123 normal metabolizers who received desloratadine and 258 placebo patients. Patients received desloratadine for 15-36 days in these studies.

There were no serious adverse events in patients after receiving desloratadine who were poor metabolizers. The incidence of adverse reactions in poor metabolizers is greater than that in normal metabolizers based on data overall from multiple and single dose studies but in the multiple dose studies the incidence was essentially the same as seen after administration of placebo and in the single dose studies the difference was small. Moreover, there was no significant difference noted between poor metabolizers and patients who received placebo in terms of individual adverse events, which were small in number in most studies, consistently mild, rarely considered even possibly related to the study drug and generally expected from any clinical study, e.g. headache, drowsiness. There was one patient who was a poor metabolizer and who was withdrawn from study 2994 because of somnolence and abdominal pain after receiving desloratadine, and abdominal pain did occur more frequently in poor metabolizers in some studies, although this was not a consistent finding. The sponsor has provided data on adverse event profiles in children 2-11 years of age who are poor metabolizers of desloratadine that supports the safety of desloratadine when administered to this subset of patients.

The database for cardiovascular safety based on ECG determinations included 32 poor metabolizers from studies 2798 and 3016, 16 poor metabolizers from studies 302 and 303, 10 poor metabolizers from study C98-566 and 48 poor metabolizers from study 2994. Studies 2798 and 3016 are important studies from a cardiovascular standpoint, especially study 2798. In study 2798, ECGs were obtained at screening, baseline, on day 1 and 10 prior to drug administration, and on days 9 and 17 prior to drug administration as well as 2, 4, 8, 12 and 24 hours after drug administration. In study 3016, ECGs were performed at baseline and 3 hours after drug administration on days 8, 15, 22, and 29. In both studies ECGs were transferred via modem to an independent, blinded, third party evaluator who manually read the ECGs. The primary pharmacodynamic parameters were mean change from baseline in manually read ventricular rate, and ECG intervals including QTc intervals corrected by both the Bazett and Fridericia methods. All variables were analyzed using ANOVA. In studies 302 and 303, ECGs were machine read at the study site at baseline and on days 8 and 15, 3 hours after drug administration. In study 2994, ECGs were done at baseline and on days 8, 15, 22, 29, and 36, 3 hours after drug administration. They were read by a cardiologist away from the study site.

As seen in the table below, in some studies there was a greater mean prolongation of the QTc interval in children who are poor metabolizers and received desloratadine than in children who are normal metabolizers and received desloratadine or children who received placebo. Bazett's overcorrects for the ventricular rate but this effect was also seen using Fridericia's correction.

On the other hand, there were only a few patients who developed prolongation of the QTc interval that was greater than 440 msec (470 msec or less which was considered the upper limit of normal for females) and this occurred at least as frequently in normal metabolizers or patients who received placebo. In most studies, differences in prolongation of the QTc interval between poor metabolizers and other study groups disappeared when Fridericia's correction was used. In addition, no adverse cardiovascular events were reported in any of the treatment groups and there was no clinically significant change in any ECG tracing from baseline in children who were poor metabolizers. Looking at the individual patient data in study 2798, there were a comparable number of time points at which poor metabolizers, normal metabolizers and placebo patients had a 20 msec or greater change in QTc interval from baseline. Only at 4 hours after drug administration was the average QTc interval significantly higher in poor metabolizers than in either the normal metabolizer or placebo group in this study.

**Conclusion:** Although there was a greater mean prolongation of the QTc interval in children who are poor metabolizers of desloratadine in some studies in this submission, the differences that were seen are not known to be clinically significant. Therefore, the differences in prolongation of the QTc interval between poor and normal metabolizers that was seen in some studies submitted with this Complete Response does not raise a safety concern that would preclude the approval of Clarinex syrup for patients 6 months to 11 years of age. The sponsor has demonstrated the safety of desloratadine administration in children 6 months-11 years of age who are poor metabolizers of desloratadine.

Summary Table on mean differences in ventricular rate and QTc interval in poor metabolizers, normal metabolizers and placebo patients based on all multiple dose studies in children submitted under NDA

Study	Vent rate	Vent rate	Vent rate	QTcB	QTcB	QTcB	QTcF	QTcF	QTcF
	bpm	bpm	bpm	msec	msec	Msec	Msec	msec	msec
	Poor	Normal	placebo	Poor	Normal	Placebo	Poor	Normal	placebo
2798	↑ 9.8	↑ 2.8	↑ 1.4	↑ 9.6	↑ 3.8	↑ 6.3	↑ 1.8	↑ 1.6	↑ 4.8
2994	↑ 5.8	-	↑ 1	↑ 5.7	-	↓ 2.4	↑ 1.1	-	↓ 2.8
3016	↑ 8.1	↑ 0.2	↑ 5.6	↑ 19.4	↓ 6.4	↑ 14.5	↑ 12.4	↓ 6.1	↑ 9.7
302	↓ 7	↓ 0.6	↓ 3.65	↑ 3.61	↓ 1.14	↓ 1.51	↑ 8.94	↓ 0.37	↑ 1.84
303	↑ 2.38	↓ 1.44	↓ 8.8	↑ 4.8	↑ 2.48	↓ 0.86	↑ 2.67	↓ 3.23	↑ 4.66
C98-566	↑ 1.2	↑ 1.8	↓ 2.1	↓ 2.3	↓ 2.42	↓ 2.72	↓ 2.65	↓ 2.56	↓ 0.96

#### 1.3.4 Dosing Regimen and Administration

The dosing regimen for Clarinex syrup proposed by the sponsor is 2.5 mg (1 teaspoon) once daily for patients 6-11 years of age, 1.25 mg (1/2 teaspoon) once daily for patients 1-5 years of age and 1 mg (2 ml) once daily for patients 6-11 months of age. In terms of children 6 months to 5 years of age, the drug should be administered with a commercially available measuring dropper or syringe that is calibrated to deliver 2 mL or 2.5 mL (1/2 teaspoonful). There is insufficient data to make a recommendation on dosing in children with liver or renal impairment. The sponsor's proposed dosing regimen and administration is acceptable. The selection of a dose of 1.25 mg per day for patients 2-5 years of age and 2.5 mg per day for patients 6-11 years of age was based on comparable bioavailability of a dose of 1.25 mg of Clarinex syrup in children 2-5 years of age, a dose of 2.5 mg of Clarinex syrup in children 6-11 years of age and a dose of 5 mg in adults when administered as the tablet formulation. Based on comparison of the data from the pharmacokinetic study 1341 in which patients 6-23 months of age received either 0.0625 or 1.25 mg of desloratadine with data from studies in adults who received 5 mg of the tablet formulation, it was concluded that patients 6-11 months of age should receive a dose of 1.00 mg and patients 12-23 months of age should receive a dose of 1.25 mg.

#### 1.3.5 Drug-Drug Interactions

No drug interaction studies were done in children 2-11 years of age. Clinical Pharmacology drug interaction studies in adults with concomitant administration of erythromycin, fluoxetine,

cimetidine, azithromycin, and ketoconazole produced increased plasma concentrations of desloratadine and 3-OH desloratadine. However, in these studies, no clinically relevant changes in ECGs or other safety parameters were observed. The sponsor did extensive in-vitro studies attempting to identify the enzyme(s) responsible for the metabolism of desloratadine to 3-OH desloratadine and was not able to identify the enzyme(s) responsible. These studies showed that the formation of 3-OH desloratadine was not catalyzed by any of the known CYP450 enzymes. In addition, neither desloratadine nor 3-OH desloratadine inhibit CYP450 enzymes responsible for the metabolism of most medications. Therefore, the potential for drug interaction is low.

#### 1.3.6 Special Populations

The sponsor has adequately assessed the incidence of poor metabolism of desloratadine in children and adults and showed that the prevalence is similar in adults and children. Moreover, the sponsor has shown that the difference in C<sub>max</sub> and AUC that is demonstrated in poor and normal metabolizers is similar for children 2-5 and 6-11 years and adults. Safety parameters were analyzed for children 2-5 years of age and 6-11 years of age and no significant differences were seen. There were no significant differences noted in either PK data or safety parameters between males and females. The incidence of poor metabolizers is greater in Black patients (17%) than in Caucasian or Hispanic patients (2%). However, there was no indication, based on the safety data provided by the sponsor, that Black patients were at any greater risk after administration of Clarinex syrup than non-Black patients.

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## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Antihistamines are used in the treatment of allergic rhinitis and chronic idiopathic urticaria. Clarinex (desloratadine), a second generation relatively non-sedating tricyclic antihistamine, is approved in the tablet formulation (film coated tablets (NDA 21-165) and orally-disintegrating RediTabs [NDA 21-312]) for use in the United States for allergic rhinitis and chronic idiopathic urticaria in patients 12 years of age and older and has been approved in the EU for patients with these conditions who are 2 years of age and older. The proposed indication for the syrup formulation in patients 6 months to 2 years of age is allergic rhinitis and chronic idiopathic urticaria at a dose of 1-2.5 mg once a day. The NDA for the syrup formulation of Clarinex (NDA 21-300) was submitted on 8 December 2001 for patients 2 years of age and older. The sponsor submitted on 6 April 2001 a 4 month safety update for the syrup formulation (see MOR of 2 October 2001) with data on 2154 patients who received Clarinex in repetitive dose studies of 2-6 weeks duration in adult and adolescent patients. Included in this submission were two pediatric studies of 2 weeks duration but no pharmacokinetic data was obtained in these studies, leading to the conclusion of the Division that there was inadequate data in children to support a determination of safety in children who were poor metabolizers. A conference call was held with the sponsor on 5 September 2001 to discuss the need for data in pediatric poor metabolizers (see minutes of telephone conversation). As a result, in the Approvable letter of 1 October 2001, the sponsor was asked to provide data on the pharmacokinetics and safety of desloratadine when administered on a repetitive basis to patients 2-12 years of age who were poor metabolizers. On 8 March 2002, a meeting was held with the sponsor, at which time the Division reiterated that additional safety and pharmacokinetic data in children who are poor metabolizers of desloratadine was needed and that safety data on approximately 100 poor metabolizers would be reasonable. As a follow-up to this meeting, the sponsor submitted the results of results of study 2818 and the proposed study design for study 3016. On 24 May 2002, a conference call was held between the sponsor and the Division to discuss aspects of study 2798, at which time there was discussion of the stratification in the study based on age and other considerations. On 4 March 2003, the Division again met with the sponsor.

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and 20% of Black children. It occurs in 2% of Hispanic adults and 2% of Hispanic children and in 8% of Caucasian children. Overall, the prevalence of poor metabolizer phenotype in patients 2-70 years of age is 9%. In single dose pharmacokinetic studies in children, the frequency of poor metabolism was 24% in Blacks and 9% in Caucasians (see below)

Frequency of Poor Metabolizers (submission 9 July 2004, p24, t2)

Overall

Adults – 6%; Children – 6%

Ethnic Background

Caucasians – overall 2%

Adults – 2%

Children – 3%

Blacks – overall 17%

Adults – 18%

Children – 16%

Hispanic – overall 2%

Adults – 2%

Children – 1%

## 2.2 Currently Available Treatment for Indications

Clarinx is indicated for the treatment of allergic rhinitis and chronic idiopathic urticaria. The treatment of allergic rhinitis involves avoidance, pharmacotherapy and allergen immunotherapy. The treatment of chronic idiopathic urticaria is based on pharmacotherapy. The pharmacotherapy for allergic rhinitis includes antihistamines, intranasal corticosteroids, mediator inhibitors, nasal decongestants, and intranasal saline solutions. Other antihistamines include first generation OTC antihistamines, e.g. diphenhydramine, second generation non-sedating antihistamines such as fexofenadine and intranasal antihistamines, e.g. Astelin. The two most common pharmacotherapeutic approaches for the management of allergic rhinitis are: 1) antihistamine-decongestants; and 2) intranasal corticosteroids. The pharmacotherapeutic management of chronic urticaria is based primarily on the use of antihistamines, e.g. hydroxyzine, cetirizine, diphenhydramine.

## 2.3 Availability of Proposed Active Ingredient in the United States

A NDA for the 5 mg tablet formulation has been approved for patients 12 years of age and older (NDA 21-165). On 8 December 2000 an NDA (21-300) was submitted by the sponsor for Clarinx syrup under section 505(b). On 5 September 2001, a conference call was held with the sponsor to discuss the finding that there was a subset of patients who were poor metabolizers of desloratadine. On 2 October 2001 an approvable letter was issued for Clarinx syrup. On 8 March 2002 a meeting was held with the sponsor in regard to the issue

on poor metabolizers. Loratadine, the parent compound for desloratadine has been marketed in the United States since 1993. Loratadine syrup was approved for SAR and chronic urticaria in patients down to 6 years of age in October 1996 and for these conditions in patients down to 2 years of age in December 2000.

#### 2.4 Important Issues With Pharmacologically Related Products

Some antihistamines of this class, i.e. broadly referred to as non-sedating antihistamines, have been shown to prolong the QTc interval. This has not been shown to occur with desloratadine or the parent compound, loratadine. In fact, the safety of loratadine is reflected in the decision to make it available OTC. Nevertheless, prolongation of the QTc interval and resultant cardiovascular events have been an important issue with some non-sedating antihistamines and led to the withdrawal from the market of terfenadine and astemizole and the non-approval of others, e.g. ebastine, norastemizole. On the other hand, no evidence of clinically significant prolongation of the QTc interval has been demonstrated for loratadine, desloratadine, fexofenadine or cetirizine.

#### 2.5 Presubmission Regulatory Activity

An approvable letter for patients 2-11 years of age was sent to the sponsor on 1 October 2001. In that letter the sponsor was asked to address 21 deficiencies. Comments 1-17 and 22 dealt with Chemistry issues. Questions 1-17 were included in an FDA Discipline Review Letter on 8 February 2001, a response to which was made by the sponsor on 28 June 2001. After discussion with the CMC reviewer, it appears that the sponsor has adequately responded to any outstanding Chemistry issues. A response to comments 18-21 which dealt with clinical issues have been included in this submission. These are:

Comment 18: "From the submitted pharmacokinetic data, it appears that a substantial number of children whose pharmacokinetic profiles were determined after a single dose had significantly higher exposure (AUC) than most patients to desloratadine and very low levels of 3-hydroxydesloratadine. The exposure to desloratadine resulting from multiple doses has not been determined in children, and in particular, those children with apparent poor metabolism. Moreover, there are no data provided to identify the underlying cause of these high exposure levels. Consequently, there is no means of prospectively identifying those patients who may have such high levels. If these patients are inherently poor metabolizers of desloratadine, then the number of patients who experience these high exposure levels may be much greater, particularly if there is a deficient metabolic pathway involved that may be vulnerable to inhibition with concomitant medications.

Therefore, it will be necessary for you to characterize the pharmacokinetics of repetitive-dose administration with desloratadine in a population determined to be "poor metabolizers" of desloratadine. Once an upper limit of exposure with repetitive dosing has been determined, the safety of this level of exposure will need to be adequately supported in order to gain approval."

In summary, in comment 18 in the Approvable letter of 2 October 2001, the sponsor was asked to:

1. Characterize the pharmacokinetics of repetitive dose administration of desloratadine in pediatric poor metabolizers.
2. Support the safety of the upper limit of exposure with repetitive dose administration in children.

Comment 19: "You are encouraged to determine the mechanism accounting for higher levels of drug exposure observed in some patients, and to assess the potential for drug-drug interactions that might be expected based on the explanatory mechanism."

The sponsor responds that radiolabeled desloratadine and loratadine were incubated under various conditions with human liver micorsomes, S9 fraction, hepatocytes (freshly isolated and cryopreserved) and liver slices and that no 3-OH desloratadine was detected in any of these preparations. Loratidine was readily converted to hydroxylated loratadine metabolites and to desloratadine but desloratadine underwent only minimal metabolism, demonstrating that under these in-vitro conditions which allowed conversion of loratadine to desloratadine, there was no CYP450-mediated conversion of desloratadine to 3-OH desloratadine. In addition, there was no metabolism of desloratadine to 3-OH desloratadine in lung, kidney and gastrointestinal tract slices, including microsomal preparations, whole blood cells, non-CYP450 human liver enzymes, and human liver microsomes treated with additional cytochrome b5 and ionic detergent. No 3-OH desloratadine was produced after evaluation of other hepatic enzyme systems. Desloratadine and 3-OH desloratadine do not inhibit CYP450 enzymes. The sponsor concludes that they have not been able to identify the enzyme or enzymes that facilitate the conversion of desloratadine to 3-OH desloratadine, but such conversion is not catalyzed by any of the known CYP450 enzymes. In addition, in vitro studies have shown that neither desloratadine nor 3-OH desloratadine inhibit CYP450 enzymes responsible for the metabolism of most medications. The major route of elimination by poor metabolizers is by excretion of unchanged drug in urine and feces.

COMMENT: *The sponsor has been unable to identify the enzyme or enzymes responsible for the conversion of desloratadine to 3-OH desloratadine, although studies have shown that the formation of 3-OH desloratadine is not catalyzed by an of the major CYP450 enzyme systems.*

*The sponsor has made a reasonable effort to determine the mechanism for poor metabolism of desloratadine in some patients. Therefore, the sponsor's response to Comment 19 in the approvable letter of 1 October 2001 is a complete response and no further studies to define the mechanism of action of desloratadine in regard to poor metabolism is required at this time. Nevertheless, since the mechanism has not been found through the studies done so far, the sponsor should continue to consider other possible mechanisms for this phenomena.*

In the approvable letter of 14 May 2003 under NDA 21-563, the Division stated that the sponsor should "provide a complete response to the deficiencies listed in our Approvable letter for NDA 21-300 dated October 2, 2001 and CMC discipline review letter dated November 19, 2001." and that, "The proposed dose for younger children will be 2 ml and 2.5 ml. Provide a discussion of how these small volumes will be measured and delivered by caregivers and how this will be

addressed in the labeling.” In addition, the following changes were to be made in the labeling (see section 10.2 of this review): 1) “Throughout the labeling, patients should be referred to as 6 to 11 months of age or 12 to 23 months of age.”; 2) “Under the Adverse Reactions section, the listing of adverse events should be divided into those that were seen in patients 6 to 11 months of age and those that were seen in patients 12 to 23 months of age.”; 3) “Under the Precautions: Pediatric Use subsection, indicate that not only the tablet but also the syrup formulation has not been demonstrated to be safe and effective for patients less than 6 months of age.”; 4) the title of table 5 should be changed.; and 5) The Dosage and Administration section should be revised.

In addition, the sponsor submitted a response to the Division’s Pediatric Written Request on 6 June 2000. Studies 302 and 303 of the Written Request were submitted under NDA 21-300 on 8 December 2000 and a NDA for patients 6 months to 2 years of age was submitted on 4 December 2002 under NDA 21-563. Because NDA 21-300 was in approvable status, a response could not be submitted to the NDA. Therefore, a new NDA was opened under NDA 21-563 on 4 December 2002. This supplemental NDA was found to be approvable pending resolution of the issues under NDA 21-300 and labeling comments that were sent to the sponsor on 14 May 2003. There are, therefore, three submissions by the sponsor on 27 February 2004: 1) a response to the NDA 21-300 approvable letter; 2) a response to the NDA 21-300 CMC DRL; and 3) response to the NDA 21-563 approvable letter. In addition, the sponsor submitted on 24 June 2004 a request for a name change from Clarinex to Aeries for all Clarinex formulations. The sponsor also submitted carton and container labeling on 29 July 2004. In response to questions raised by the Medical Officer, on 7 July 2004, the sponsor informed the Division that an error had been made in the original submission for this NDA by inclusion of the June 2003 version instead of the February 2004 version. In response to the letter of 14 May 2003 under NDA 21-563, which stated that the sponsor should provide a complete response to the deficiencies listed in the approvable letter under NDA 21-300 and that the sponsor should provide the Division with a discussion about how the small volumes would be measured to provide the proposed dose in younger children of 2 ml and 2.5 ml and how they would be delivered by caregivers and how this would be addressed in the labeling.

## 2.6 Other Relevant Background Information

There is no other relevant background information related to this submission.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

Chemistry has recommended approval while acknowledging the commitment of the sponsor to re-evaluate the proposed shelf life acceptance criteria for certain impurities, revise the acceptance criteria for all impurities, and to report within 6 months the status report on a good faith effort to develop and validate a direct test method for quantifying impurities in [REDACTED] that are associated with higher levels of [REDACTED].

### 3.2 Animal Pharmacology/Toxicology

There are no animal pharmacology/toxicology data in this submission and no issues related to previous submission of data for this drug product for this indication in this patient population.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The data reviewed in this submission came from studies conducted by the applicant and a short summary of foreign post-marketing safety data provided by the sponsor.

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On Original**

## 4.2 Tables of Clinical Studies

Study #	Study design	Age range	Dose and duration administered	Number of patients	Disease	Primary PK parameters	PD parameters safety
2818 v9, v11	SD, open, screening	2-11 years	One dose of 10 mg loratadine	359; 53 poor metab, 16 2-5 yrs, 37 6-11 yrs	Allergic rhinitis	Plasma 3-OH DSL and DSL ratio	AEs, VS
2798 v5-8	MD, P, R, PC, IB	2-11 years	1.25 mg (2-5 yrs) 2.5 mg (6-11 yrs) desloratadine for 17 days	48; 17 poor metab; 21 normal metab, 10 placebo	Allergic rhinitis	Cmax, AUC,	AEs, ECGs, VS, lab tests
3016 v24-26	MD, DB, PC	2-11 years	1.25 mg (2-5 yrs) 2.5 mg (6-11 yrs) desloratadine for 29 days	42; 15 poor metab; (6 2-5 yrs, 9 6-11 yrs); 5 normal metab, 22 placebo	Allergic rhinitis	Cmin (assessment of steady state)	AEs, VS, ECGs, physical exam, lab tests
2781 v2-4 v10	SD, open	2-11 years	5 mg loratadine 2.5 mg (2-5 yrs) 5 mg (6-11 yrs) desloratadine	162; 51 from study C98-566, 60 from study 302, 51 from study 303	Allergic rhinitis, ch idiopathic urticaria	Plasma 3-OH DSL and DSL ratio	VS
302 v2-4 v10	R, DB, PC, P	6-11 years	2.5 mg desloratadine for 15 days	120; 8 poor metab, 52 normal metab, 60 placebo	Allergic rhinitis, ch idiopathic urticaria	Plasma 3-OH DSL and DSL ratio	AEs, VS, ECGs, physical exam, lab tests
303 v2-4 v10	R, DB, PC, P	2-5 years	1.25 mg desloratadine for 15 days	107; 8 poor metab, 43 normal metab, 56 placebo	Allergic rhinitis, ch idiopathic urticaria	Plasma 3-OH DSL and DSL ratio	AEs, VS, ECGs, physical exam, lab tests
C98-566 V2-4 V10	MD, R, PC, P, DB	2-5 years	5 mg loratadine syrup for 14 days	41 normal metab 10 poor metab., 61 placebo	Allergic rhinitis, ch idiopathic urticaria	Plasma 3-OH DSL and DSL	ECGs
3031 v1	SD, open, screening	2-11 years	One dose of 10 mg loratadine	2075: 79 poor metab, 27 2-5 yrs, 52 6-11 yrs	Atopy, ch idiopathic urticaria	Plasma 3-OH DSL and DSL ratio	AEs
2994 v12-23	RD, DB, PC, MC	2-11 years	1.25 mg (2-5 yrs) 2.5 mg (6-11 yrs) desloratadine for 36 days	97: 58 poor metab, 48 poor metab Rx; 49 placebo	Atopy, ch idiopathic urticaria	Cmin (assessment of steady state)	AEs, ECGs, VS, physical exam, lab tests
117 v1	MD, open, R, CX	19-41	10 mg loratadine 5 mg DSL for 10 days	25	Healthy volunteers	Plasma 3-OH DSL and DSL	
1341 v1	SD, open	6 mo to < 2 yrs	0.625 mg < 1 yr 1.25 mg if 1 yr	58		Plasma 3-OH DSL and DSL ratio	

### 4.3 Review Strategy

All studies submitted were reviewed. Emphasis was placed on the safety data, especially ECG data, from studies 2798, 3016 and 2994. These studies were prospective repetitive dose studies with desloratadine administration to a patient population that included poor metabolizers. A review of the clinical literature was not done.

### 4.4 Data Quality and Integrity

There was no DSI audit of the data submitted.

### 4.5 Compliance with Good Clinical Practices

The studies submitted by the sponsor were conducted appropriately to address the questions raised in the approvable letter for this drug product and were performed in compliance with good clinical practice, e.g. with informed consent, noting protocol violations and were conducted with acceptable ethical standards.

### 4.6 Financial Disclosures

Financial disclosure was appropriately submitted by the sponsor at the time of the original submission of this NDA.

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

1. Study 2798: Study 2798 was a multiple dose study over 17 days in which 38 patients received desloratadine, there were 17 poor metabolizers, 4 in the 2-5 year age group, 13 in the 6-11 year age group. This study was done to characterize the PK of repetitive dose administration of desloratadine in poor metabolizers. Poor metabolizers and placebo patients received twice the recommended daily dose for their age group for a period of 3 days followed by the recommended daily dose on the remaining 14 days of the study in order to reach steady state by day 15. Normal metabolizers received twice their daily dose on the first day only. Blood samples were obtained at baseline and on days 14, 15 and 16. All groups were at steady state by day 15.

C<sub>max</sub> after repetitive dose administration showed that the median levels for poor and normal metabolizers were comparable in patients 2-11 years of age and adults (v1,p32, f2), being somewhat higher in adults who were poor metabolizers than in children who were poor metabolizers, especially children 2-5 years of age (v1, p32, f3). Median values for AUC were also comparable between poor metabolizers 2-11 years of age and adults, but to a greater degree in patients 6-11 years of age than in patients 2-5 years of age (v1, page 33, figures 4, 5)(see tables below).

Comparison of median (range) AUC and Cmax following multiple dose administration of desloratadine in children 2-11 years of age and median (range) AUC and Cmax in adults (v1, p34, t7)

Patient population	2-5 years	6-11 years	Adults
AUC (ng.hr.mL)			
Normal metabolizer	23.4 (14-62)	30.4 (24-73)	44.3 (14.2-158)
Poor metabolizer	143 (138-149)	223 (125-300)	271 (179-406)
Cmax (ng/mL)			
Normal metabolizer	2.05 (1.1-4.3)	2.53 (1.7-3.9)	3.26 (0.6-11.6)
Poor metabolizer	6.78 (6.5-7.0)	10.8 (5.9-14.6)	13.7 (8.9-23.7)

Median (range) 3-OH desloratadine concentrations following multiple dose administration of desloratadine in children 2-11 years of age and adults (v1, p35, t9)

Patient population	2-5 years of age	6-11 years of age	Adults
AUC (ng.hr.mL)			
Normal metabolizer	13.4 (8.81-17)	18.3 (11.9-28.7)	28.8 (13.5-59)
Poor metabolizer	2.4 (1.87-4.56)	3.58 (2.1-11.7)	4.86 (1.64-18.3)
Cmax (ng/mL)			
Normal metabolizer	0.76 (0.55-0.97)	1.22 (0.7-1.76)	1.64 (0.11-3.96)
Poor metabolizer	0.12 (0.09-0.37)	0.19 (0.11-0.77)	0.2 (0.03-3.63)

In terms of mean AUC on day 17 in study 2798, values were comparable for normal metabolizers 2-5 and 6-11 years of age but different for poor metabolizers in these age ranges (see table below). OCPB has analyzed this data and does not consider these differences to be significant (see OCPB review).

Mean (range) for Cmax and AUC of desloratadine on day 17; Study 2798 (v1, p31, f6)

Parameter	2-5 years of age	6-11 years of age
Cmax normal metabolizers	2.29 (1.1-4.3)	2.56 (1.71-3.89)
Cmax poor metabolizers	6.78 (6.53-7.04)	10.4 (5.94-14.6)
AUC normal metabolizers	29.5 (14-61.8)	34.7 (24-72.6)
AUC poor metabolizers	143 (138-149)	220 (125-300)

2. Study 3016: In a prospective analysis of study 3016, a multiple dose study of 29 days duration, there were 15 poor metabolizers, 6 patients 2-5 years of age and 9 patients 6-11 years of age. Based on trough concentration of desloratadine and 3OH desloratadine, steady state was achieved in desloratadine treated poor metabolizers on day 15. An analysis of comparative PK in pediatric and adult poor and normal metabolizers, the mean Cmax was 2.3 ng/mL in normal metabolizers 2-5 years of age compared with 6.8 ng/mL in poor metabolizers of the same age group, a ratio of 6:1. In children 6-11 years of age, the mean Cmax in normal metabolizers was 2.6 ng/mL compared to 10.4 ng/mL in poor metabolizers, a ratio of 7:1. In terms of AUC, the mean for 2-5 year old patients with normal metabolism was 29.5 ng.hr/mL compared to 143 ng.hr/mL in poor metabolizers, a ratio of 3:1, while in the 6-11 year age group, patients with normal metabolism had an AUC of 35 ng.hr/mL compared to 220 ng.hr/mL in patients with poor metabolism, a ratio of 4:1. In a cross study comparison with pharmacokinetic studies in adults there was a ratio of approximately 6:1 for Cmax and approximately 4:1 for AUC comparing poor metabolizers to normal metabolizers. For adults (12-70 years) the poor metabolizer population is derived from clinical pharmacology studies in this patient population in which there were 1124 normal metabolizers (94%) and 70 poor metabolizers (6%). Of the poor metabolizers, 53 (18%) were Black, 13 (2%) were Caucasian and 4 (2%) were Hispanic.

The sponsor has responded that the PK of repetitive dose administration of desloratadine in poor metabolizers has been characterized by the studies submitted at this time and the safety of desloratadine at steady state exposure in multiple dose studies in patients 2-11 years of age has been demonstrated. In these studies, the sponsor showed that the upper limit of exposure in pediatric and adult poor metabolizers was similar and was 6-7 times higher than that seen in normal metabolizers (see table below).

Median (range) AUC and Cmax following multiple dose administration of desloratadine in children 2-11 years of age in study 2798, compared to adults (v1, p34, t7)

Patient population	N	2-5 years	N	6-11 years	N	Adults
AUC (ng hr/mL)						
Normal metabolizers	8	23.4 (14-62)	12	30.4 (24-72.6)	364	44.3 (14-158)
Poor metabolizers	4	143 (138-149)	13	223 (125-300)	33	271 (179-406)
Cmax (ng/mL)						
Normal metabolizers	8	2.05 (1.1-4.3)	12	2.53 (1.7-3.9)	364	3.26 (0.6-11.6)
Poor metabolizers	4	6.8 (6.5-7.0)	13	10.8 (6-15)	33	13.7 (8.9-23.7)

*COMMENT: The sponsor has adequately characterized the pharmacokinetics of desloratadine after repetitive dose administration in children 2-11 years of age and demonstrated the upper limit of exposure in children who are poor metabolizers. Therefore, the sponsor has provided a complete response to Comment 18 in the Approvable letter of 1 October 2001.*

Biopharmaceutics has concluded that the sponsor is correct in stating that the exposure of poor metabolizers to desloratadine is approximately 6 times greater than patients with normal metabolism regardless of age and that the prevalence of poor metabolizers appears to be higher in Black patients. Biopharmaceutics is recommending approval for this supplemental NDA (see OCPB Review).

## 5.2 Pharmacodynamics

A discussion of pharmacodynamic studies, especially those evaluating QTc interval, are discussed below as part of the Integrated Review of Safety.

## 5.3 Exposure-Response Relationships

See discussion of safety of desloratadine in poor metabolizers below.

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication

No efficacy data was included in this submission.

### 6.1.1 Methods

No efficacy data was included in this submission.

### 6.1.2 General Discussion of Endpoints

No efficacy data was included in this submission.

### 6.1.3 Study Design

No efficacy data was included in this submission.

### 6.1.4 Efficacy Findings

No efficacy data was included in this submission.

### 6.1.5 Clinical Microbiology

No efficacy data was included in this submission.

### 6.1.6 Efficacy Conclusions

No efficacy data was included in this submission.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

The sponsor submitted 26 volumes of data on clinical studies done to identify 2-11 year old poor metabolizers of desloratadine and to assess the safety of desloratadine administration in such patients. Safety assessments included adverse events, vital signs, laboratory tests and ECGs.

#### 7.1.1 Deaths

There were no deaths in the studies submitted.

#### 7.1.2 Other Serious Adverse Events

There were no serious adverse events reported in the studies submitted. A review of post-marketing surveillance reports provided spontaneous adverse events in 28 children less than 12 years of age who received desloratadine syrup (sub 9 July 2004, p51-52). Five of these reports were for serious adverse events which were: 1) a 5 year old male who 12 hours after a dose of 1.25 mg presented with severe somnolence, diplopia, dizziness, motor incoordination and bradycardia from which there was complete recovery; 2) a 5 year old male who developed symptoms of an extrapyramidal disorder, somnolence and disorientation two days after starting treatment with 1.25 mg per day of desloratadine and loss of consciousness one week after starting treatment from which he recovered without sequelae; 3) a 4 year old female who developed spasms of the upper half of her body about one week after starting treatment with 2.5 mg per day of desloratadine associated with mood change and depression which gradually subsided when she discontinued treatment; 4) a 9 year old female who developed respiratory crisis, facial edema and articular pain on the first day of treatment with an unknown dose of medication which subsided after treatment was discontinued; and 5) a 5 year old patients who developed "giant" urticaria after an unknown dose without any additional information.

#### 7.1.3 Dropouts and Other Significant Adverse Events

##### 7.1.3.1 Overall profile of dropouts

There was one patient, who received desloratadine and was a poor metabolizer, who was discontinued from study 2994 because of this adverse event that was considered possibly related

to the study drug. No other patients who received desloratadine were discontinued from any other study. No placebo patients were discontinued from any study.

#### 7.1.3.2 Adverse events associated with dropouts

A 3 year old male who developed somnolence and abdominal pain after receiving 5 doses of desloratadine and was a poor metabolizer was discontinued from study 2994 because of this adverse event that was considered possibly related to the study drug. No placebo patients were discontinued.

#### 7.1.3.3 Other significant adverse events

There were no clinically significant adverse events related to the administration of desloratadine.

#### 7.1.4 Other Search Strategies

No other search strategies were utilized.

#### 7.1.5 Common Adverse Events

Common adverse events are discussed below.

##### 7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited by the investigator in each study at each study visit by asking the patient general questions about how they had been feeling.

##### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were appropriate.

##### 7.1.5.3 Incidence of common adverse events

a. Adverse event profile in multiple dose studies with desloratadine (studies 2798, 3016, 302, 303 and 2994)(submission of 20 July 2004): In multiple dose studies there were 94 poor metabolizers 2-11 years of age, 32 of whom were 2-5 years of age and 62 of whom were 6-11 years of age. Overall, in these studies, the incidence of adverse events was greater in patients who were poor metabolizers (31%)(n=94) than in patients who were normal metabolizers (5%)(n=123) but not as great in patients who received placebo (37%)(n=81). However, there were only a few adverse events that were considered related to the study drug in poor metabolizers and adverse events in this patient population were generally mild, not unexpected and occurred with an incidence similar to placebo.

Adverse events in the 2-11 year old age group in multiple dose studies with desloratadine where more than 2 patients who received desloratadine had a specific adverse event included:

*somnolence*

poor metabolizers - 4 (4%); (n=94)

normal metabolizers – none, (n=123)

placebo group – 5 (3%); (n=81); 3 (17%) were poor metabolizers (n=18)

headache

poor metabolizers – 8 (9%)

normal metabolizers – 1 (1%)

placebo group – 8 (10%); 3 (17%) were poor metabolizers

fever

poor metabolizers – 5 (5%)

normal metabolizers – 3 (2%)

placebo group – 5 (4%); 3 (17%) were poor metabolizers

diarrhea

poor metabolizers – 3 (3%)

normal metabolizers – none

placebo group - 2 (1%) (both were poor metabolizers)

Treatment emergent and treatment related adverse events that were prominent in poor metabolizer patients 2-11, 2-5 and 6-11 years of age who received desloratadine in repetitive dose studies occurred with an even higher incidence in poor metabolizers who received placebo in these studies (20 July 2004 submission, attachments 1-4).

Adverse events in patients 2-5 years of age that occurred in multiple dose studies with desloratadine where more than one patient had a specific adverse event included:

headache

poor metabolizers – 2 (6%)

normal metabolizers – none

placebo patients - 1 (2%)

somnolence

poor metabolizers – 2 (6%)

normal metabolizers – none

placebo patients – 2 (3%)

fever

poor metabolizers – 2 (6%)

normal metabolizers – 3 (6%)

placebo patients – 1 (2%)

varicella

poor metabolizers – 2 (6%)

normal metabolizers – none

placebo patients – none

Adverse events in patients 6-11 years of age that occurred in multiple dose studies with desloratadine where more than one patient in the poor metabolizer group had a specific adverse event were (v1, s7/904, p43-5, t11)

somnolence

poor metabolizers – 2 (3%)

normal metabolizers – none

placebo patients - 3 (3%)

nausea

poor metabolizers – 2 (3%)

normal metabolizers – none

placebo patients - 1 (2%)

diarrhea

poor metabolizers – 3 (5%)

normal metabolizers – none

placebo patients - 2 (2%)

fever

poor metabolizers – 3 (5%)

normal metabolizers – none

placebo patients - 4 (3%)

headache

poor metabolizers – 6 (10 %)

normal metabolizers – 1 (1%)

placebo patients - 7 (12%)

Treatment emergent and treatment related adverse events that were prominent in poor metabolizer patients 2-11, 2-5 and 6-11 years of age who received desloratadine in repetitive dose studies occurred with an even higher incidence in poor metabolizers who received placebo in these studies (20 July 2004 submission, attachments 1-4).

1) Study 2798: In this study, there were 48 patients that included 7 poor metabolizers who received desloratadine, 21 normal metabolizers who received desloratadine and 10 placebo patients. Patients were treated with 1.25 mg (2-5 years) or 2.5 mg (6-11 years) of desloratadine per day for 17 days. There were 2 desloratadine treated poor metabolizers (29%), one desloratadine treated normal metabolizer (5%) and one placebo treated patient (10%) who reported treatment emergent adverse events (v5, p61). All adverse events were mild-moderate and resolved spontaneously. One poor metabolizer developed hyperkinesia and the other developed somnolence. Both the placebo patient and the normal metabolizer developed hyperkinesias (v5, p62, t26).

2) Study 3016: In this study, there were 42 patients, 15 poor metabolizers who received desloratadine, 5 normal metabolizers who received desloratadine and 22 placebo patients. Patients were treated with 1.25 mg (2-5 years) or 2.5 mg (6-11 years) of desloratadine per day for 29 days. There were 3 adverse events reported in the poor metabolizer group (20%), none in the normal metabolizer group and 10 (45%) in the placebo group. In the poor metabolizer group, there was one patient who developed headache and 2 patients who developed somnolence. In the placebo group, there were 5 patients who developed headache, 3 patients who developed somnolence, and one patient who developed both abdominal pain and nausea. There was also one accidental injury reported in the placebo group (v24, p45-46, t16).

3) Study 303: Study 303 was a repetitive dose study with 15 days of treatment with 1.25 mg of desloratadine per day in patients 2-5 years of age. There were 111 patients enrolled for phenotyping in study 2781. There were 8 poor metabolizers who were included along with 43 normal metabolizers and 56 placebo patients in the retrospective analysis of adverse events. There were 4 patients who did not participate in the phenotyping protocol. There were 6 recorded adverse events in 6 patients who were normal metabolizers who had received desloratadine. These included fever (3), viral infection, rash and urinary tract infection. There were 4 adverse events recorded in 4 poor metabolizers who received desloratadine and included headache, varicella (2), and urinary tract infection. There were 8 adverse events reported in patients who received placebo and included fever (3), headache (3), viral infection and otitis media. All adverse events were mild and only rash in a normal metabolizer was considered possibly related to the treatment (v2, p32, t9).

4) Study 302: Study 302 was a repetitive dose study with 15 days of treatment with 2.5 mg of desloratadine per day in patients 6-11 years of age. There were 120 patients enrolled for phenotyping in study 2781. Phenotyping revealed that there were 8 poor metabolizers, 52 normal metabolizers and 60 placebo patients in the retrospective analysis of adverse events. There was one report of headache in a normal metabolizer who received desloratadine. There were 8 reports of adverse events in patients who

received placebo that included headache (4), gastroenteritis (2) and vomiting (2). There were no reports of adverse events in poor metabolizers. All events were mild and none was considered related to the study treatment (v2, p33, t10).

5) Study C98-566: In study 117, the sponsor demonstrated that the exposure to desloratadine is the same after loratadine administration as after administration of desloratadine. Therefore, the safety of loratadine when given at a dose of 5 mg per day to poor metabolizers 2-5 years of age for 14 days can be used as a means of assessing the safety of desloratadine in poor metabolizers. Study C98-566 was a repetitive dose study with 14 days of treatment with 5 mg per day of loratadine in patients 2-5 years of age. There were 121 patients enrolled for phenotyping in study 2781. Phenotyping revealed that there were 10 poor metabolizers, 41 normal metabolizers and 61 placebo patients. There were 9 patients who did not participate in the phenotyping protocol.

In the group of patients who were normal metabolizers and received loratadine (n=41), there were 15 adverse events, including, fever (3), headache (3), influenza-like symptoms (1), diarrhea (2), dyspepsia (1), loose stool (1), stomatitis (1), tooth disorder (1), vomiting (2), drowsiness (4), viral infection (1), allergic rhinitis (1), coughing (1), epistaxis (1), pharyngitis (2) and rash (1).

There were 25 adverse events in the placebo group (n=61) that included lacrimation (1), fever (5), headache (4), hyperkinesias (2), constipation (1), dyspepsia (4), loose stool (2), nausea (2), vomiting (3), body aches (2), appetite increased (1), drowsiness (4), allergic rhinitis (2), coughing (3), nasal congestion (1), pharyngitis (1), sinus congestion (1), sneezing (1) and nocturia (1).

There were 2 adverse events in the poor metabolizers who received loratadine (n=10) which were fatigue (1) and constipation (1), neither of which was considered treatment-related (v2, p39, t14).

6) Study 2994: This study was a multiple dose study with 36 days of treatment in patients 2-11 years of age with desloratadine 1.25 mg (2-5 years) or 2.5 mg (6-11 years). There were 97 patients in the study, of whom 46 poor metabolizers and 2 normal metabolizers received desloratadine and 49 patients received placebo. Adverse events occurred in 21 patients (45.7%) who were poor metabolizers and 19 (38.8%) of placebo patients. Treatment related adverse events occurred in 6.5% of poor metabolizers and 4.1% of placebo patients. The only adverse event that occurred more frequently in poor metabolizers who received desloratadine than in placebo patients was headache, which occurred in 13% of the desloratadine group (all poor metabolizers) and 6.1% of the placebo group, driven by the greater incidence of this adverse event in patients 6-11 years of age and in African-American patients. Overall, the frequency of adverse events in patients 2-5 years of age was 57.1% in the desloratadine group and 46.2% in the placebo group. Overall, the frequency of adverse events in patients 6-11 years of age was 40.6% in the desloratadine group and 36.1% in the placebo group. One poor metabolizer in study 2994 who received desloratadine was discontinued after 5 days of treatment due to an adverse event - a 3 year old Caucasian male who developed somnolence and abdominal pain. No placebo patients were discontinued from the study (v12, p80-84, t20; v12, 147-307).

7) Study 1368: This study was a randomized, placebo-controlled, parallel group, double-blind, multicenter, repetitive dose study in 131 patients 6-23 months of age stratified into patients 6-11 months of age and patients 12-23 months of age with allergic rhinitis, urticaria or a strong personal or family history of atopy amenable to treatment with antihistamines. Patients received 0.625 mg once a day for a period of 15 days. Adverse events, vital signs, laboratory tests and ECGs were evaluated. In this study, 56% were male and 44% were female, while 23% were Caucasian, 9% were African-American, 2% were Asian and 65% were Hispanic.

b. Adverse event profile in individual single dose studies:

1) Study 2818: Study 2818 was a single dose screening study to identify a poor metabolizer subset of patients for inclusion in multiple dose studies 2798 and 3016. Patients received a single dose of 10 mg of loratadine. All adverse events in the poor metabolizer group were mild. The incidence of adverse events in poor metabolizers was 19% compared with 13% in normal metabolizers. Treatment-emergent adverse events in study 2818 can be seen in the table below. All adverse events in the poor metabolizer group were considered possibly related to the study drug except for one patient who developed stinging of the tongue that was considered probably related to the study drug (v11, p644).

2) Study 2781: Study 2781 was a single dose study phenotyping patients from studies 302, 303, and C98-566. There were 162 patients phenotyped. There were 71 patients who were normal metabolizers of desloratadine and were 6 years of age or older, 24 patients who were normal metabolizers of desloratadine and were less than 6 years of age, 16 patients who were poor metabolizers and were 6 years of age or older, 10 patients who were poor metabolizers of loratadine and 41 patients who were normal metabolizers of loratadine (v2, 26). Patients received a single dose of 5 mg of loratadine or 2.5 mg (2-5 years of age) or 5 mg (6-11 years of age) of desloratadine. There were 4 patients who reported adverse events, 3 normal metabolizers and 1 poor metabolizer. The 2 adverse events reported in normal metabolizers who had received desloratadine were headache and somnolence. One normal metabolizer who had received loratadine developed nausea. The adverse event reported in the poor metabolizer who had received desloratadine was headache (v2, p30, t8).

3) Study 3031: This study was a single dose screening study to identify patients who were poor metabolizers after administration of loratadine. There were 2075 patients who were enrolled and 2058 patients who completed the study. Of these, 79 were determined to be poor metabolizers and 1917 normal metabolizers (37 were considered indeterminate metabolizers). The frequency of adverse events was 3.8% in poor metabolizers and 4.2% in normal metabolizers. The frequency of treatment-related adverse events was 1.3% in poor metabolizers and 1.2% in normal metabolizers. The frequency of treatment-related adverse events was 1.9% in poor metabolizers 6-11 years of age and 1% in normal metabolizers in the same age range. There were no treatment-related adverse events in poor metabolizers 2-5 years of age while the frequency in normal metabolizers in that age range was 1.5% (v12, p67, 79, 80, t19).

7.1.5.4 Common adverse event tables

a. See listings above under 7.1.5.3 for repetitive dose studies.

b. See tables below for single dose studies.

Adverse event profile in single dose studies with desloratadine (2818, 2718, and 1341)(v1, p46, t12)

Adverse event	Poor metabolizers	Normal metabolizers
Overall	11 (13%)	45 (9%)
Headache	4 (5%)	17 (3%)
Somnolence	2 (2%)	18 (4%)
Abdominal pain	3 (4%)	1 (<1%)
Loose stools	None	2 (<1%)
Dry mouth	None	2 (<1%)
Nausea	1 (1%)	3 (1%)
Tongue disorder	1(1%)	None
MS pain	None	1 (<1%)

Comparison of adverse events in poor and normal metabolizers in study 2818

Adverse event	Poor metabolizers (n=53)	Normal metabolizers (n=306)
Headache	3 (6%)	16 (5%)
Somnolence	2 (4%)	17 (6%)
Abdominal pain	3 (6%)	1 (< 1%)
Loose stools	None	2 (1%)
Dry mouth	None	2 (1%)
Nausea	1 (2%)	2 (1%)
Tongue disorder	1 (2%)	None
Musculoskeletal pain	None	1 (<1%)

Adverse events in study C98-566 (v1, p48, t13) by treatment group

Adverse event	Unknown metabolism	Normal metabolizers	Poor metabolizers	Placebo
Overall	2 (22%)	15 (37%)	2 (20%)	25 (41%)
Fatigue	None	None	1 (10%)	None
Constipation	None	None	1(10%)	1 (2%)
Coughing	None	1 (2%)	1 (10%)	3 (5%)

Adverse events in study 2994 that occurred in more than one poor metabolizer compared to placebo patients

Parameter	Desloratadine poor metabolizers	Placebo patients
All adverse events	21 (45.7%)	19 (38.8%)
Fever	5 (10.9%)	5 (10.2%)
Headache	6 (13%)	3 (6.1%)
Abdominal pain	2 (4.3%)	2 (4.1%)
Diarrhea	3 (6.5%)	2 (4.1%)
Nausea	2 (4.3%)	None
URI	2 (4.3%)	None
Coughing	2 (4.3%)	5 (10.2%)

**Conclusion:** Based on the adverse event profile for desloratadine in children who are poor metabolizers, there is no concern about the safety of desloratadine in this patient population.

#### 7.1.5.5 Identifying common and drug-related adverse events

See discussion of adverse events in sections 7.1.5.3 and 7.1.5.4 above.

#### 7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were done.

#### 7.1.6 Less Common Adverse Events

Less common adverse events seen in poor metabolizers 2-11 years of age (n=1) included hyperkinesias, otitis media, pharyngitis, bone fracture, dyspnea and rales. All of these adverse

events except for bone fracture were seen in at least one patient in this age range who received placebo.

#### 7.1.7 Laboratory Findings

##### 7.1.7.1 Overview of laboratory testing in the development program

The laboratory testing done by the sponsor included chemistry, hematology and urinalysis and compared tests done during screening and those done at the conclusion of the study. The laboratory tests that were done and the timing of the testing were adequate to evaluate the possible effect of desloratadine on laboratory tests in poor metabolizers and compare any risk with both normal metabolizers who received desloratadine and patients who received placebo.

##### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory test results were compared in patients who were poor metabolizers and patients who were normal metabolizers and received desloratadine and patients who received placebo.

- a. Study 2798: (v7, pgs830-859) no significant mean or individual changes were noted in laboratory tests done in this study.
- b. Study 3016 (v26, pgs687-716) no significant mean or individual changes (v26, pgs were noted in laboratory tests done in this study.
- c. Study 2994: (v12, p90, t23) Based on the sponsor's criteria, there were "clinically meaningful" laboratory values after treatment in 3 desloratadine patients and none of the placebo patients. Two patients had elevated triglyceride levels and one patient had a GGT value of 66 U/L on day 15 and 54 U/L on day 36 (NRR = 3-22)(patient # 113).
- d. Study C98-566: A retrospective analysis of laboratory test results based on metabolizer status was not done as part of study 2781.

COMMENT: *Based on laboratory tests, there is no safety concern associated with the administration of desloratadine to children 2-11 years of age who are poor metabolizers.*

##### 7.1.7.3 Standard analyses and explorations of laboratory data

The analysis of laboratory data was done for each study. No overall analysis of laboratory data combined for all the studies that were performed was submitted by the sponsor. Analysis focused on patients who had laboratory values outside the normal reference range or changed substantially from baseline, and were not seen in other treatment groups. There were no patients who laboratory values deviated substantially from the normal reference range.

###### 7.1.7.3.1 Analyses focused on measures of central tendency

There were no clinically significant changes in mean values for any laboratory test after treatment with desloratadine in poor metabolizers.

###### 7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

An analysis of patients who had normal baseline laboratory values and developed a laboratory value outside the normal reference range after treatment was done, comparing the incidence and degree of such changes between treatment groups. No increased incidence of such patients was

seen after administration of desloratadine in poor metabolizers compared to normal metabolizers who received desloratadine and patients who received placebo.

#### 7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outliers or dropouts because of laboratory abnormalities.

#### 7.1.7.4 Additional analyses and explorations

No additional analyses or explorations of the laboratory values were done.

#### 7.1.7.5 Special assessments

No special assessments were done.

#### 7.1.8 Vital Signs

##### 7.1.8.1 Overview of vital signs testing in the development program

In studies 3016 and 2994, vital signs were measured at screening, on day 1 at baseline, and treatment days 8, 15, 22, and 29 and changes from baseline on day 1 were noted for days 8, 15, 22, and 29. In study 2798, vital signs were measured at screening, at baseline prior to study day 1 and on treatment days 9 and 17 and the change from baseline on treatment days 9 and 17 was determined.

##### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

All studies that measured vital signs before and after treatment with desloratadine in poor metabolizers were evaluated. Studies 2798, 3016, and 2994 were of special importance because they were repetitive dose studies with adequate measurement at appropriate times of vital signs to allow assessment of any difference between patients who received desloratadine and were poor metabolizers and patients who received desloratadine and were normal metabolizers and patients who received placebo.

##### 7.1.8.3 Standard analyses and explorations of vital signs data

a. Study 2798: (v7. p865, 870) Mean pulse rate in the poor metabolizer group increased 12 bpm after 17 days of treatment compared to an increase of 4 bpm in the normal metabolizer group and essentially no change in the placebo group. There was a 10 bpm increase in patients 2-5 years of age and a 13 bpm increase in patients 6-11 years of age.

b. Study 3016: (v24, p51, t19; v26, pgs717-748): There was no significant mean change in either systolic or diastolic blood pressure in either patients who were normal or patients who were poor metabolizers. There was a mean increase in pulse rate 13 bpm in poor metabolizers but a mean increase of 14 bpm in normal metabolizers. There were no individual changes in vital signs that were clinically significant (v26, pgs894-905).

c. Study 2994: Vital signs were measured on days 1, 8, 15, 22, 29, and 36. Changes in heart rate of 30% or more occurred in 7 desloratadine patients and 4 placebo patients. Changes in systolic blood pressure of 30% or more occurred in only 3 placebo patients while this degree

of change in diastolic blood pressure occurred in 3 desloratadine patients and 4 placebo patients.

*COMMENT: In some studies, there was a greater mean change in heart rate in patients who were poor metabolizers after administration of desloratadine than in patients who were normal metabolizers of desloratadine or in patients who received placebo. Overall, however, based on vital signs, there is no safety concern associated with the administration of desloratadine to children 2-11 years of age.*

#### 7.1.8.3.1 Analyses focused on measures of central tendencies

Mean changes from baseline were compared across treatment groups.

#### 7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

No analyses were done on outliers or shifts from normal to abnormal.

#### 7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no marked outliers or dropouts because of vital signs.

#### 7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were done.

#### 7.1.9 Electrocardiograms (ECGs)

##### 7.1.9.1 Overview of ECG testing in the development program

Database and Assessment Techniques: The database for cardiovascular safety based on ECG determinations included 32 poor metabolizers from studies 2798 and 3016, 16 poor metabolizers from studies 302 and 303, 10 poor metabolizers from study C98-566 and 48 poor metabolizers from study 2994. In study 2798, ECGs were obtained at screening, baseline, on day 1 and 10 prior to drug administration, and on days 9 and 17 prior to drug administration as well as 2, 4, 8, 12 and 24 hours after drug administration. In study 3016, ECGs were performed at baseline and 3 hours after drug administration on days 8, 15, 22, and 29. In both studies ECGs were transferred in both studies via modem to an independent, blinded, third party evaluator who manually read the ECGs in terms of intervals. The primary PD parameters were mean change from baseline in manually read ventricular rate, and ECG intervals including QTc intervals corrected by both the Bazett and Fridericia methods. In study 2798, changes from baseline were also computed for difference in maximum, differences in maximum following repetitive dose administration compared to the minimum value at baseline and differences in time-normalized QTc AUC. All variables were analyzed using ANOVA. In studies 302 and 303, ECGs were machine read at the study site at baseline and on days 8 and 15, 3 hours after drug administration. In study 2994, ECGs were done at baseline and on days 8, 15, 22, 29, and 36, 3 hours after drug administration. They were read by a cardiologist away from the study site.

#### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Study 2798 was of most importance in assessing ECG data, especially QTc intervals, on poor metabolizers of desloratadine because an average of time points at baseline over 24 hours were used for comparison with an average of time point over 24 hours on days 9 and 17 of the study. In this study, ECGs were done at baseline and on study days 9 and 17, on each day prior to drug administration and 2, 4, 8, 12, and 24 hours after drug administration. QTc interval was corrected using both Bazett's and Fridericia's correction. Studies 3016 and 2994 provided information on ECG changes with repetitive dose administration after administration of desloratadine in poor metabolizers compared to normal metabolizers and patients who received placebo.

#### 7.1.9.3 Standard analyses and explorations of ECG data

Mean and median analyses were done for all studies and individual patient analysis was done for study 2798.

Study 2798: In this study, there were 48 patients, 17 poor metabolizers who received desloratadine, 21 normal metabolizers who received desloratadine and 10 placebo patients. Patients were treated with 1.25 mg (2-5 years) or 2.5 mg (6-11 years) per day of desloratadine for 17 days. ECGs were transferred via modem to an independent, blinded, third party evaluator who manually read the ECGs. ECGs were obtained at screening, on day 1 and 10 prior to drug administration and at baseline and on days 9 and 17 prior to drug administration and 2, 4, 8, 12, and 24 hours after drug administration. The baseline ECG evaluation and the change from baseline on days 9 and 17 was the arithmetic mean of the 6 ECG evaluations at 0, 2, 4, 6, 12 and 24 hours after drug administration.

There was one patient in the poor metabolizer group and one patient in the normal metabolizer group who had a normal ECG at baseline who had a possibly abnormal ECG after 17 days of treatment in study 2798 (v7, p886). Poor metabolizers had an increase in the mean ventricular rate (10 bpm) that was greater than the increase seen in normal metabolizers (3 bpm) or placebo patients (1 bpm). The mean increase in QTc using Bazett's correction was greater in poor metabolizers (10 msec) than in normal metabolizers (4 msec) or placebo patients (6 msec) in the same study. There was no significant difference between poor and normal metabolizers in increase from baseline of 0-30 msec using either Bazett's or Fridericia's correction and there were no changes > 60 msec or QTc intervals > 500 msec. in study 2798 (see table below [v1, p53-58, t14-16] for comparison with ECG findings in other studies) (unless noted, there was no statistically significant difference between poor metabolizers and either normal metabolizers or placebo). There were no patients in any of the three treatment groups who had a change in QTc interval of 10% of more after 17 days of treatment.

Study 3016: In this study, there were 42 patients, 15 poor metabolizers who received desloratadine, 5 normal metabolizers who received desloratadine and 22 placebo patients. Patients were treated with 1.25 mg per day (2-5 years) or 2.5 mg per day (6-11 years) of desloratadine for 29 days. One of the primary endpoints was ECG intervals at 3 hours after drug administration compared to pretreatment values on days 8, 15, 22 and 29.

There were no patients in study 3016 who had a normal ECG at baseline who had a possibly abnormal ECG after 29 days of treatment. No significant ECG changes occurred in individual patients in study 3016 (v26, pgs941-964). No patient had a QTc interval of 500 msec or more.

On day 22, one poor metabolizer (#206) had a 73 msec increase in QTc with Bazett's correction. The patient's ventricular rate was 113 bpm. When corrected with Fridericia's correction the increase in QTc interval was 37 msec. On day 29, this patient's ventricular rate was 92 msec, the increase in QTc was 24 msec using Bazett's correction and 16 msec using Fridericia's correction.

Study 303: Study 303 was a repetitive dose study with 15 days of treatment with desloratadine in patients 2-5 years of age. There were 111 patients enrolled for phenotyping in study 2781. There were 8 poor metabolizers who were included along with 43 normal metabolizers and 56 placebo patients in the retrospective analysis of ECG changes. There were 4 patients who did not participate in the phenotyping protocol. Patients in this study received 1.25 mg of desloratadine.

There were 5 patients who had a QTc value > 450 msec using Bazett's correction (3 normal metabolizers and 2 placebo patients) but none using Fridericia's correction.

Study 302: Study 302 was a repetitive dose study with 15 days of treatment with desloratadine in patients 6-11 years of age. There were 120 patients enrolled for phenotyping in study 2781. There were 8 poor metabolizers, 52 normal metabolizers and 60 placebo patients in the retrospective analysis of ECG findings. Patients in this study received 2.5 mg of desloratadine.

Study C98-566: In study 117, the sponsor demonstrated that the exposure to desloratadine is the same after loratadine administration as after administration of desloratadine. Therefore, the safety of loratadine when given at a dose of 5 mg per day to poor metabolizers 2-5 years of age for 14 days can be used as a means of assessing the safety of desloratadine in poor metabolizers. Study C98-566 was a repetitive dose study with 14 days of treatment with loratadine in patients 2-5 years of age. There were 121 patients enrolled for phenotyping in study 2781. There were 10 poor metabolizers, 41 normal metabolizers and 61 placebo patients. There were 9 patients who did not participate in the phenotyping protocol.

Study 2994: This study was a multiple dose study with 36 days of treatment in patients 2-11 years of age. There were 97 patients in the study, of whom 46 poor metabolizers and 2 normal metabolizers received desloratadine and 49 patients received placebo. No cardiovascular adverse event occurred in patients receiving treatment. A 12 lead ECG was obtained at screening, baseline, and on days 8, 15, 22, 29, and 36. ECG reading was done manually by a cardiologist at a central site. No patients in either treatment group had a change in QTc interval of 60 msec or more, except for one 8 year old female in the desloratadine treatment group who had a 70 msec change from baseline using Bazett's correction. In the poor metabolizer group, there was a patient who had an increase in QTc prolongation based on Bazett's correction from 454 msec at baseline to 470 msec after 36 days of treatment with desloratadine (#120, a 3 year old Black female)(v22, p1044). Based on the sponsor's criteria of > 470 msec being prolonged in females, this value is not abnormal. There was another patient in the same group (#232, a 7 year old Black female) who had QTc (B) prolongation of 462 and 464 msec on days 15 and 22 of treatment, with a decrease to 401 msec on day 36 (v22, p100). One normal metabolizer (#265, a 10 year old Hispanic female) had a QTc prolongation to 453 msec on day 29, without baseline value of 424 msec and 36 day value of 391 msec (v22, p1071). After 36 days of treatment, there were 5 patients (15%) of the desloratadine poor metabolizer group and 2 (5%) of the placebo group who had normal ECGs at baseline who had an abnormal ECG that was considered not clinically significant (v121, p100, t27)

#### 7.1.9.3.1 Analyses focused on measures of central tendency

Maximum, mean and AUC ventricular rate and QTc interval change from baseline to days 9 and 17 in study 2798 (v6, p487-491, t2, 3)(v8, p911-922)

	Poor metabolizer	Normal metabolizer	Placebo
Mean ventricular rate baseline	80.9 bpm	87.7 bpm	88.5 bpm
Mean change ventricular rate Day 17	9.8 bpm	2.8 bpm	1.4 bpm
Maximum baseline QTc msec (B)	415 msec	413 msec	418 msec
Max change from baseline day 17 (B)	9.4 msec (2.4%)	3.6 msec (1%)	5.2 msec (1.4%)
Maximum baseline QTc msec (F)	393	385	387
Max change from baseline day 17 (F)	0.9 msec (0.3%)	2.8 msec (0.7%)	7.5 msec (2%)
Mean change from baseline day 17 (F)	1.8 msec	1.6 msec	4.8 msec
Mean change from baseline day 17 (B)	9.6 msec	3.8 msec	6.3 msec
AUC baseline QTc (B)	399	397	399
Max change from baseline day 17 (B)	10 msec/hr (2.5%)	5.3 msec/hr (1.4%)	7.2 msec/hr (1.8%)
AUC baseline QTc (F)	380	374	375
Change from baseline day 17 (F)	1.5 msec/hr (0.4%)	2.5 msec/hr (0.7%)	4.5 msec/hr (1.2%)

Mean change from baseline QTc interval and ventricular rate comparing response in 2-5 and 6-11 year age groups in studies 2798 (v6, p475-484, t2a-6b) and 3016 (v26, p762-766)(v8, p911-922)

Study 2798	2-5 years	6-11 years	2-5 years	6-11 years	2-5 years	6-11 years
Patient population	Mean change ventricular rate baseline to day 17	Mean change ventricular rate baseline to day 17	Mean QTc change from baseline to day 17 (F)	Mean QTc change from baseline to day 17 (F)	Mean QTc change from baseline to day 17 (B)	Mean QTc change from baseline to day 17 (B)
Poor metabolizers	↑ 7.1 bpm	↑ 10.7 bpm	↓ 0.3 msec	↑ 2.5 msec	↑ 5 msec	↑ 11.1 msec
Normal metabolizers	↑ 3.8 bpm	↑ 2.2 bpm	↓ 5.3 msec	↑ 5.8 msec	↓ 2.8 msec	↑ 7.9 msec
Placebo patients	↓ 1.6 bpm	↑ 3.5 bpm	↑ 0.4 msec	↑ 7.7 msec	↓ 0.3 msec	↑ 10.2 msec
Study 3016	2-5 years	6-11 years	2-5 years	6-11 years	2-5 years	6-11 years
Poor metabolizers	↑ 11.2 bpm	↑ 6.1 bpm	↑ 9.6 msec	↑ 14.4 msec	↑ 18.2 msec	↑ 20.1 msec
Normal metabolizers	↓ 0.7 bpm	↑ 8.5 bpm	↑ 5 msec	↑ 11.9 msec	↑ 4.7 msec	↑ 19.5 msec
Placebo patients	None	↑ 0.2 bpm	None	↓ 6.1 msec	None	↓ 6.4 msec

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Mean change from baseline on day 29 in study 3016 (v24, p286-290, t2-6)(p292-303, t1a-6b)( p306-310, t2-6)(v26, p790-800)

Patient group	Ventricular rate	QTc (B)	QTc (F)
Poor metabolizer (n=15) 2-11 years	8.1 bpm baseline 86.5 bpm	19.4 msec baseline 409 msec	12.4 msec baseline 385 msec
Normal metabolizer (n=5) 2-11 years •	0.2 bpm baseline 85 bpm	-6.4 msec baseline 417 msec	-6.1 msec baseline 393 msec
Placebo (n=22) 2-11 years	5.6 bpm baseline 86 bpm	14.8 msec baseline 406 msec	9.7 msec baseline 383 msec
P value ••	P = 0.52	P = 0.43	P = 0.57
Poor metabolizer 2-5 years	11.2 bpm baseline 89 bpm	18.2 msec baseline 407 msec	9.6 msec baseline 382 msec
Placebo	-0.7 bpm baseline 101 bpm	4.7 msec baseline 415 msec	5 msec baseline 381 msec
Poor metabolizer 6- 11 years	6.1 bpm baseline 85 bpm	20.2 msec baseline 410 msec	14.4 msec baseline 387 msec
Normal metabolizer 6-11 years	0.2 bpm baseline 85 bpm	-6.4 msec baseline 417 msec	-6.1 msec baseline 393 msec
Placebo	8.5 bpm baseline 80 bpm	19.5 msec baseline 402 msec	11.9 msec baseline 385 msec

- statistical comparison between poor and normal metabolizers was not done because of the small number of normal metabolizers included in the study
- p values represent statistical comparison of poor metabolizers and placebo patients

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Mean change from baseline on all study days in study 3016 (v24, p42,43, t11,13,140)

Visit	N	Poor metabolizers	N	Placebo patients	P value *
Ventricular rate		Baseline 86.5 bpm		Baseline 86.3 bpm	
Day 8	15	8.7	22	7.0	0.6
Day 15	15	6.2	22	3.6	0.5
Day 22	15	9.4	22	-2.2	0.01
Day 29	15	8.1	22	5.6	0.5
QTc (B)		Baseline 409 msec		Baseline 406 msec	
Day 8	15	6.7	22	7.1	0.9
Day 15	15	11.8	22	12.8	0.9
Day 22	15	18.5	22	10.0	0.3
Day 29	15	19.4	22	14.8	0.4
QTc (F)		Baseline 384.8 msec		Baseline 383.2 msec	
Day 8	15	0.1	22	1.8	0.8
Day 15	15	6.7	22	9.2	0.7
Day 22	15	10.6	22	10.8	0.9
Day 29	15	12.4	22	9.7	0.6

\* comparison of poor metabolizers and placebo patients

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Mean change from baseline for selected ECG parameters in study 303 (v2, p36, t12)

Parameter	Normal metabolizers (n=43)	Poor metabolizers (n=8)	Placebo (n=56)
Ventricular rate (bpm)			
Baseline mean	104.5	88.38	104.8
Mean change from baseline to day 15	↓ 1.44	2.38	↓ 8.8
QTc interval (Bazett)			
Baseline mean	421.8 msec	410.9 msec	416.9 msec
Mean change from baseline to day 15	2.48 msec	4.8 msec	↓ 0.86 msec
QTc interval (Fridericia)			
Baseline mean	377.6 msec	385.5 msec	380.7 msec
Mean change from baseline to day 15	3.23 msec	2.67 msec	4.66 msec

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Mean change from baseline for selected parameters in study 302 (v2, p36-37, t13)

Parameter	Normal metabolizers (n=52)	Poor metabolizers (n=8)	Placebo (n=60)
Ventricular rate (bpm)			
Baseline mean	81.75	88.75	80.4
Mean change from baseline to day15	↓ 0.6	↓ 7	↓ 3.65
QTc interval (Bazett)			
Baseline mean	413.8 msec	419.1 msec	414.4 msec
Mean change from baseline to day 15	↓ 1.14 msec	3.61 msec	↓1.51
QTc interval (Fridericia)			
Baseline mean	393.5 msec	392.7 msec	395.1 msec
Mean change from baseline to day 15	↓ 0.37 msec	8.94 msec	1.84 msec

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Mean change from baseline for selected ECG parameters in study C98-566 comparing poor metabolizers to normal metabolizers and placebo patients (v2, p41, 42, t15)

Parameter	Normal metabolizers (n=41)	Poor metabolizers (n=10)	Placebo (n=61)
Ventricular rate (bpm)			
Baseline mean	97	100	100.4
Mean change from baseline to day 15	1.80	1.2	↓ 2.1
QTc interval (Bazett)			
Baseline mean	418.9 msec	414.5 msec	416.3 msec
Mean change from baseline to day 15	↓ 2.42 msec	↓ 2.3 msec	↓ 2.72 msec
QTc interval (Fridericia)			
Baseline mean	387.1 msec	381.3 msec	382.9 msec
Mean change from baseline to day 15	↓ 2.56	↓ 2.65	↓ 0.96

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Mean change from baseline to endpoint study 2994 using all randomized patients (v12, p93, t24; v14, pgs782-786, t2,3,6)\*

Parameter	Poor metabolizers	Placebo	P value
Ventricular rate (bpm)	5.8 (8%)	1 (1.9%)	0.09 ***
	Poor metabol 2-5 yrs	Placebo	
	7.5	- 0.5	
	Poor metabo 6-11 yrs	Placebo	
	5	1.5	
QTc (B)(msec)	5.7 (1.6%)	-2.4 (-0.5%)	0.09 **
	Poor metabol 2-5 yrs	Placebo	
	9.1	-0.3	
	Poor metabol 6-11 yrs	Placebo	
	4.4	-3.2	
QTc (F)(msec)	1.1 (0.5%)	-2.8 (-0.6%)	0.3 **
	Poor metabol 2-5 yrs	Placebo	
	3.6	0.5	
	Poor metabol 6-11 yrs	placebo	
	0.1	-4.1	

\* The changes seen in poor metabolizers and placebo patients did not change significantly based on including only “per protocol” patients (see definition of this patient group in the description of the study). The p value for the difference between treatments was 0.07 for QTc using Bazett’s correction, 0.3 for QTc using Fridericia’s correction and 0.06 for ventricular rate (v14, pgs789-793, t2,3,6)

\*\* The difference between poor metabolizers and placebo patients in change from baseline in QTc was driven by the difference in females and Blacks for QTc interval using both Fridericia’s (3.1 msec in female poor metabolizers and -2.8 msec in female placebo patients compared with -2.5 msec in male poor metabolizers and -2.9 msec in male placebo patients; 2.1 msec in Black

poor metabolizers and -2.5 msec in Black placebo patients compared with -1.7 msec in non-Black poor metabolizers and -3.1 msec in non-Black placebo patients ) and Bazett's correction (7.7msec in female poor metabolizers and - 3.1 msec in female placebo patients compared to 2.1 msec in male poor metabolizers and - 1.7 msec in male placebo patients; 7.9 msec in Black poor metabolizers and -4.1 msec in Black placebo patients compared with -0.1 msec in non-Black poor metabolizers and -0.8 msec in non-Black placebo patients)(v14, p831-847, t2a,b, 3a,b)

\*\*\* The difference in the ventricular rate between poor metabolizers and placebo patients was also driven by the response in Black patients. Black poor metabolizers had a mean change of 7.3 bpm and Black placebo patients had a mean change of -1.6 bpm compared with non-Black poor metabolizers who had a mean change from baseline of 1.6 bpm and non-Black placebo patients who had a mean change of 3.5 bpm.(v14, p852-853, t6a,b).

Comparison of mean QTc interval change from baseline in study 2994 comparing change in males and females and in Black and non-Black children

Patient population	QTcB (msec)	QTcF (msec)
Female poor metab	7.7	3.1
Female placebo pts	- 3.1	- 2.8
Male poor metabolizers	2.1	- 2.5
Male placebo patients	- 1.7	- 2.9
Black poor metabolizers	7.9	2.1
Black placebo pts	- 4.1	- 2.5
Non-Black poor metab	- 0.1	- 1.7
Non-Black placebo pts	- 0.8	- 3.1

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c. Combined Data from studies 2798, 3016, 303, 302, and C98-566:

Mean change from baseline QTc interval and ventricular rate (v5, p56-59, t20-23)(v6, p467-468, 471, t2,3,6) patients 2-11 years of age in studies 2798, 3016, 303, 302, C98-566

Study 2798			
Patient population	Mean change ventricular rate baseline to day 17	Mean QTc change from baseline → day 17(F)	Mean QTc change from baseline → day 17 (B)
Poor metabolizers (n=17)	↑ 9.8 bpm ***	↑ 1.8 msec	↑ 9.6 msec **
Normal metabolizers (n=21)	↑ 2.8 bpm	↑ 1.6 msec	↑ 3.8 msec
Placebo (n=10)	↑ 1.4 bpm (6.7 bpm poor metabolizers, -0.8 bpm normal metabolizers)	↑ 4.8 msec (1.9 msec poor metabolizers, 6 msec normal metab)	↑ 6.3 msec (7.1 msec poor metab, 5.9 msec normal metabolizers)
Study 3016			
Patient population	Mean change ventricular rate baseline to day 17	Mean QTc change from baseline → day 29 (F)	Mean QTc change from baseline → day 29 (B)
Poor metabolizers (n=15)	↑ 8.1 bpm	↑ 12.4 msec	↑ 19.4 msec
Normal metabolizers (n=5) *	↑ 0.2 bpm	↓ 6.1 msec	↓ 6.4 msec
Placebo (n=22)	↑ 5.6 bpm	↑ 9.7 msec	↑ 14.8 msec
Study 302			
Patient population	Mean change ventricular rate baseline to day 17	Mean QTc change from baseline → day 15 (F)	Mean QTc change from baseline → day 15 (B)
Poor metabolizers (n=8)	↓ 7 bpm	↑ 8.94 msec	↑ 3.61 msec
Normal metabolizers (n=52)	↓ 0.6 bpm	↓ 0.37 msec	↓ 1.14 msec
Placebo (n=60)	↓ 3.7 bpm	↑ 1.84 msec	↓ 2.72 msec
Study 303			
Patient population	Mean change ventricular rate baseline to day 17	Mean QTc change from baseline → day 15 (F)	Mean QTc change from baseline → day 15 (B)
Poor metabolizers (n=8)	↑ 2.4 bpm	↑ 2.67 msec	↑ 4.8 msec
Normal metabolizers (n=43)	↓ 1.4 bpm	↑ 3.23 msec	↑ 2.5 msec
Placebo (n=56)	↓ 8.8 bpm	↑ 4.66 msec	↓ 0.9 msec
Study C98-566			
Patient population	Mean change ventricular rate baseline to day 17	Mean QTc change from baseline → day 15 (F)	Mean QTc change from baseline → day 15 (B)
Poor metabolizers (n=10)	↑ 1.8	↓ 2.56 msec	↓ 2.4 msec
Normal metabolizers (n=41)	↑ 1.2	↓ 2.65 msec	↓ 2.3 msec
Placebo (n=61)	↓ 2.1	↓ 0.96 msec	↓ 2.7 msec

\* statistical comparison not done between poor and normal metabolizers because the 5 normal metabolizers were thought to be poor metabolizers when enrolled in the study and the sample size was too small to do a statistical comparison

\*\* p value for comparison of poor and normal metabolizers 0.07

\*\*\* p value for comparison of poor metabolizers with both normal metabolizers and placebo < 0.001

Summary Table on mean differences in ventricular rate and QTc interval in poor metabolizers, normal metabolizers and placebo patients based on all multiple dose studies in children submitted under NDA

Study	Vent rate	Vent rate	Vent rate	QTcB	QTcB	QTcB	QTcF	QTcF	QTcF
	bpm	bpm	bpm	Msec	msec	msec	Msec	msec	msec
	Poor	Normal	placebo	Poor	Normal	Placebo	Poor	Normal	placebo
2798	↑ 9.8 *	↑ 2.8	↑ 1.4	↑ 9.6 **	↑ 3.8	↑ 6.3	↑ 1.8	↑ 1.6	↑ 4.8
2994	↑ 5.8 *	-	↑ 1	↑ 5.7 **	-	↓ 2.4	↑ 1.1 **	-	↓ 2.8
3016	↑ 8.1 *	↑ 0.2	↑ 5.6	↑ 19.4 **	↓ 6.4	↑ 14.5	↑ 12.4 **	↓ 6.1	↑ 9.7
302	↓ 7	↓ 0.6	↓ 3.65	↑ 3.61 **	↓ 1.14	↓ 1.51	↑ 8.94 **	↓ 0.37	↑ 1.84
303	↑ 2.38 *	↓ 1.44	↓ 8.8	↑ 4.8 **	↑ 2.48	↓ 0.86	↑ 2.67	↓ 3.23	↑ 4.66
C98-566	↑ 1.2	↑ 1.8	↓ 2.1	↓ 2.3	↓ 2.42	↓ 2.72	↓ 2.65	↓ 2.56	↓ 0.96

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### 7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Number (%) of patients with specified degrees of change from baseline in QTc interval on day 17 in studies 2798 and 3016 (v1, p59, adapted from t17)

	QTc change from baseline to day 9 (F)	QTc change from baseline to day 9 (F)	QTc change from baseline → day 9 (F)	QTc change from baseline to day 9 (B)	QTc change from baseline to day 9 (B)	QTc change from baseline → day 9 (B)
Study 2798	0-30 msec	31-60 msec	≥ 61 msec	0-30 msec	31-60 msec	≥ 61 msec
Poor (n=17) metabolizers	10 (59%)	None	None	13 (76%)	None	none
Norm (n=21) metabolizers	12 (57%)	none	None	13 (62%)	None	none
Placebo (n=10)	6 (60%)	None	None	6 (60%)	None	none
	QTc change from baseline to day 17 (F)	QTc change from baseline to day 17 (F)	QTc change from baseline → day 17 (F)	QTc change from baseline to day 17 (B)	QTc change from baseline to day 17 (B)	QTc change from baseline → day 17 (B)
Study 2798	0-30 msec	31-60 msec	≥ 61 msec	0-30 msec	31-60 msec	≥ 61 msec
Poor (n=17) metabolizers	11 (65%)	None	None	13 (76%)	none	None
Norm (n=21) metabolizers	13 (62%)	none	None	15 (71%)	none	None
Placebo (n=10)	5 (50%)	None	None	6 (60%)	none	None
Study 3016	0-30 msec	31-60 msec	≥ 61 msec	0-30 msec	31-60 msec	≥ 61 msec
Poor (n=15) metabolizers	11 (73%)	1 (7%)	None	8 (53%)	5 (33%)	None
Norm (n=5) metabolizers	2 (40%)	None	None	1 (20%)	none	None
Placebo	16 (73%)	2 (9%)	None	13 (59%)	5 (23%)	None

Percent change from baseline to day 9 and day 17 in QTc interval in study 2798 (v8, p923-925)

Patient population	10-14%	15-19%	≥ 20%
Poor metabolizers	None	none	None
Normal metabolizers	None	None	None
Placebo patients	None	None	None

Percent of patients with degree of change in QTc (msec) on each evaluation day in study 3016 (v24, p43, t15)

Change in QTcB	Day 8	Day 8	Day 15	Day 15	Day 22	Day 22	Day 29	Day 29
	poor metab	placebo						
< 0	27%	45%	27%	36%	27%	36%	13%	18%
0-30	60%	41%	47%	45%	33%	45%	53%	59%
31-60	13%	14%	27%	18%	33%	18%	33%	23%
>60	none	none	none	none	7%	none	none	none
Change in QTcF								
< 0	47%	50%	33%	27%	20%	27%	20%	18%
0-30	47%	50%	67%	64%	67%	64%	73%	73%
31-60	7%	None	None	9%	13%	9%	7%	9%
> 60	none	none	none	none	none	none	none	none

Individual patient changes in QTc interval in study 2994 (v12, p99, t26)

Change in QTc interval (F) day 36	Desloratadine poor metabolizer (n=39)	placebo (n=46)
1-29 msec	21 (54%)	19 (41%)
30-60 msec	1 (3%)	1 (2%)
> 60 msec	none	None
Change in QTc interval (B) day 36		
1-29 msec	17 (47%)	17 (39%)
30-60 msec	6 (17%)	3 (7%)
> 60 msec	1 (3%)	None

Percent change from baseline: # of patients: QTc interval and ventricular rate study 2994 (v14, p943)

Parameter	10-14%	15-19%	≥ 20%
QTc (Fridericia correct)			
Poor metabolizers	1 (2%)	0	0
Placebo patients	0	0	0
QTc (Bazett correction)			
Poor metabolizers	2 (4%)	1 (2%)	0
Placebo patients	0	0	0
Ventricular rate			
Poor metabolizers	4 (9%)	4 (9%)	9 (20%)
Placebo patients	4 (8%)	3 (6%)	7 (15%)

#### 7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Individual patient QTc interval change from baseline at specific time points in study 2798

Time after Clarinex	2 hrs	2 hrs	4 hrs	4 hrs	8 hrs	8 hrs	12 hrs	12 hrs	24 hrs	24 hrs
Patient number poor metab	F msec	B msec								
41 (5BF)	-12	-3	-21	4	25	39	-1	9	-17	15
44 (5BM)	8	0	16	30	3	7	26	-32	-4	-1
46 (4BF)	-1	-15	7	15	6	-4	-4	-1	1	-2
51 (5BM)	-22	-33	-5	3	-7	4	-9	-9	-13	24
Average 2-5	-7	-13	-1	13	7	12	3	-8	-8	9
61 (6BF)	2	-2	7	27	7	17	-3	11	-1	14
66 (6BM)	1	12	8	29	-7	11	-3	13	1	20
69 (6BF)	9	10	13	30	3	9	5	20	17	28

81 (8BF)	13	23	8	32	20	32	-6	6	16	33
83 (8 BM)	-16	-18	-11	6	10	33	-14	-5	4	18
86 (8 BM)	7	-2	16	-5	0	7	-9	0	-4	-7
87 (8CF)	11	11	9	28	-13	-6	5	18	6	21
91 (9BM)	8	8	5	9	21	36	1	13	-4	4
93 (9BM)	12	17	18	28	-5	8	9	13	13	23
101 (10BF)	20	22	4	-1	-3	13	-8	3	6	17
106 (10BM)	1	-3	-9	2	5	26	29	35	0	9
111 (11BM)	3	1	3	13	4	2	3	4	11	5
113 (11BM)	-10	4	4	22	-5	8	-22	-19	-27	-43
Average	3	4	4	16	4	12	0	5	1	10
Normal metabolizers	2 hrs F	2 hrs B	4 hrs F	4 hrs B	8 hrs F	8 hrs B	12 hrs F	12 hrs B	24 hrs F	24 hrs B
Pt 23	4	13	11	14	-16	-14	-6	-13	-9	-12
Pt 25	1	-1	8	9	-15	-3	3	7	1	7
Pt 29	-14	-22	-9	-18	-8	0	-6	-4	8	14
Pt 30	22	-26	-11	-6	-17	-18	1	10	-7	-2
Pt 42	9	12	26	41	-5	-2	36	47	11	22
Pt 45	6	3	-9	5	-10	-1	-16	-12	-16	-18
Pt 47	-10	-1	-17	-1	3	4	-27	-11	-34	-40
Pt 50	10	8	-5	-9	1	1	1	1	4	9
Pt 62	21	13	2	-5	20	13	4	7	17	16
Pt 64	2	2	23	33	6	3	-3	-7	-15	-18
Pt 73	6	-4	9	20	8	13	9	-17	7	9
Pt 75	-1	-1	-10	1	7	11	15	37	10	12
Pt 82	7	9	-1	10	18	20	-32	-36	0	7
Pt 84	-1	-4	17	29	16	20	50	-8	13	21
Pt 92	0	-8	0	7	8	12	23	19	7	1
Pt 95	17	24	12	7	4	11	4	4	1	10
Pt 102	-15	-19	-15	-12	1	5	-2	4	9	20

Pt 103	14	21	24	30	28	22	49	50	10	-1
Pt 104	0	-7	-4	0	15	13	2	8	-5	4
Pt 112	7	5	7	6	-9	-9	3	13	20	24
Pt 114	18	24	12	21	-13	-9	-4	-5	8	17
Average	5	2	7	9	2	3	5	6	2	5
Placebo patients	2 hrs F	2 hrs B	4 hrs F	4 hrs B	8 hrs F	8 hrs B	12 hrs F	12 hrs B	24 hrs F	24 hrs B
Pt 21	-13	-22	-3	-6	5	7	-19	-20	0	4
Pt 68	-13	-15	3	20	22	38	20	29	15	28
Pt 72	-3	2	25	42	-1	9	-5	9	-3	12
Pt 28	30	17	4	-5	27	38	33	30	-38	-39
Pt 43	-11	-8	-18	-6	18	19	-4	-1	-17	-10
Pt 48	13	6	-13	-9	11	5	-16	-16	-11	-11
Pt 65	-3	-15	-9	-10	-5	-4	-5	-4	0	19
Pt85	14	-1	9	25	9	9	15	5	11	21
Pt 105	4	2	28	36	19	27	35	42	13	16
Pt 115	27	18	-9	-10	18	16	7	2	10	-1
Average	4	-18	2	8	12	16	6	8	-2	4

COMMENT: As seen in the tables above, there is a trend in some studies toward greater mean prolongation of the ventricular rate and QTc interval, especially using Bazett's correction, in children who are poor metabolizers and received desloratadine than in children who are normal metabolizers and received desloratadine or children who received placebo. Bazett's correction, however, overcorrects for heart rate and in some studies greater mean prolongation of the QTcd interval in poor metabolizers was not seen using Fridericia's correction. In addition, only in study 2798 were ECGs done at serial time points up to 24 hours after drug administration on evaluation days at baseline and during treatment. Therefore, a determination regarding the effect of desloratadine on the QTc interval in poor metabolizers should be based primarily on the data from study 2798. In study 2798, mean QTc prolongation was 1.8 msec after treatment with desloratadine in poor metabolizers and 4.8 msec in the placebo group using Fridericia's correction and there was no indication based on individual patient data that a greater prolongation of the QTc interval was being seen in individual patients who were poor metabolizers and received desloratadine than in normal metabolizers or patients who received placebo.

*In study 2994, based on ECGs that were done only 3 hours after drug administration, greater prolongation of the QTc interval in children who were poor metabolizers was seen in females, Black patients, and patients 2-5 years of age. In study 2994, based on Bazett's correction of the QTc interval, there were more patients who were poor metabolizers of desloratadine who had 30 msec or greater change from baseline or a 10% or greater change from baseline than placebo patients, although the differences were small.*

*On the other hand, there were, overall, only a few patients who developed prolongation of the QTc interval that was slightly greater than 440 msec and this occurred at least as frequently in normal metabolizers or patients who received placebo and in most studies differences in prolongation of the QTc interval between poor metabolizers and other study groups disappeared when Fridericia's correction was used. In addition, no adverse cardiovascular events were reported in any of the treatment groups and there was no clinically significant change in any ECG tracing from baseline in children who were poor metabolizers. Looking at the individual patient data in study 2798, there were a comparable number of time points at which poor metabolizers, normal metabolizers and placebo patients had a 20 msec or greater change in QTc interval from baseline. Only at 4 hours after drug administration was the average QTc interval significantly higher in poor metabolizers than in either the normal metabolizer or placebo group in study 2798.*

*The possible effect of desloratadine in poor metabolizers less than 2 years has not been studied and has been studied only in a very small number of patients 2-3 years of age. Nevertheless, as stated in the review by OCPB, from an analysis of the data, no clear signal of QTc prolongation has been observed in poor metabolizers who received desloratadine when compared to normal metabolizers who received desloratadine and patients who received placebo (see OCPB review of 23 August 2004).*

#### 7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were done.

#### 7.1.10 Immunogenicity

This drug product does not contain therapeutic proteins.

#### 7.1.11 Human Carcinogenicity

Human carcinogenicity studies were not performed.

#### 7.1.12 Special Safety Studies

There were no special safety studies.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no withdrawal phenomena or abuse potential with this drug product.

#### 7.1.14 Human Reproduction and Pregnancy Data

There is no human reproduction or pregnancy data to review. Based on animal data, desloratadine is rated Pregnancy Category C.

#### 7.1.15 Assessment of Effect on Growth

There is no assessment of effect on growth to review. Clarinex is an antihistamine that is not been shown to have any effect on growth.

#### 7.1.16 Overdose Experience

The sponsor has submitted post-marketing experience with this drug product in which there was one accidental overdose in a 7 year old child who took 50 mL of desloratadine syrup (10 times the recommended dose) and did not experience any adverse reaction.

#### 7.1.17 Postmarketing Experience

Desloratadine syrup has been approved in 41 countries including the EU and Canada. Based on data submitted up to 4 April 2003, spontaneous adverse events in children under the age of 12 years had been reported for 15 children after administration of desloratadine syrup. Included in these were two serious adverse events which were: 1) a 5 year old male who 12 hours after the last dose 5 days after starting treatment developed marked somnolence, diplopia, dizziness, motor incoordination, and bradycardia requiring hospitalization. The patient recovered completely 72 hours after the adverse event started; 2) a 5 year old male who two days after starting treatment developed an extrapyramidal disorder, somnolence and disorientation and one week after starting treatment had an episode of loss of consciousness. The patient recovered completely one day after discontinuing treatment. While these adverse events could be associated with the administration of antihistamines, they are less likely to occur with administration of a non-sedating antihistamine such as desloratadine. Nevertheless, post-marketing adverse events reporting is too sketchy to allow any determination about the causality of these adverse events.

### 7.2 Adequacy of Patient Exposure and Safety Assessments

There were 455 patients 2-12 years of age who received repetitive doses of desloratadine syrup at the recommended dose for periods from 2-5 weeks. Of these, 104 patients who were poor metabolizers received desloratadine. This was an adequate database on which to base a determination of the safety of desloratadine with repetitive dose administration in children who were poor metabolizers and consistent with previous guidance by the Agency.

#### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

There were 455 patients 2-12 years of age who received repetitive doses of desloratadine syrup at the recommended dose for periods from 2-5 weeks. Of these, 104 patients who were poor metabolizers received desloratadine. There were 581 Black patients, 742 Caucasian patients, 861 Hispanic patients and 212 patients of other race who were included in all the studies submitted by the sponsor. Of these, there were 112 poor metabolizers who were Black, 22 who were Caucasian and 24 who were of another race.

### 7.2.1.1 Study type and design/patient enumeration

Study #	Study design	Age range	Dose and duration administered	Number of patients	Disease	Primary PK parameters	PD parameters safety
2818 v9, v11	SD, open, screening	2-11 years	One dose of 10 mg loratadine	359; 53 poor metab, 16 2-5 yrs, 37 6-11 yrs	Allergic rhinitis	Plasma 3-OH DSL and DSL ratio	AEs. VS
2798 v5-8	MD, P, R, PC, IB	2-11 years	1.25 mg (2-5 yrs) 2.5 mg (6-11 yrs) desloratadine for 17 days	48; 17 poor metab; 21 normal metab, 10 placebo	Allergic rhinitis	Cmax. AUC.	AEs. ECGs. VS. lab tests.
3016 v24-26	MD, DB, PC	2-11 years	1.25 mg (2-5 yrs) 2.5 mg (6-11 yrs) desloratadine for 29 days	42; 15 poor metab; (6 2-5 yrs, 9 6-11 yrs); 5 normal metab, 22 placebo	Allergic rhinitis	Cmin (assess of steady state)	AEs. VS. ECGs. physical exam, lab tests
2781 v2-4 v10	SD, open	2-11 years	5 mg loratadine 2.5 mg (2-5 yrs) 5 mg (6-11 yrs) desloratadine	162; 51 from study C98-566, 60 from study 302, 51 from study 303	Allergic rhinitis. ch idiopathic urticaria	Plasma 3-OH DSL and DSL ratio	VS
302 v2-4 v10	R, DB, PC, P	6-11 years	2.5 mg desloratadine for 15 days	120; 8 poor metab, 52 normal metab, 60 placebo	Allergic rhinitis, ch idiopath urticaria	Plasma 3-OH DSL and DSL ratio	AEs. VS. ECGs. physical exam, lab tests
303 v2-4 v10	R, DB, PC, P	2-5 years	1.25 mg desloratadine for 15 days	107; 8 poor metab, 43 normal metab, 56 placebo	Allergic rhinitis, ch idiopath urticaria	Plasma 3-OH DSL and DSL ratio	AEs. VS. ECGs. physical exam. lab tests
C98-566 V2-4 V10	MD, R, PC, P, DB	2-5 years	5 mg loratadine syrup for 14 days	41 normal metab 10 poor metab., 61 placebo	Allergic rhinitis, ch idiopath urticaria	Plasma 3-OH DSL and DSL	ECGs
3031 v1	SD, open, screening	2-11 years	One dose of 10 mg loratadine	2075: 79 poor metab, 27 2-5 yrs, 52 6-11 yrs	Atopy. ch idiopathic urticaria	Plasma 3-OH DSL and DSL ratio	AEs
2994 v12-23	RD, DB, PC, MC	2-11 years	1.25 mg (2-5 yrs) 2.5 mg (6-11 yrs) desloratadine for 36 days	97; 58 poor metab, 48 poor metab Rx; 49 placebo	Atopy, ch idiopathic urticaria	Cmin (assess of steady state)	AEs. ECGs, VS. physical exam. lab tests
117 v1	MD, open, R, CX	19-41	10 mg loratadine 5 mg DSL for 10 days	25	Healthy volunteers	Plasma 3-OH DSL and DSL	
1341 v1	SD, open	6 mo to < 2 yrs	0.625 mg < 1 yr 1.25 mg if 1 yr	58		Plasma 3-OH DSL and DSL ratio	

### 7.2.1.2 Demographics

See review of individual studies under Appendix.

### 7.2.1.3 Extent of exposure (dose/duration)

There were 2434 patients who received a single dose of 10 mg of loratadine in prospective studies. There were 112 patients who received 1.25 mg or 2.5 mg of desloratadine for 14 days, 42 patients who received either of these doses for 4 weeks and 97 patients who received either of these doses for 5 weeks.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There was no secondary clinical data source used to evaluate safety.

### 7.2.2.1 Other studies

Study 117 was a repetitive dose 10 day study done previously in adult healthy volunteers, 19-41 years of age, who received 10 mg of loratadine and 5 mg of desloratadine in a crossover design, the data from which was used referred to in comparing the metabolism of desloratadine in adults and in children and also to show that patients who were poor metabolizers of desloratadine following loratadine administration were also poor metabolizers of desloratadine following desloratadine administration. Study 1341 was a single dose study done in children 6 months to 2 years of age was used to supplement the pharmacokinetic and safety database. Only summaries of these two studies were submitted.

### 7.2.2.2 Postmarketing experience

The sponsor has only submitted a short summary of summary of post-marketing experience and spontaneous adverse events that are reviewed elsewhere in this MOR.

### 7.2.2.3 Literature

No literature search was done by the reviewer in regard to this submission. The sponsor submitted the results of a literature search but the abstracts of the articles submitted did not address the issues pertaining to this submission.

## 7.2.3 Adequacy of Overall Clinical Experience

An adequate number of patients were exposed to the drug, including an adequate number of demographic subsets, e.g. Black patients who might have been at increased risk, to assess the safety of desloratadine in patients who are poor metabolizers of desloratadine.

## 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical studies were performed for the previous submission of this NDA and found to be adequate to support the safety of desloratadine. No further preclinical studies were considered necessary to assess the safety of desloratadine in poor metabolizers.

#### 7.2.5 Adequacy of Routine Clinical Testing

The clinical safety evaluation done by the sponsor is adequate to demonstrate the safety of desloratadine in patients 2-12 years of age who are poor metabolizers and by extrapolation to support the safety of desloratadine in poor metabolizers 6-11 months of age.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This drug has been studied previously in regard to metabolism, clearance and drug-drug interaction and found to be approvable.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor has adequately evaluated the effect of desloratadine on prolongation of the QTc interval in patients 2-12 years of age who are poor metabolizers. ECGs were performed over 24 hours at baseline and at selected time points including the end of the study for comparison of QTc intervals after repetitive dose administration.

#### 7.2.8 Assessment of Quality and Completeness of Data

The sponsor has submitted a complete database for the key studies submitted. The quality of the data accumulated is adequate to make a judgment on the safety of desloratadine when administered to patients 2-12 years of age who are poor metabolizers.

#### 7.2.9 Additional Submissions, Including Safety Update

This submission is a response by the Applicant to the approvable letter for this drug product in this population of patients which was required because the initial NDA submission did not contain all the information pertinent to the safety evaluation, i.e. repetitive dose administration in patients 2-12 years of age who were poor metabolizers.

### 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The reader is referred to Section 7.1.5.3 in this Integrated Review of Safety.

### 7.4 General Methodology

The reader is referred to Section 7, the Integrated Review of Safety.

#### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

In regard to desloratadine metabolizer status, for comparison between age groups, the sponsor pooled data from adult studies in patients 12-70 years of age and pediatric studies in patients 2-11 years of age. In evaluating adverse events, the sponsor pooled data from studies with patients 2-5 years of age and studies with patients 6-11 years of age. The sponsor also pooled ECG data from studies 2994 and 3016 "due to similarity in study design". Pooling of data was analyzed in an appropriate manner.

#### 7.4.1.1 Pooled data vs. individual study data

Data was analyzed in terms of pooled data and individual study data. Analysis of pooled data did not change the conclusions reached by this reviewer on the basis of review of individual study data.

#### 7.4.1.2 Combining data

The methods for pooling data were not described.

#### 7.4.2 Explorations for Predictive Factors

No adverse events reported were considered to be definitely related to the study drug.

##### 7.4.2.1 Explorations for dose dependency for adverse findings

The type and frequency of adverse events was not significantly different in patients 2-5 years of age who received a dose of 1.25 mg once a day and patients 6-11 years of age who received a dose of 2.5 mg once a day. This was seen in both normal and poor metabolizers in regard to dose. Therefore, adverse events and other safety parameters were not dependent upon the dose of desloratadine that was administered.

##### 7.4.2.2 Explorations for time dependency for adverse findings

Adverse events were not related to the time of drug administration.

##### 7.4.2.3 Explorations for drug-demographic interactions

The incidence or type of adverse events was not related to race, either in normal or poor metabolizers. Black patients who appear to have a higher incidence of poor metabolism did not have a significantly greater incidence of adverse events, different types of adverse events or more severe adverse events than Caucasian or Hispanic patients.

##### 7.4.2.4 Explorations for drug-disease interactions

Desloratadine is approved for patients with allergic rhinitis or idiopathic chronic urticaria. Patients with those conditions comprised the patient population for the studies submitted by the sponsor in this Complete Response. There was no analysis of the safety data based on whether patients had allergic rhinitis, chronic idiopathic urticaria or atopy in general.

##### 7.4.2.5 Explorations for drug-drug interactions

No studies were performed evaluating desloratadine when given concomitantly with other drugs.

#### 7.4.3 Causality Determination

Causality determination was based on temporal association with drug administration and whether other etiologies were likely or unlikely. There were no rare or serious adverse events reported.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The dosing regimen and administration proposed by the sponsor, i.e. 5 mg once daily for patients 12 years of age and older. 2.5 mg once daily for patients 6-11 years of age, 1.25 mg once daily

for patients 12 months to 5 years of age, and 1 mg once daily for patients 6-11 months, is acceptable. These doses have been previously determined to be safe and effective.

## 8.2 Drug-Drug Interactions

In clinical pharmacology studies done prior to this submission in healthy volunteers desloratadine was administered with erythromycin, ketoconazole, azithromycin, and fluoxetine without any clinically relevant changes in the safety profile of desloratadine, including ECG measurements.

## 8.3 Special Populations

The studies performed suggest that there is a higher incidence of poor metabolizers in Black patients.

## 8.4 Pediatrics

The safety of desloratadine syrup in patients 2-12 years of age who are poor metabolizers has been demonstrated from the data submitted by the Applicant. In the submission of 14 May 2003 under NDA 21-563, the sponsor included a claim for pediatric exclusivity. On 4 February 2000, the sponsor asked for a Written Request for Pediatric Exclusivity for Clarinex syrup. In the Written Request to the sponsor of 6 June 2000, 4 studies were requested – safety studies in patients 6-11 years of age, 2-5 years of age and 6-23 months of age and pharmacokinetic study in patients 6-23 months of age. The latter two studies were part of the submission of 14 May 2003. The first two studies, safety studies in patients 2-11 years of age (studies 302 and 303), were submitted to NDA 21-300 and formed part of the database that led to the approvability of the syrup formulation in patients 2-11 years of age.

## 8.5 Advisory Committee Meeting

There has been no Advisory Committee meeting on this drug product.

## 8.6 Literature Review

No literature review was done.

## 8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan.

## 8.8 Other Relevant Materials

There are no other relevant materials.

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

The sponsor has adequately characterized the pharmacokinetics of repetitive dose administration in children who are poor metabolizers and shown that the upper limit of exposure in pediatric and adult poor metabolizers is similar and 6-7 times higher than is seen in normal metabolizers. In terms of safety, the sponsor has shown in 6 multiple dose studies, that there is no significant

difference in adverse events, laboratory tests or vital signs between pediatric poor metabolizers who receive desloratadine and pediatric normal metabolizers who receive desloratadine or children who receive placebo. Under NDA 21-165, the NDA for the approved tablet formulation for Clarinex, a dose of 45 mg of desloratadine (9 times the recommended dose) (study 357 – see MOR for Clarinex tablets) was given to healthy volunteers for 10 days and did not produce a clinically significantly greater prolongation of the QTc interval than placebo, based on machine reading of the QTc interval and maximum QTc from serial ECGs. Although the sponsor has submitted no ECG data on children 6 months to 2 years of age who are poor metabolizers, there is no reason to believe that this age group would be more likely to develop prolongation of the QTc interval after administration of desloratadine. The sponsor has provided data to support the proposed dosing of Clarinex, dosing that in the initial review of this NDA was found to be safe and effective for administration to patients 6 months-11 years of age and in this complete response to the approvable letter has been shown to be safe in children who are poor metabolizers of desloratadine.

## 9.2 Recommendation on Regulatory Action

Clarinex syrup should be approved for administration to children 6 months to 12 years of age.

## 9.3 Recommendation on Postmarketing Actions

No post-marketing action is required.

### 9.3.1 Risk Management Activity

No post-marketing risk management activity is required.

### 9.3.2 Required Phase 4 Commitments

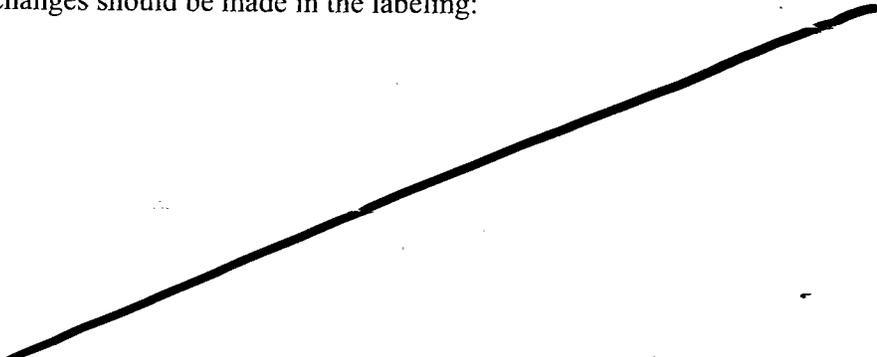
There are no required phase 4 commitments.

### 9.3.3 Other Phase 4 Requests

There are no phase 4 requests.

## 9.4 Labeling Review

In the approvable letter of 14 May 2003 under NDA 21-563, the Division stated that the following changes should be made in the labeling:



[Redacted]

[Redacted]

9.5 Comments to Applicant

1. Clinical Pharmacology, Metabolism section:

[Redacted]

[Redacted]

y  
/

2. Adverse Reactions section:

[Redacted]

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

- A. Study 2818: This screening study was designed to prospectively characterize the metabolic phenotype of desloratadine after administration of loratadine in pediatric patients 2-11 years of age so that poor metabolizers could be enrolled into a multiple dose study. It was an open-label, single dose study in which 359 patients with allergic rhinitis were given 10 mg of loratadine syrup. Plasma concentrations of 3-OH desloratadine and desloratadine were measured 12 hours after drug administration. Plasma concentrations were determined using high performance liquid chromatography with tandem mass spectrometric methods. Patients were classified as poor metabolizers if the ratio of 3-OH desloratadine to desloratadine was  $< 0.10$  (10%). This was a descriptive study with no analysis of the results. Vital signs were assessed prior to drug administration and 12 hours after drug administration. Adverse events were recorded.

Demographics of patients in study 2818

Category	Poor metabolizers	Normal metabolizers
Number of patients	53	306
Mean age	7 years	6.3 years
Age range	2-11 years	2-11 years
Females	29 (55%)	147 (48%)
Males	24 (45%)	159 (52%)
Caucasian	5 (9%)	103 (34%)
Black	48 (91%)	203 (66%)

Overall, there were 53/359 patients (15%) who were poor metabolizers. This included 48 African-American patients (19.1%) and 5 Caucasian patients (4.6%). Although 5 poor metabolizers in each one year age group was planned, there were only 4 patients identified as poor metabolizers of desloratadine in the 2 year age group, of whom 1 was enrolled in study 2798 and two were enrolled in study 3016. Of the two patients enrolled in study 3016, one was 3 years of age at the time of randomization and the other was randomized to the placebo group. The patient enrolled in study 2798 was subsequently identified as a normal metabolizer. Therefore, the only PK data in patients 2 years of age came from a single dose study (study 1341) in patients 6 months to  $< 2$  years of age in which there were 4 poor metabolizers (see discussion of study 1341 below). In addition, there were only 3 poor metabolizers identified in the 3 and 4 year age groups (see table below).

Number of poor and normal metabolizers in each one year age group in study 2818

Patient age (years)	# Poor metabolizers	# Normal metabolizers	Total number patients
2	4 (8%)	22 (7%)	26 (7%)
3	3 (6%)	29 (9%)	32 (9%)
4	3 (6%)	42 (14%)	45 (13%)
5	6 (11%)	44 (14%)	50 (14%)
6	6 (11%)	27 (9%)	33 (9%)
7	7 (13%)	30 (10%)	37 (10%)
8	7 (13%)	33 (11%)	40 (11%)
9	5 (9%)	35 (11%)	40 (11%)
10	5 (9%)	27 (9%)	32 (9%)
11	7 (13%)	17 (6%)	24 (7%)

Study 2818 (359 patients phenotyped ; 46 poor metabolizers)→ study 2798 (17 poor metabolizers) + study 3016 (15 poor metabolizers)(see table below)

Study #	# patients	# Black patients	# Caucasian patients	Poor metab overall	Poor metab Black	Poor metab Caucasian	Normal metab
2818	359	251 (70%)	108 (30%)	53 (14.8%) *	48 (19.1% prevalence)	5 (4.6% prevalence)	306
Study #	# patients	Placebo	Desloratadine	poor metab desloratadine (overall)	Poor metab desloratadine (2-5 years)	Poor metab desloratadine (6-11 years)	normal metab
2798	48 5 Caucasian 43 Black	10 **	38	17	4	13	21
3016	42 5 Caucasian 37 Black	22 **	20	15	6	9	5

\* 43 of these 53 patients were enrolled in either study 2798 or 3016; 6 patients considered to be poor metabolizers were subsequently found to be normal metabolizers; 5 poor metabolizers were treated with placebo; Therefore, 32 poor metabolizers received desloratadine in studies 2798 & 3016.

\*\* 3 of the placebo patients in study 2798 were poor metabolizers and 7 were normal metabolizers, while 5 of the placebo patients in study 3016 were poor metabolizers and 17 were normal metabolizers

In order to assess the safety profiles of pediatric patients who were poor metabolizers and whether such profiles differed from patients who were normal metabolizers, the sponsor conducted two multiple dose studies – studies 2798 and 3016 in patients 2-11 years of age who were identified as poor metabolizers in study 2818. Data from these studies were used to characterize the PK of repetitive dose administration of desloratadine and to assess the overall safety and specifically the cardiovascular safety at steady state desloratadine exposure. Additional safety data were obtained from 141 children who were treatment in two multiple dose safety studies – studies 302 and 303. Supplemental data for poor metabolizers less than 2 years of age were extracted from a previously conducted single dose PK study – study 1341.

- B. Study 2798: This study was a multiple dose, parallel, randomized, placebo-controlled, double-blinded to treatment but not to dose, to characterize the steady state PK of desloratadine (based on no systematic increase in C<sub>min</sub> levels on succeeding days after day 14,15 and the maximum difference of the daily concentration relative to the mean of days 14 on succeeding days after day 14,15 and the maximum difference of the daily concentration relative to the mean of days 14-18 for that individual did not exceed 25%). The study included 17 poor metabolizers with allergic rhinitis, of whom 4 were 2-5 years of age and 13 were 6-11 years of age, who were compared to 8 patients 2-5 years of age and 12 patients 6-11 years of age who were normal metabolizers (see table below). In the placebo group, 3 were poor metabolizers and 7 were normal metabolizers. All patients enrolled were to have been from screening protocols 2818 and 2781, but no patients from study 2781 were entered into the study. Patients enrolled were randomized based on their metabolism in study 2818. However, based on PK data obtained on day 17 of the study, the metabolism status of two patients was redefined – this included one patient who was randomized as a poor metabolizer and found to be a normal metabolizer and one patient who was a normal metabolizer but had been assigned poor metabolizer status by mistake. These two patients were included in the normal metabolizer group for analysis. One patient did not have measurable desloratadine or 3 OH desloratadine levels on day 17 and since one placebo patient did have measurable levels of both on day 17 it was assumed that mislabeling had occurred. In addition, three other patients in the placebo treated group had measurable desloratadine on days 14-17 attributed by the sponsor to use of OTC loratadine.

The objectives of this study were: 1) to assess steady state exposure to desloratadine based on C<sub>min</sub> concentrations (patients were considered to have reached steady state on day 14 or day 15 if there was no systematic increase in C<sub>min</sub> concentrations for succeeding days and the maximum difference of the daily concentrations relative to the mean of days 14-18 for that individual did not exceed 25%); and 2) to evaluate the safety of desloratadine following repetitive dosing in poor metabolizers. The primary PK endpoint was a comparison of C<sub>max</sub> and AUC in poor and normal metabolizers. Safety assessment was based on laboratory tests, vital signs, post study physical examination, serial ECGs and treatment emergent adverse events over a period of 17 days (v5, p28, t7). ECGs were performed at screening, baseline, and on days 1 and 10 prior to drug administration. In addition, ECGs were performed on days 9 and 17 at 2, 4, 8, 12 and 24

hours after drug administration (v5, p84-86, study design and flow charts). QTc was analyzed using both Bazett's and Fridericia's correction. Primary PD parameters were the change in mean ventricular rate, PR interval, QRS interval, QT and QTc intervals from baseline to days 9 and 17). Patients 2-5 years of age received a dose of 1.25 mg and patients 6-11 years of age received a dose of 2.5 mg.

Demographics of poor metabolizers, normal metabolizers and placebo patients in study 2798

	Total	Poor metabolizers	Normal metabolizers	Placebo
Number of patients	48	17	21	10
Mean age	6.9	7.6	6.7	6.3
Age range	2-11	4-11	2-11	3-11
Number (%) 2-5yrs	16 (33%)	4 (24%)	8 (38%)	4 (40%)
Number (%) 6-11 yrs	32 (67%)	13 (76%)	13 (62%)	6 (60%)
Females	21 (44%)	7 (41%)	10 (49%)	4 (40%)
Males	27 (56%)	10 (59%)	11 (52%)	6 (60%)
Caucasian	5 (10%)	1 (6%)	2 (10%)	2 (20%)
Black	43 (90%)	16 (94%)	19 (90%)	8 (80%)

C. Study 3016: This was a multiple dose, patient and investigator blinded to treatment but not dose, placebo-controlled study in which 15 poor metabolizers with allergic rhinitis stratified by age (6 patients 2-5 years of age and 9 patients 6-11 years of age) were treated with desloratadine. Patients 2-5 years of age received a dose of 1.25 mg and patients 6-11 years of age received a dose of 2.5 mg for a period of 29 days. Poor metabolizers were defined as those patients with a 3OH desloratadine /desloratadine ratio of < 10% while normal metabolizers were defined as patients who had a ratio of > 25%. All patients enrolled in this study (n=42) were identified in screening study 2818. There were 5 normal metabolizers who received desloratadine and 22 patients in the placebo group, of whom 5 were poor metabolizers and 17 were normal metabolizers (see table below; v24, p36, t6). There were 5 patients who were enrolled as poor metabolizers based on data from study 2818 who were found to be normal metabolizers based on PK assessment in this study.

The objectives of this study were: 1) to assess steady state exposure to desloratadine based on C<sub>min</sub> concentrations (patients were considered to have reached steady state on day 14 or day 15 if there was no systematic increase in C<sub>min</sub> concentrations for succeeding days and the maximum difference of the daily concentrations relative to the mean of days 14-18 for that individual did not exceed 25%); and 2) to evaluate the safety of desloratadine following repetitive dosing in poor metabolizers.

Safety was based on laboratory tests, once weekly ECGs, physical examination, vital signs, and treatment emergent adverse events. ECGs were performed at baseline and on study days 8, 15, 22 and 29, 3 hours after drug administration and evaluated by the investigator. ECGs were then transferred by telephone modem and read manually by an independent blinded third-party evaluator. Laboratory tests were done at baseline and on

days 15 and 29. Vital signs were measured at baseline on prior to drug administration on days 1, 8, 15, 22 and 29. Physical examination was performed at screening and at the conclusion of the study. Blood samples were obtained prior to drug administration (Cmin) on days 15, 22 and 29 for determination of plasma desloratadine and 3-OH desloratadine with the ratio of 3OH desloratadine/desloratadine determined. The primary outcome variables were safety assessment of ECGs and adverse events. The primary ECG parameters were ventricular rate, PR interval, QRS interval, QT interval, and QTc interval.

#### Demographics of poor and normal metabolizers and placebo patients in study 3016

	Total	Poor metabolizers	Normal metabolizers	Placebo
Number of patients	42	15	5	22
Mean age	7	7	8	7
Age range	2-11	3-11	7-9	2-11
Number (%) 2-5yrs	13 (31%)	6 (40%)	NONE	7 (32%)
Number (%) 6-11 yrs	29 (69%)	9 (60%)	5 (100%)	15 (68%)
Females	22	9	4	9
Males	20	6	1	13
Caucasian	5	3	None	2
Black	37	12	5	20

D. Studies 302 (patients 6-11 years of age) and 303 (patients 2-5 years of age) were submitted as part of the NDA for this drug product. They were randomized, double-blind, placebo-controlled, parallel group studies in patients with a history of allergic rhinitis or chronic idiopathic urticaria. Patients 2-5 years of age (study 303) received a 1.25 mg dose of desloratadine syrup and patients 6-11 years of age (study 302) received a dose of 2.5 mg of desloratadine syrup for a period of 15 days. ECGs were obtained at screening and within 1-3 hours after drug administration on days 8 and 15. Laboratory tests and vital signs were also assessed. Patients who received treatment with desloratadine in these studies were enrolled in a single dose phenotyping study (study 2781) to determine their metabolizer status. In study 302, 13% (8 patients) overall were poor metabolizers, 13% of the African-Americans (n=4) and 14% of the Caucasians (n=4) in the study. In study 303, 16% (8 patients) overall were poor metabolizers, 15% of the African-Americans (n=6) and 17% of the Caucasians (n=2) in the study. In studies 302 and 303 therefore, there were 16 poor metabolizers out of 111 patients, 8 of whom were 2-5 years and 8 of whom were 6-11 years.

Demographics of study 302 based on metabolizer status (v2, p44, t16)

Category	Poor metabolizers Rx with desloratadine (n=8)	Normal metabolizers Rx with desloratadine (n=52)	Placebo patients  (n=60)
Mean age (years)	9.8	10	8.5
Age range (years)	8-12	8-13	6-11
Females/males	4/4	25/27	39/21
Caucasian	4 (50%)	24 (46.2%)	21 (35%)
Black	4 (50%)	26 (50%)	38 (63%)
Hispanic	none	None	1 (2%)
Asian	none	2 (3.8%)	None

Demographics of study 303 based on metabolizer status (v2, p45, t17)

Category	Poor metabolizer Rx with desloratadine (n=8)	Normal metabolizer Rx with desloratadine (n=43)	Placebo patients  (n=56)
Mean age (years)	6.6	5.3	3.4
Age range (years)	6-7	3-7	2-5
Females/males	4/4	18/25	25/31
Caucasian	32 (25%)	8 (18.6%)	13 (23%)
Black	6 (75%)	3 (81.4%)	42 (75%)
Hispanic	None	None	1 (2%)

- E. Study 117: This study was a multiple dose, open label, randomized, three way crossover study in adults designed to demonstrate that exposure after 10 mg of loratadine was similar to exposure after 5 mg of desloratadine given once daily for 10 days. Twenty-five adult healthy volunteers 19-41 years of age were evaluated. Patients who were poor metabolizers of desloratadine after loratadine administration were also poor metabolizers after desloratadine administration.
- F. Study C98-566: This study was a multiple dose, randomized, placebo-controlled, parallel group, double-blind loratadine safety study in 121 patients 2-5 years of age, 60 of whom

received 5 mg of loratadine syrup, with a history of allergic rhinitis or chronic idiopathic urticaria, 51 of whom were phenotyped for desloratadine metabolizer status in study 2781. There were 10 patients (19.6%) in this study who were poor metabolizers, of whom 4 were African-American and 6 were Caucasian. Patients were treated for 14 days. ECGs were obtained at screening and within 1-3 hours after drug administration on study days 8 and 15.

Demographics of study C98-566 based on metabolizer status (v2, p46, t18)

Category	Poor metabolizers Rx with desloratadine (n=10)	Normal metabolizers Rx with desloratadine (n=41)	Placebo patients (n=61)
Mean age (years)	6.8	6.1	3.5
Age range (years)	6-8	4-8	2-5
Females/males	7/3	22/19	34/27
Caucasian	6 (60%)	37 (90.2%)	53 (86.9%)
Black	4 (40%)	4 (9.8%)	7 (11.5%)
Asian	None	None	1 (1.6%)

G. Study 2781: This study was a single center, single dose, open label, phenotyping PK study to determine the desloratadine metabolic phenotype of patients previously treated with 5 mg of loratadine in study C98-566 and patients treated with 2.5 mg (2-5 years of age) or 5 mg (6-11 years of age) of desloratadine in studies 302 and 303 (see table below). In this study, patients received a single dose of either loratadine 5 mg (syrup), desloratadine 5 mg (syrup)(patients 6-11 years of age), or 2.5 mg (syrup)(patients 2-5 years of age). There were 162 patients enrolled, of whom 51 had been enrolled in study C98-566 and were 2-5 years of age, 60 patients 6-11 years of age from study 302 and 51 patients 2-5 years of age from study 303. Poor metabolizers were defined as patients whose % ratio of 3-OH desloratadine to desloratadine was less than 10%. If 3-OH desloratadine was not measured, a  $\frac{1}{2}$  life of 50 hours or more for desloratadine was used to define a poor metabolizer. The concentration ratio 12 hours after drug administration was best correlated with AUC ratio and therefore this time point was used to identify poor metabolizers in studies 302, 303, and C98-566.

There were 16 poor metabolizers identified from the 111 patients who received desloratadine (14.4%) and 10 poor metabolizers identified from the 51 patients who received loratadine. After determination of metabolizer status, retrospective analysis of the safety data was conducted to compare the safety of desloratadine when administered to poor metabolizers compared to safety of desloratadine after administration to normal metabolizers and compared to patients who received placebo. In addition, vital signs were obtained prior to drug administration and 12 hours after drug administration. Plasma levels for 3-OH desloratadine and desloratadine were obtained 4 and 12 hours after drug

administration. Plasma concentrations were determined by liquid chromatography with tandem mass spectrometric methods.

Study 302 (8 poor metabolizers) + study 303 (8 poor metabolizers) + C98-566 (10 poor metabolizers) → study 2781

Poor metabolizer patient inclusion in study 2781 (v2, p27, t6) \*

Study #	# pts enrolled	# pts who got active Rx	Number of patients phenotyped	Number of Caucasians phenotyped	Number of Blacks phenotyped	Number of Others phenotyped	Caucasian poor metabolizers	Black poor metabolizers	Other poor metab
302	120	60	60	28	30	2	4	4	0
303	111	55	51	10	41	0	2	6	0
C98-566	121	60	51	43	8	0	6	4	0

\* Plasma levels for desloratadine and 3-OH desloratadine were obtained 4 and 12 hours after drug administration. There were 2 patients who did not meet the criteria for a poor metabolizer based on levels at 4 hours but did based on levels at 12 hours. They were included as poor metabolizers. There were also two patients who fit the criteria for poor metabolizer at 4 hours but not at 12 hours. They were included as normal metabolizers (v2, p28).

H. Study 3031: This was a multicenter (24 centers), single dose, open-label screening study in the US and Latin America evaluating the prevalence of poor metabolizer phenotype in atopic children and children with chronic idiopathic urticaria 2-11 years of age. It is linked to study 2994 (see below). This study was designed to characterize the metabolic phenotype of desloratadine following a single dose of 10 mg of loratadine syrup. Poor metabolizers were defined as patients who had an AUC for 3OH desloratadine/desloratadine < 0.10 (10%) and for the purposes of this study normal metabolizers were defined as those patients who had an AUC 3OH desloratadine/desloratadine of 0.25 (25%) or greater. There were 2075 patients enrolled in this study, 2058 completed the study and 2033 were phenotyped for desloratadine metabolizer status. There were 79 patients who were poor metabolizers, 27 being 2-5 years of age and 52 being 6-11 years of age (see table below). The prevalence of poor metabolism was 3.9% overall, 13.8% of African Americans, 1.4% of Hispanics and 0.9% of Caucasians. Plasma levels for 3 OH desloratadine and desloratadine were obtained 12 hours after drug administration.

Comparison of age and number of poor metabolizers in each age range between studies 3031 and 2994

Poor metabolizers	Study 3031	Study 2994
Mean age	6.5 years	6.8 years (DSL treatment)
Age range	2-11 years	2-11 years (DSL treatment)
Number 2-5 years	27	14 DSL Rx; 4 placebo
Number 6-11 years	52	32 DSL Rx, 6 placebo
2 years of age	7 (9%)	3 (7%) DSL Rx
3 years of age	4 (5%)	3 (7%) DSL Rx
4 years of age	9 (11%)	3 (7%) DSL Rx
5 years of age	7 (9%)	5 (11%) DSL Rx
6 years of age	15 (19%)	6 (13%) DSL Rx
7 years of age	7 (9%)	8 (17%) DSL Rx
8 years of age	8 (10%)	5 (11%) DSL Rx
9 years of age	12 (15%)	6 (13%) DSL Rx
10 years of age	5 (6%)	3 (7%) DSL Rx
11 years of age	5 (6%)	4 (9%) DSL Rx
Females	41 (52%)	29 (63%) DSL Rx
Males	38 (48%)	17 (37%) DSL Rx
Caucasian	5 (6%)	4 (9%)
African-American	50 (63%)	33 (72%)
Hispanic	12 (15%)	5 (11%)
Other	12 (16%)	4 (8%)

- I. Study 2994: Multicenter (14 centers in the United States and Latin America), repetitive dose, double-blind in regard to treatment but not dose, placebo-controlled, parallel, randomized, safety study in atopic patients or patients with chronic idiopathic urticaria 2-11 years of age with treatment for 5 weeks. All patients enrolled in this study had previously been identified as poor or normal metabolizers in study 3031. There were 97 patients randomized to this study from study 3031, 29 patients 2-5 years of age, 68 patients 6-11 years of age. There were 48 poor metabolizers randomized to receive desloratadine (2 of these patients were found to be normal metabolizers), and 49 patients randomized to receive placebo (10 poor metabolizers and 39 normal metabolizers).

Normal metabolizers were only in the placebo group. There were two patients randomized as poor metabolizers who were subsequently found to be normal metabolizers but they were not included in the primary analysis. Patients 1-5 years of age received a dose of 1.25 mg of desloratadine and patients 6-11 years of age received a dose of 2.5 mg of desloratadine using the syrup formulation. Patients were evaluated at screening, baseline, after treatment on day 1, and after 8, 15, 22, 29 and 36 days of treatment. In regard to duration of treatment, 80% (37/46) of poor metabolizers in the desloratadine treatment group completed treatment for 35 days (v15, p1013).

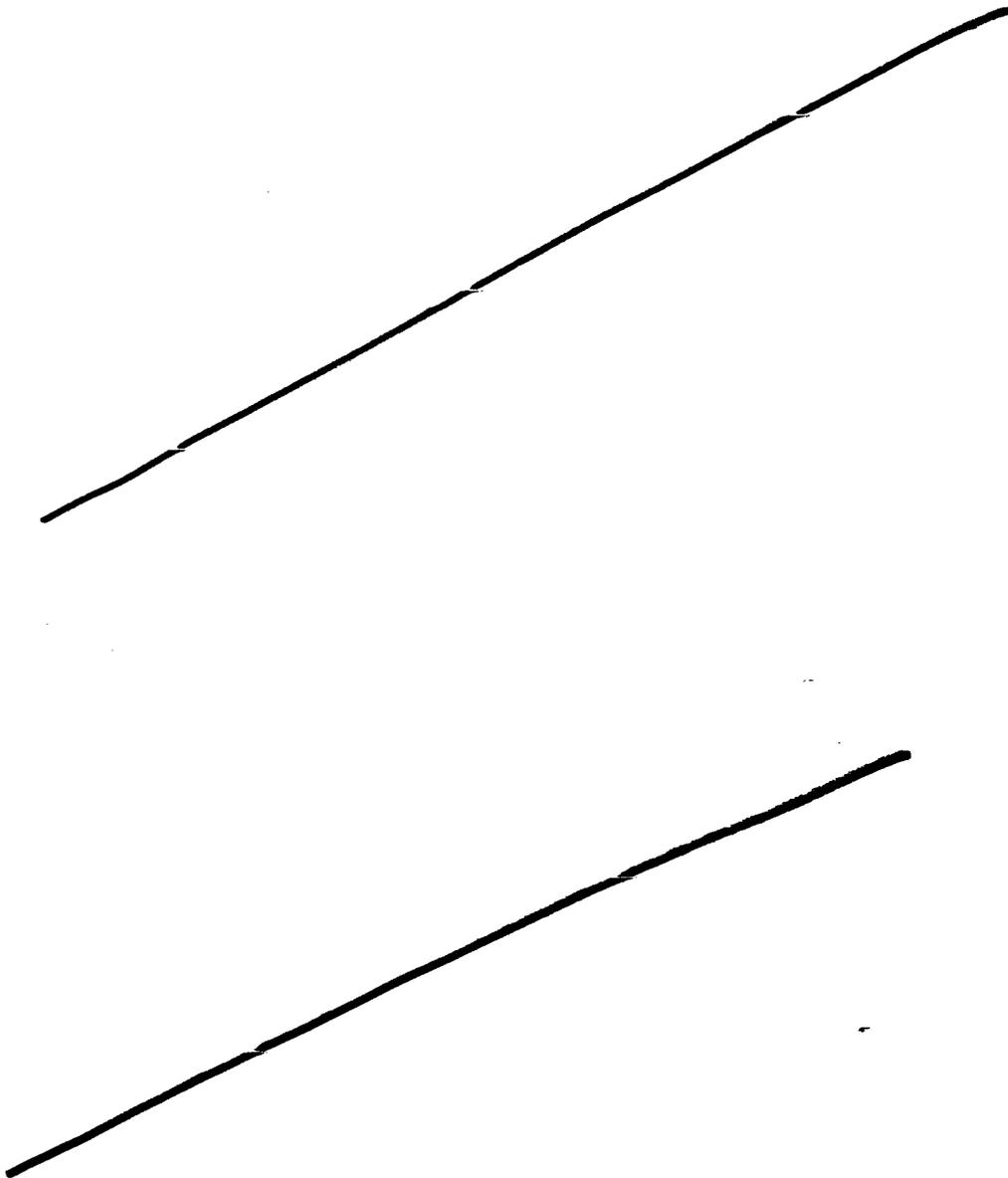
Safety evaluation included physical examination, ECGs, vital signs, laboratory tests and assessment of adverse events. Lab tests were done at screening and on days 15 and 36 prior to drug administration. Physical examination was performed at screening and at the conclusion of the study. ECGs were done 3 hours after drug administration on each of the study days. ECGs were obtained by an ECG machine at the study site and transmitted by standard telephone lines to \_\_\_\_\_, a CRO for central reading and interpretation by a cardiologist. Vital signs were done at each visit. Plasma levels were analyzed for 3 OH desloratadine and desloratadine prior to drug administration on days 15 and 36 to determine if patients were at steady state. Steady state was reached by day 15. The primary safety outcome variables were mean change from baseline on study days 8, 15, 22, 29, and 36 for ECG parameters, including QTc interval. QTc intervals were considered prolonged if > 450 msec in males and > 470 msec in females. The study was powered to show a 12 msec difference in mean change from baseline in QTc interval between desloratadine and placebo treatment groups. Adverse events were considered treatment-emergent if they occurred on or after the start of the study or up to 30 days after the completion of the study, or if they began prior to initiation of treatment but worsened in severity during treatment.

Analysis was done on all patients who were randomized to treatment. In addition, a change in the planned analysis was made so that mean changes in ECG parameters were analyzed "extracting sources of variation due to treatment" in a subset of patients defined as "per protocol". "Per protocol patients were those who had taken prohibited medications during treatment, had satisfied the minimum specified washout period for prohibited medications, whose overall dosing compliance was 75%-125% of planned compliance, who had baseline safety data, and whose last day of drug administration was 3 days or less prior to the last visit of the treatment period in which ECG data was collected (v12, p63, s9.8.2). As a result, there were 9 poor metabolizers in the desloratadine treatment group and 3 normal metabolizers in the placebo group who were excluded from the protocol evaluable data set (v15, p1007).

1. Study 1341: This was a single dose PK study in 58 children 6 months to < 2 years of age who received 0.625 mg if they were 6 months to < 1 year of age and 1.25 mg if they were 1 to < 2 years of age. There were 20 patients 6-11 months of age of whom none were poor metabolizers and 38 patients 12-23 months of age of whom 4 were poor metabolizers. The poor metabolizers in this study were all African-American children, one year of age. Two were treated with a dose of 0.625 mg and 2 were treated with a dose of 1.25 mg. Because of the small number of poor metabolizers in this study, the data from this study was not pooled with other studies in the analyses. The data for AUC

from this study was estimated from individual Bayesian predictions and compared with the AUC seen in study 2798 (2-11 year olds) and pooled adult multiple dose studies (9 July 2001 submission, p38, f6) as box and whisker plots. The AUC for desloratadine was higher in the poor metabolizer group than in patients with normal metabolism but less than seen in children 2-11 years of age who were poor metabolizers and significantly less than was seen in adults who were poor metabolizers based on cross-study comparison.

## 10.2 Line-by-Line Labeling Review





     / Page(s) Withheld

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

     § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical-   1

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**This is a representation of an electronic record that was signed electronically and  
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/s/  
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Richard Nicklas  
8/31/04 12:20:50 PM  
MEDICAL OFFICER

Eugene Sullivan  
8/31/04 12:34:11 PM  
MEDICAL OFFICER  
Agree with recommendation. See my memorandum.

**Appendix 1: Secondary Clinical Review of NDA 21-300 (Original Submission)**

**MEDICAL TEAM LEADER MEMORANDUM**

DATE: September 20, 2001  
TO: NDA 21-300  
FROM: Badrul A. Chowdhury, MD, PhD  
Clinical Team Leader, Division of Pulmonary and Allergy Drug Products  
SUBJECT: Secondary medical review of Clarinex<sup>TM</sup> (desloratadine) Syrup  
CC: HFD-570: Meyer, Nicklas, Hilfiker

**Administrative**

NDA 21-300 for Clarinex (desloratadine) Syrup was submitted by Schering Corporation on December 8, 2001. The PDUFA action due date on this application is October 8, 2001. Clarinex Tablets is currently the subject of two pending NDAs. NDA 21-165, for use of Clarinex Tablet 5mg in seasonal allergic rhinitis in adults and adolescents ages 12 years and older, and NDA 21-297 for use of Clarinex Tablet 5mg in chronic idiopathic urticaria in adults and adolescents ages 12 years and older. The applicant is seeking approval of the syrup formulation of Clarinex in children 2-11 years of age for the same indications.

Schering has submitted results from five clinical pharmacology studies and two clinical safety studies to support the pediatric indication. The clinical pharmacology studies are: (a) Study 270, a single dose PK study in 6-11 year old healthy subjects, (b) Study 1126, a single dose PK study in 6-11 year old healthy subjects, (c) Study 225, a single dose PK study in 2-5 year old healthy subjects, (d) Study 1125, a single dose PK study in 2-5 year old healthy subjects, and (e) Study 213, a food effect study. The clinical safety studies are: (a) Study 302, a safety study in 6-11 year old children, (b) Study 303, a safety study in 2-5 year old children. In the clinical safety studies children with seasonal allergic rhinitis or urticaria were enrolled.

**Chemistry and Manufacturing**

Clarinex Syrup contains 0.5 mg/mL desloratadine. The syrup contains the following inactive ingredients: propylene glycol USP, sorbitol solution USP, citric acid (anhydrous) USP, sodium citrate dihydrate USP, sodium benzoate NF, disodium edetate USP, purified water USP. It also contains granulated sugar, natural and artificial flavor for bubble gum and FDC Yellow #6 dye. Schering Corporation has not yet resolved the manufacturing problem that is holding up the marketing of the entire Clarinex line of products, which will also have an impact on the ultimate approvability of this application.

## **Pharmacology and Toxicology**

The applicant has referenced all preclinical pharmacology and toxicology data to NDA 21-165 for Clarinex Tablet 5mg. There are no outstanding preclinical issues.

### **Clinical Program:**

This was primarily a clinical pharmacology program. As mentioned above, the clinical program of Clarinex Syrup consists of five clinical pharmacology and two clinical safety studies (Table 1). The studies are briefly reviewed in the subsequent sections. Detail reviews of the clinical pharmacology and clinical safety studies can be found in the primary reviews of Dr. Suarez and Dr. Nicklas.

**Table 1. Overview of the clinical studies**

Study No.	Type of study	Diagnosis, age of subjects	Clarinex dose mg	Length of treatment	Number All (M, F) (C, B)*
270	Clinical pharmacology	Healthy, 6-11 yrs	5 mg	Single dose	18 (10, 8) (8, 10)
1126	Clinical pharmacology	Healthy, 6-11 yrs	2.5 mg	Single dose	18 (9, 9) (16, 2)
225	Clinical pharmacology	Healthy, 2-5 yrs	2.5 mg	Single dose	18 (12, 6) (11, 7)
1125	Clinical pharmacology	Healthy, 2-5 yrs	1.25 mg	Single dose	18 (10, 8) (16, 2)
213	Food effect	Healthy, 19-45 yrs	5 mg	Single dose	30 (24, 6) (16, 2)
302	Clinical safety	SAR, CIU, 6-11 yrs	2.5 mg	15 days	120 (52, 68)
303	Clinical safety	SAR, CIU, 2-5 yrs	1.25 mg	15 days	111 (62, 49)

\* M=male, F=Female, C=Caucasian, B=Black

### **Study 270: Single dose PK study in 6-11 year old healthy subjects**

This was a single-arm, single-dose, single-center, open-label study. The primary objective of the study was to characterize the pharmacokinetic profile of desloratadine (DL) and 3-OH DL following an oral dose 5mg DL syrup to healthy subjects 6-11 years of age. The study was conducted by Jerry M. Herron, MD, in a single center in Little Rock, Arkansas between April 1999 and May 1999.

A total of 18 subjects, 10 males, and 8 females (mean age 8.5 years) were enrolled and completed the study. There were at least 3 subjects in each one-year age group. Subjects were screened within 3 weeks of dosing. Screening included history, physical examination, ECG, and clinical laboratory tests that included blood chemistry, hematology, and urinalysis. Eligible subjects were confined to the study center at least 12 hours prior to dosing (day -1). Upon confinement safety laboratory tests and ECG were repeated. In the morning of day 1, following overnight fast, at approximately 8 AM each subject received a single dose of 10mL (5mg) dose of DL syrup (0.5mg/mL) orally followed by water to rinse the mouth. The subjects remained awake and ambulatory for the next 4 hours. They were confined in the study site for 24 hours after dosing and then discharged home. The subjects were instructed to report any unusual experience or discomfort and questioned for possible adverse events. The subjects returned to the study site on days 3, 4, and 5 for the 48-hour, 72-hour, and 96-hour study related procedures.

Ten milliliters of blood were collected just prior to drug administration and at 1, 1.5, 2, 4, 8, 12, 24, 48, 72, and 96 hours after each dosing for the pharmacokinetic profile. On day 4, for safety evaluation, physical examination, vital signs, ECG, and clinical laboratory tests were repeated. On day 5 the subjects were discharged from the study.

Mean pharmacokinetic parameters of DL and 3-OH DL after administration of DL 5mg is shown in Table 2. To determine the appropriate dose in the 6-11 year age group, the applicant compared the results of this study to those obtained in healthy adults after 5mg DL in study P00213. The 5mg oral dose of DL syrup was associated with median DL and 3-OH DL AUC values that were approximately 2-fold greater in the 6-11 year age group compared to adults who receive the same dose of DL. The sponsor concluded that the dose of DL for the 6-11 age group needs to be reduced by approximately 50% to obtain similar exposure to DL in adults.

Two black subjects (subject no. 3 a 6-year old male; and subject no. 18, a 11-year old male) appeared to be slow metabolizers of DL evidenced by higher than average plasma concentration of DL and lower than average plasma concentration of 3-OH DL. The AUC of DL in these subjects were 419 and 207 ng.hr/mL and corresponding values for 3-OH DL were 3 and 13 ng.hr/mL. The median AUC of DL for the study group was 68.5 ng.hr/mL. Plasma concentration-time profile of subject no. 3 as compared to the whole group is shown in Figure 1.

The drug was well tolerated in this study. No serious or unexpected adverse events were reported. No subjects discontinued participation in the study. Three subjects (no. 2, 4, and 10) required acetaminophen for headache. Neither of the subjects that were slow metabolizers experienced an adverse event.

**Table 2. Mean pharmacokinetic parameters following single dose of DL 5mg**

Parameters	DL	3-OH DL
C max (ng/mL)	5.30	1.77
Tmax (hr)	2.00	4.00
AUC <sub>0-t</sub> (ng.hr/mL)	101	43.0
AUC <sub>0-i</sub> (ng.hr/mL)	111	45.9

Source: Section 6, Study 270, page 25

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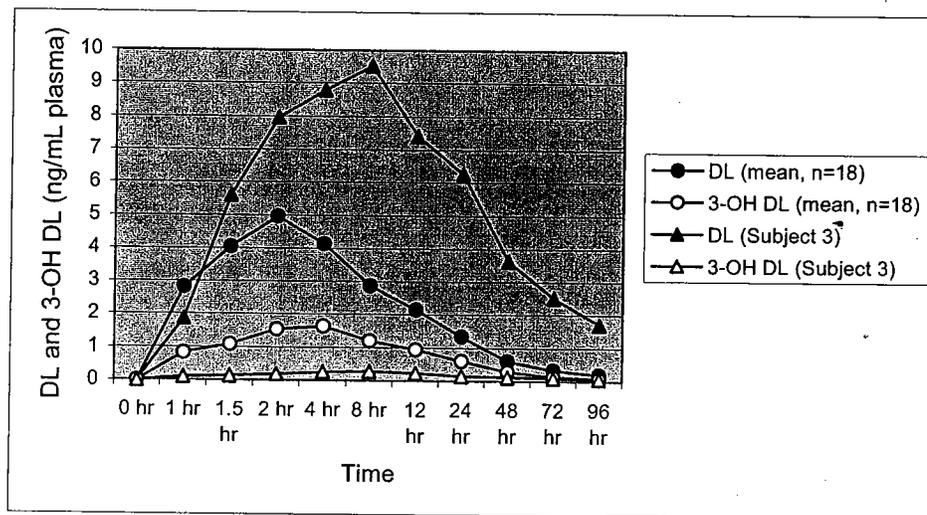


Figure 1. Mean plasma concentration-time profiles of DL and 3-OH DL of the study group, and of study subject no. 3 (Source: Section 6, study 270, pages 159, 168, 169, 175, 184, 185)

#### Study 1126: Single dose PK study in 6-11 year old healthy subjects

The design and conduct of this study was identical to study 270, except that each subject received a single dose of 5mL (2.5mg) dose of DL syrup (0.5mg/mL) orally. This study was also conducted by Jerry M. Herron, MD, in a single center in Little Rock, Arkansas in November 1999. A total of 18 subjects, 9 males, and 9 females (mean age 8.5 years) were enrolled and completed the study. There were at least 3 subjects in each one-year age group.

Mean pharmacokinetic parameters of DL and 3-OH DL after administration of DL 2.5mg is shown in Table 3. The mean AUC and Cmax after administration of 2.5mg DL in this study resulted in approximately half the UAC and Cmax seen after administration of 5mg DL in study 207. The applicant states that plasma AUC for DL seen in this study was comparable to that seen in adults in study P00213 who received 5mg DL syrup (38.1 ng.hr/mL) or tablet (38.5 ng.hr/mL). Based on this data the applicant is recommending a dose of 2.5mg of DL syrup for patients 6-11 years of age. This is a reasonable recommendation.

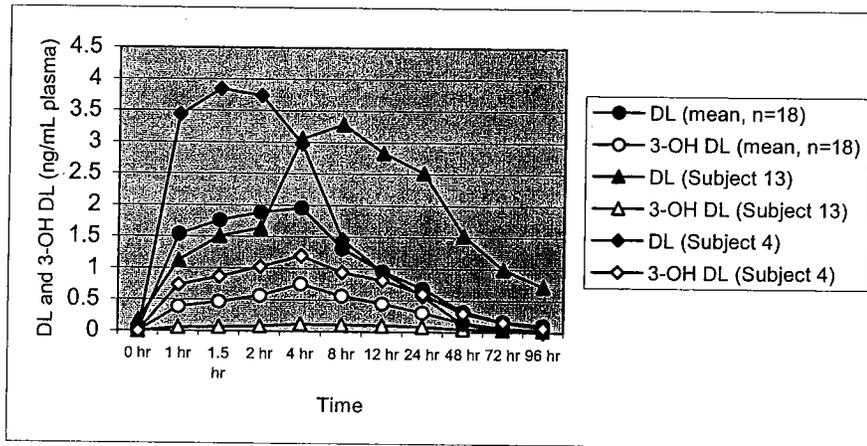
Three subjects (subject no. 13, an 8 year old Caucasian male; subject no. 16, a 10 year old black male; and subject no. 17, an 8 year old black male) appeared to be slow metabolizers of DL. The AUC of DL in these subjects were 163, 7.1, and 155 ng.hr/mL and corresponding values for 3-OH DL were 6, 0.04, and 1.39 ng.hr/mL. The median AUC of DL for the study group was 38.1 ng.hr/mL. Plasma concentration-time profile of subject no. 13 and 4 as compared to the whole group is shown in Figure 2. Subject no. 4 (9 year old Caucasian female) is included because this subject did not appear to be a slow metabolizer, however had a high Cmax (3.85 ng.mL). The AUC of this subject was 45.6 ng.hr/mL, which is comparable to the median value of the group.

The drug was well tolerated in this study. No adverse events were reported.

**Table 3. Mean pharmacokinetic parameters following single dose of DL 5mg**

Parameters	DL	3-OH DL
C max (ng/mL)	2.23	0.76
Tmax (hr)	3.67	4.44
AUC <sub>0-t</sub> (ng.hr/mL)	48.6	20.5

Source: Section 6, Study 1126, page 26



**Figure 2. Mean plasma concentration-time profiles of DL and 3-OH DL of the study group, and of study subject no. 13 and 4 (Source: Section 6, study 1126, pages 167, 176, 177, 183, 192, 193)**

**Study 225: Single dose PK study in 2-5 year old healthy subjects**

The design and conduct of this study was identical to the above two studies, except that the study subjects were 2-5 years of age, and each subject received a single dose of 5mL (2.5mg) dose of DL syrup (0.5mg/mL) orally. This study was also conducted by Jerry M. Herron, MD, in a single center in Little Rock, Arkansas in April 1999. A total of 18 subjects, 12 males, and 6 females (mean age 3.4 years) were enrolled and completed the study. There were at least 3 subjects in each one-year age group.

Mean pharmacokinetic parameters of DL and 3-OH DL after administration of DL 2.5mg is shown in Table 4. As expected from the previous two studies, the plasma AUC following 2.5mg DL in this 2-5-year age group was approximately two-fold higher compared to adults, adolescents, and children 6-11 years of age who received 5mg dose of DL.

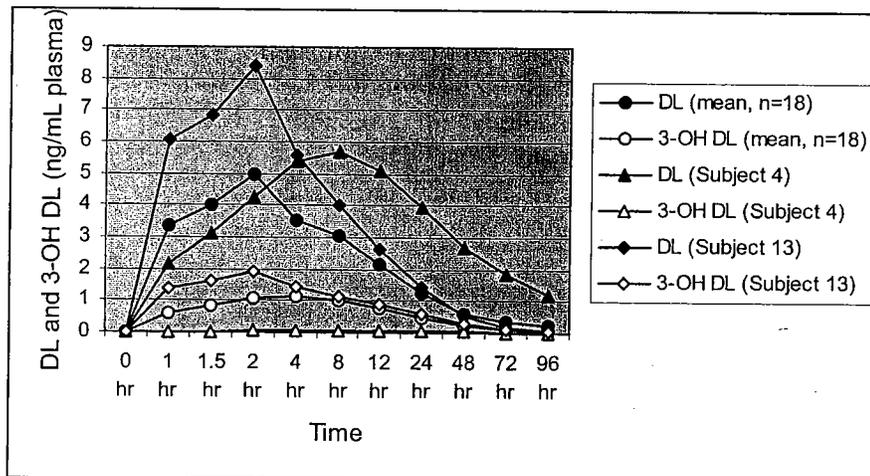
Three subjects (subject no. 4, a 2 year old black male; subject no. 8, a 3 year old Caucasian female; and subject no. 16, a 5 year old Caucasian female) appeared to be slow metabolizers of DL. The AUC of DL in these subjects were 284, 244 and 220 ng.hr/mL and corresponding values for 3-OH DL were 2.75, 8.28, and 7.25 ng.hr/mL. The median AUC of DL for the study group was 68.2 ng.hr/mL. Plasma concentration-time profile of subjects 4 and 13 as compared to the whole group is shown in Figure 3. Subject no. 13 (4 year old black male) is included because this subject did not appear to be a slow metabolizer, however had a high C<sub>max</sub> (8.41 ng/mL). The AUC of this subject was 116 ng.hr/mL, which was modestly elevated compared to the median value of the group.

The drug was well tolerated in this study. No serious or unexpected adverse event was reported.

**Table 4. Mean pharmacokinetic parameters following single dose of DL 5mg**

Parameters	DL	3-OH DL
C max (ng/mL)	5.36	1.27
Tmax (hr)	2.00	4.00
AUC <sub>0-t</sub> (ng.hr/mL)	98.6	33.7
AUC <sub>0-i</sub> (ng.hr/mL)	111.0	35.9

Source: Section 6, Study 225, page 28



**Figure 3. Mean plasma concentration-time profiles of DL and 3-OH DL of the study group, and of study subject no. 4 (Source: Section 6, study 225, pages 159, 168, 169, 175, 184, 185)**

### Study 1125: Single dose PK study in 2-5 year old healthy subjects

The design and conduct of this study was identical to study 225, except that each subject received a single dose of 2.5mL (1.25mg) dose of DL syrup (0.5mg/mL) orally. This study was also conducted by Jerry M. Herron, MD, in a single center in Little Rock, Arkansas in November 1999. A total of 18 subjects, 10 males, and 8 females (mean age

3.4 years) were enrolled and completed the study. There were at least 3 subjects in each one-year age group.

Mean pharmacokinetic parameters of DL and 3-OH DL after administration of DL 2.5mg is shown in Table 5. The mean AUC and Cmax after administration of 1.25mg DL in this study resulted in approximately half the UAC and Cmax seen after administration of 2.5mg DL in study 225. The applicant states that plasma AUC for DL seen in this study was comparable to that seen in adults in study P00213 who received 5mg DL syrup (38.1 ng.hr/mL) or tablet (38.5 ng.hr/mL). Based on this data the applicant is recommending a dose of 1.25mg of DL syrup for patients 2-5 years of age. This is a reasonable recommendation.

Two subjects (subject no. 16, an 5 year old Caucasian female; and subject no. 17, a 4 year old Caucasian female) appeared to be slow metabolizers of DL. The AUC of DL in these subjects were 75.9, and 87.1 ng.hr/mL and corresponding values for 3-OH DL were 1.57, and 2.60 ng.hr/mL. The median AUC of DL for the study group was 38.8 ng.hr/mL. Plasma concentration-time profile of subjects 17 and 5 as compared to the whole group is shown in Figure 4. Subject no. 5 (2 year old Caucasian female) is included because this subject did not appear to be a slow metabolizer, however had a high Cmax (6.96 ng.mL). The AUC of this subject was 51.5 ng.hr/mL, which is modestly elevated compared to the median value of the group.

The drug was well tolerated in this study. No adverse events were reported.

**Table 5. Mean pharmacokinetic parameters following single dose of DL 5mg**

Parameters	DL	3-OH DL
C max (ng/mL)	2.68	0.64
Tmax (hr)	3.17	4.89
AUC <sub>0-t</sub> (ng.hr/mL)	42.0	26.2

Source: Section 6, Study 1125, page 25

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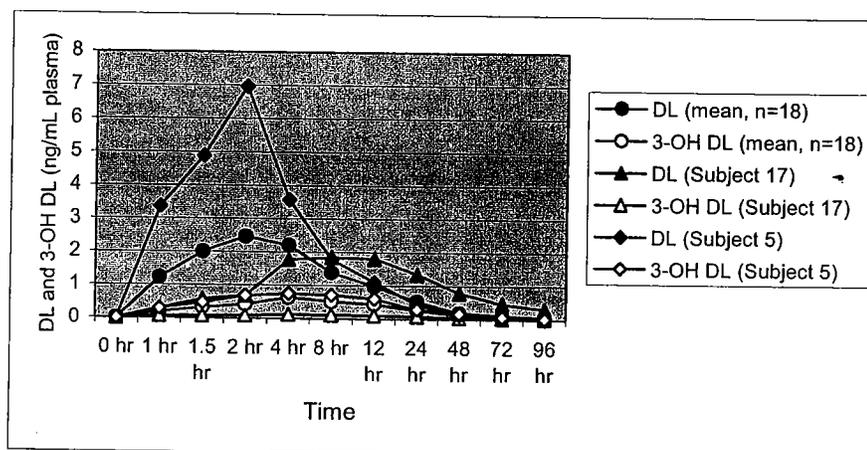


Figure 4. Mean plasma concentration-time profiles of DL and 3-OH DL of the study group, and of study subjects no. 17 and 5 (Source: Section 6, study 225, pages 159, 168, 169, 175, 184, 185)

### Study 213: Food effect study in healthy adult subjects

This was a single-dose, single-center, open-label, three-way random sequence crossover study. The primary objective of the study was to determine the bioequivalency of DL tablet and syrup formulations and to evaluate the effect of food on the bioavailability of DL following administration of the syrup formulation. The study was conducted by Jerry M. Herron, MD, in a single center in Little Rock, Arkansas between April 1999 and May 1999.

A total of 30 healthy subjects, 24 males, and 6 females, 18-45 years of age (mean age 8.5 years) were enrolled and completed the study. Subjects were screened by history, physical examination, ECG, urine drug screen, and clinical laboratory tests that included blood chemistry, hematology, and urinalysis. Eligible subjects were confined to the study center at least 12 hours prior to dosing (day -1). Upon confinement safety laboratory tests and ECG were repeated. In the morning of day 1, following overnight fast, at approximately 8 AM each subject received a single dose of the study medication. The study medications in the three periods were one 5mg DL tablet in fasting state, 10mL (5mg) dose of DL syrup (0.5mg/mL) in fasting state, and 10mL (5mg) dose of DL syrup (0.5mg/mL) immediately following a standardized high-fat and high-caloric breakfast. The tablet was swallowed whole with 6oz water. The syrup was followed by 20ml water to rinse the mouth. The subjects continued fasting for the next 4 hours, at which time lunch was provided. They were confined in the study site for 120 hours for study related procedures. Each treatment period was separated by at least 14 days washout. The subjects were instructed to report any unusual experience or discomfort and questioned for possible adverse events. Vital signs, ECGs, and blood samples were collected at prespecified times for safety and pharmacokinetic evaluations. For the pharmacokinetic

profile, 5mL of blood were collected just prior to drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours after dosing in each period.

Mean pharmacokinetic parameters of DL and 3-OH DL after administration of DL 5mg is shown in Table 6. The 5mg tablet and the syrup formulations were comparable with respect to DL and 3-OH DL. In addition, the relative bioavailability of the syrup was not affected by the subjects taking the drug under fasting or fed conditions.

The drug was well tolerated in this study. No serious or unexpected adverse events were reported. No subjects discontinued participation in the study.

**Table 6. Mean pharmacokinetic parameters following single dose of DL 5mg tablet or syrup**

Parameters	DL			3-OH DL		
	C max (ng/mL)	Tmax (hr)	AUC <sub>0-24hr</sub> (ng.hr/mL)	C max (ng/mL)	Tmax (hr)	AUC <sub>0-24hr</sub> (ng.hr/mL)
DL 5mg Tab Fasting	2.44	4.17	47.4	1.06	4.72	29.0
DL 5mg Syp Fasting	2.30	3.58	48.4	1.03	4.73	27.8
DL 5 mg Syp Fed	2.19	3.47	52.0	0.91	4.60	28.3

Source: Section 6, Study 213, page 28

### **Study 302: Clinical safety study in 6-11year old patients**

This was a two-arm, randomized, single-center, double-blind, placebo-controlled multiple-dose, parallel-group study. The primary objective of the study was to characterize the safety of DL syrup 2.5mg QD compared with placebo in children 6-11 years of age with history of allergic rhinitis or chronic idiopathic urticaria (CIU). The study was conducted by Jerry M. Herron, MD, in a single center in Little Rock, Arkansas between October 1999 and November 1999. To be eligible patients were required to have had a documented history of allergic rhinitis or CIU and be otherwise healthy.

The study had a screening visit (on days -14 to -1), a baseline visit (day 1), followed by 15-day double-blind treatment period. Follow-up visits were on days 8, and 15 of double-blind treatment. Study drug (active or placebo) was administered orally QD in the morning, approximately the same time each day, without regard for the timing of meals or other daily activities. The first dose of the study drug was administered at the baseline visit. Efficacy was not assessed in this study. Safety assessments included adverse event evaluation, vital signs, physical examination, ECG, urinalyses, CBC, and clinical chemistry. Study subject's parent or guardian was instructed to record adverse event and intercurrent illness on diary cards. The investigator also questioned the subject and the parent or guardian about adverse event and intercurrent illness since the last visit and recorded the information on the CRF. ECGs were done on screening visit (days -14 to -1), and on visits on days 8 and 15. ECGs were read for ventricular rate and various intervals. The intervals, including Bazett and Fridericia corrected QT were presumably calculated from machine read values. To ensure that ECGs were done 1-3 hours after

dosing, the subjects were administered study drugs on those days in the clinic. Clinical laboratory tests were done on screening visits (days -14 to -1) and on visit on day 15.

A total of 120 patients (60 treated with DL and 60 treated with placebo) were randomized. The applicant reports that 100% of subjects received 13-15 days of treatment and all subjects completed the study (section 8, study 302, page 352). The treatments groups were comparable for age (overall mean age was 7.9 years for the DL group, and 8.5 years for the placebo group), gender, and race distribution. All age groups were also adequately represented. The study drug was well tolerated in this study. There were no serious adverse events reported, and no subject discontinued treatment because of adverse event. Two subjects in the placebo group had treatment interrupted for 1 day each because of adverse event (gastroenteritis and vomiting). Adverse events deemed to be treatment related were headache (reported by 1 subject in DL group, and 4 subjects in the placebo group), vomiting (reported by 2 subjects in the placebo group), and gastroenteritis (reported by 2 subjects in the placebo group). Physical examination and vital signs did not change on treatment. There were no clinically relevant changes in laboratory measures and ECG results including QT interval on treatment.

#### Study 303: Clinical safety study in 2-5year old patients

The design and conduct of this study was identical to study 302, except that the study subjects were 2-5 years of age, and each subject received 1.25 mg dose of DL during the double-blind treatment period. This study was also conducted by Jerry M. Herron, MD, in a single center in Little Rock, Arkansas between November 1999 and December 1999.

A total of 111 patients (55 treated with DL and 56 treated with placebo) were randomized. As in the previous study the applicant reports that 100% of subjects received 13-15 days of treatment and all subjects completed the study (section 8, study 303, page 342). The treatments groups were comparable for age (overall mean age was 3.5 years, for the DL group, and 3.4 years for the placebo group), gender, and race distribution. All age groups were also adequately represented. The study drug was well tolerated in this study. There were no serious adverse events reported, and no subject discontinued treatment because of adverse event. Adverse events deemed to be treatment related were mostly common childhood disease, such as fever (reported by 3 subject in DL group, and 3 subjects in the placebo group), otitis media (reported by 1 patient in placebo group). Two subjects in the DL group had urinary tract infection, which is rather unusual for this age. There were no clinically relevant changes in laboratory measures and ECG results including QT interval on treatment.

#### Efficacy assessment

The applicant has submitted no data to directly establish efficacy of Clarinex Syrup in children 2-11 years of age. Clinical pharmacology studies, as reviewed above, were part of the database linking the bioavailability of the syrup and tablet formulations. The

efficacy of the tablet formulation in adults and adolescents down to 12 years has already been demonstrated. The applicant has linked the two formulations adequately and therefore the efficacy of the syrup formulation can be extrapolated down to 2 years from the demonstrated efficacy of Clarrinex tablets in patients 12 years and older. The proposed doses of 2.5 mg in patients 6-11 years of age, and 1.25 mg in patients 2-5 years of age are supported by the submitted pharmacokinetic data.

#### Safety assessment

The applicant has submitted one clinical safety study each in children 6-11 years of age, and 2-5 years of age. The two studies, as reviewed above, support the safety of Clarinex Syrup in patients down to 2 years of age. However, in the clinical pharmacology studies some subjects were noted to have considerably high plasma concentration of DL compared to the mean values. This raises significant concerns that are discussed below.

The applicant has also submitted a four-month safety update on April 16, 2001. The submission includes safety data on additional 2154 adult and adolescent patients, including 919 who received Clarinex in multiple ongoing studies. Review of the safety database does not raise any new concerns. Detail review of the updated safety database can be found in Dr. Nicklas's primary medical review.

#### **High plasma concentration of desloratadine in some subjects**

In each the four clinical pharmacology studies, 2 to 3 subjects out of 18 subjects were slow metabolizers of as DL evidenced by high plasma concentration of DL and low plasma concentration of 3-OH DL. Of the 72 subjects enrolled in the four clinical pharmacology studies, 10 (13.89%) were slow metabolizers. Following a single administration of DL, plasma DL AUC values in these subjects were elevated approximately from 2-fold to 6-fold over the median values of the group. These high values could not be explained by age or body weight of the subjects. In additions, there were some subjects who were not slow metabolizer, but had high plasma C<sub>max</sub>. Plasma concentration-time profiles of some representative subjects of both types are shown in Figure 1, Figure 2, Figure 3, and Figure 4.

Subjects with high C<sub>max</sub> only, had plasma concentration-time profile curves comparable to the curves generated from mean values in the different studies. These subjects possibly represent outliers that may be expected in any study. However, the slow metabolizers are of concern because they are not able to clear DL. Some slow metabolizers had considerably high plasma concentration of DL even out to 96-hour, and some had almost undetectable level of 3-OH DL. The effect of repeat doses of DL in these subjects is unknown. It is likely that these subjects will accumulate DL to a very high level on repeat dosing. The applicant does not have repeat-dose pharmacokinetic data on slow metabolizers, and no clinical safety data on subjects who are known to be slow metabolizers.

The applicant has not provided any explanation or potential mechanism of this slow metabolism of DL that was seen in some subjects. The applicant has also not provided any data to support the safety of a substantial higher exposure of DL that can occur on repeat dosing in slow metabolizers. Based on the limited data on 72 children, 13.89% of subjects are slow metabolizers of DL. The impact of this may be potentially larger, because there may be yet unidentified drugs or other substances that can convert a normal metabolizer to a slow metabolizer. These concerns were discussed with the applicant at a teleconference on September 5, 2001. The applicant was told that this might be an approvability issue.

#### Financial disclosure and data integrity

Dr. Jerry Herron of Little Rock, Arkansas, conducted all the clinical pharmacology and clinical safety studies submitted in this NDA. He had no conflict of interest on financial disclosure. The applicant has submitted form FDA 3454 with the NDA. There was no reason, based on review of the data submitted, to doubt the quality or integrity of the database. Therefore, DSI audit was not request for this NDA.

#### Recommendation

From an overall risk-benefit assessment, this NDA is recommended a NON APPROVAL action. The submitted data support the efficacy of Clarinex Syrup at a dose of 2.5 mg QD in patients 6-11 years of age, and at a dose of 1.25 mg QD in patients 2-5 years of age. However, as discussed above, the safety of Clarinex in the slow metabolizers is unknown.

From the submitted data, it appears that 13.89% of children may be slow metabolizers of desloratadine. These children cannot be identified a priori, and will be exposed to an unknown high level of desloratadine when given repeat doses of the proposed therapeutic dose of desloratadine. The impact of this may be much larger, because there may be yet unidentified drugs or other substances that can convert a normal metabolizer to a slow metabolizer.

To gain approval of this NDA, the applicant will need to characterize the pharmacokinetics of repeat dosing of desloratadine in known slow metabolizers to obtain a reasonable idea of the level of exposure that can occur in these subjects in a clinical use situation. Since the slow metabolizers cannot be identified a priori, the applicant will then need to establish safety of such high exposure, i.e., a substantially higher dose of desloratadine, in a reasonably large number of subjects. This may be a difficult task, because otherwise normal children will need to be exposed to a high and potentially toxic dose of desloratadine. Even if such a safety is established, the label will need to be modified to include a statement that some children who cannot be identified a priori may be exposed to a high level of desloratadine following dosing with the recommended dose.

The sponsor should also be encouraged to identify the mechanism of this slow metabolism, and explore the possibility of blockage of the metabolic pathway of desloratadine by other drugs, foods, etc., that may be of clinical significance.

The issue of slow metabolizers raised in this review may have an implication on the overall safety assessment and labeling of other Clarinex NDAs that are currently under review.

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Badrul Chowdhury  
9/1/04 12:56:37 PM  
MEDICAL OFFICER

I conur. Note that late during review cycle Schering  
proposed a new proprietary name for all products  
containing desloratadine including this product. DMETS objected to  
the new proprietary name. The proprietary will stay  
as Clarinex.

## **DIVISION DIRECTOR MEMORANDUM**

Date: August 31, 2004  
To: NDA 21-300, and NDA 21-563  
From: Eugene J. Sullivan, MD, FCCP  
Deputy Director  
Division of Pulmonary and Allergy Drug Products (HFD-570)  
Through: Badrul Chowdhury, MD, PhD  
Director, DPADP  
Subject: Summary review of Schering Plough's February 27, 2004, complete response to prior Approvable action on Clarinex (desloratadine) Syrup for use in children aged 2 to 11 years

### **Administrative**

This memorandum refers to two closely related submissions, which are complete responses to AE actions taken on NDA 21-300 and NDA 21-563. Both of these NDAs are for Clarinex (desloratadine) Syrup for seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in children. NDA 21-563 is for children aged 6 to 23 months, and NDA 21-300 is for children aged 2-11 years. The complicated administrative history of these two NDAs is described below.

The NDA 21-300 submission is a complete response to an Approvable action taken by the Agency on October 2, 2002. NDA 21-300 was first submitted on December 8, 2000, to support the approval of Clarinex (desloratadine) Syrup for seasonal and perennial allergic rhinitis and chronic idiopathic urticaria, in children 2 to 11 years of age. The proposed dose of the syrup formulation is 2.5mg in patients 6-11 years of age, and 1.25mg in patients 2-5 years of age. In order to establish efficacy, the Applicant relied on pharmacokinetic data demonstrating that exposures at the proposed doses were comparable to exposures achieved in adults with the previously approved 5mg dose of desloratadine. Although the Division agreed with that approach, and agreed that the mean exposures were comparable, an Approvable action was taken on October 2, 2001. In addition to CMC deficiencies, one specific clinical issue precluded approval. The data indicated that a subset of children exhibit very poor metabolism of desloratadine and were thus exposed to significantly greater levels of desloratadine. The original application did not contain sufficient characterization of the multiple dose exposure in pediatric poor metabolizers, and did not contain evidence that such exposures were safe. Appendix 1 of this document contains the secondary clinical review of the original application.

The administrative background of these submissions is somewhat complicated. NDA 21-300 was the first of the two submissions, and an AE action had already been taken at the time NDA 21-563 was submitted. NDA 21-563 was submitted for the purposes of a pediatric exclusivity determination, in response to a Written Request for pediatric studies.

In it, the Applicant provided study reports for the studies done to fulfill the WR. This included studies done in younger children, ages 6 to 23 months. Based on the results of these studies, NDA 21-563 also included proposed labeling to include an Indication down to the age of 6 months. The Division took an AE action on 21-563 on May 14, 2003. The AE letter stated that before the application could be approved it would be necessary to respond to the CMC deficiencies that had previously been communicated (October 2, 2001, and November 19, 2001), to provide a discussion of how caregivers will administer the proposed small volumes of syrup, and to make specific changes in the proposed labeling.

The October 2, 2001, Approvable letter for NDA 21-300 listed 22 deficiencies. As discussed in the CMC section of this Review, the CMC deficiencies identified in comments 1-17 had previously been communicated in a Discipline Review letter, dated February 8, 2001. The Applicant has previously responded to these comments, in a submission dated June 28, 2001. The current submission contains responses to comments numbered 18-22, particularly comments 18 and 19. Comment 18 instructed the Applicant to characterize the pharmacokinetics of repetitive dose administration of desloratadine in a population determined to be poor metabolizers, and to adequately support the safety of the upper limit of exposure in this population. Comment 19 encouraged the Applicant to determine the mechanism accounting for higher levels of drug exposure observed in some patients, and to assess the potential for drug-drug interactions that might be expected based on the explanatory mechanism. Comments 20 and 21 related to other desloratadine NDAs, for which the Applicant has proposed labeling that be harmonized with the labeling for the current application. Finally, Comment 22 made reference to deficiencies noted in recent inspections of manufacturing facilities, and informed the Applicant that satisfactory inspections will be required for approval.

#### **Chemistry, Manufacturing, and Controls**

The CMC deficiencies listed in the October 2, 2001, AE letter had previously been communicated to the Applicant in a Discipline Review (DR) letter dated February 8, 2001. In fact, at the time of the AE action, the Applicant had already responded (in a submission dated June 28, 2001) to the deficiencies in the DR letter. However, review of that submission had not been completed at the time of the AE action, so the same deficiencies listed in the February 8, 2001, DR letter were repeated in the AE letter. A further complication is that, once the review of the June 28, 2001, submission was complete, the Division issued an IR letter (dated November 19, 2001) noting further CMC deficiencies. Because those deficiencies were not included in the AE letter, they have not been addressed specifically in this submission. However, the Applicant has responded to the IR letter deficiencies, in a separate submission dated February 27, 2004. Therefore, from a CMC perspective, approval of this application rests on a determination that the Applicant has adequately addressed the deficiencies listed in the October 2, 2001, AE letter, and the November 19, 2001, IR letter. The CMC review team has reviewed the materials submitted by the Applicant to address these deficiencies, and has determined that the data are sufficient to allow approval of this application.

### **Pharmacology/Toxicology**

The original NDA submission referenced all preclinical pharmacology and toxicology to NDA 21-165 (Clarinet 5mg tablet). There are no outstanding pharmacology/toxicology issues.

### **Biopharmaceutics/ Clinical Studies**

#### **NDA 21-300**

The October, 2001, Approvable letter for NDA 21-300 contained two comments that related to biopharmaceutics/ clinical issues (Comments 18 and 19).

Comment 18 instructed the Applicant to characterize the pharmacokinetics of repetitive dose administration of desloratadine (DL) in a population of subjects determined to be poor metabolizers (PMs), and to adequately support the safety of the upper limit of exposure in this population.

A PM has been defined as a subject having:

- an AUC ratio of 3-OH DL (the major metabolite) to DL of  $<0.10$
- or, if 3-OH DL was not measured, a half-life of DL of  $\geq 50$  hours
- or, in pediatric studies in which sparse sampling was used, a plasma concentration ratio of 3-OH DL to DL at 12 hours of  $<0.10$ .

It should be noted that these criteria, when applied in single-dose PK studies, are not entirely accurate. For instance, 7 of the 53 patients who were identified as being PMs in a single dose PK study (Study 2818, see below), were subsequently determined to be normal metabolizers (NMs) in multiple dose studies.

In response to Comment 18, the Applicant has submitted a collection of data from several clinical studies. In general, the Applicant's approach has been to first identify PMs by conducting three open-label, single-dose, PK studies. These studies included both patients who had previously participated in clinical studies with desloratadine or loratadine, and patients who had never participated in such studies. The Applicant then took two approaches to establishing safety in PMs. First, it analyzed the safety data from prior clinical studies, focusing on the patients who were subsequently determined to be PMs. Second, the Applicant conducted new, repetitive dose studies, in which it enrolled newly identified PMs who had not previously participated in such studies. Characterization of the repetitive-dose pharmacokinetics in PMs was also accomplished in these latter studies.

The first open-label, single-dose PK study was Study 2781, which enrolled 162 patients who had previously participated in one of three clinical studies, 302, 303, or C98-566.

- Study 302 was a randomized, double-blind, placebo controlled study of patients aged 6 to 11 years with allergic rhinitis or chronic idiopathic urticaria, who were treated with desloratadine 2.5mg once daily for 15 days.

- Study 303 was a randomized, double-blind, placebo controlled study of patients aged 2 to 5 years with allergic rhinitis or chronic idiopathic urticaria, who were treated with desloratadine 1.25mg once daily for 15 days.
- Study C98-566 was a randomized, double-blind, placebo controlled study of patients aged 2 to 5 years with allergic rhinitis or chronic idiopathic urticaria, who were treated with loratadine 5mg once daily for 14 days. The Applicant supported the relevance of including this loratadine study by citing results of a study previously performed in adults in which subjects found to be PMs of DL following loratadine administration were also PMs of DL following DL administration (Study P00117).

Study 2781 identified 26 PMs who had previously participated in one of these three prior studies (8 subjects from Study 302, 8 subjects from Study 303, and 10 subjects from Study C98-566). It is important to point out that this process might introduce an element of bias because not all of the participants in the prior studies were enrolled in Study 2781. If adverse experiences during the prior studies affected the determination to participate in Study 2781, this might result in a bias against detecting a safety signal. However, 111 of the 115 (96%) subjects who received DL in Studies 302 and 303 were phenotyped in Study 2781.

The second open-label PK study was Study P02818, in which 359 subjects aged 2 to 11 years with allergic rhinitis received a single dose of loratadine 10mg. This study identified a total of 53 PMs, 43 of whom were subsequently enrolled in either Study P02798 or Study P03016. Seven of the 43 subjects identified as PMs in Study P02818 and enrolled in Study P02798 or Study P03016 were subsequently determined to be normal metabolizers (2 subjects in Study P02798, and 5 subjects in Study P03016). These subjects were classified as normal metabolizers in the analyses of Studies P02798 and P03016. Study P02818 was also used to identify “normal metabolizers” who would then be entered into Study P02798 or Study P03016. For that purpose, and to clearly distinguish PMs from normal metabolizers, “normal metabolizers” were defined as subjects with 3-OH DL to DL concentration ratio at 12 hours post-dose  $\geq 0.25$ .

- Study P02798 was a multiple-dose PK and safety study in which 48 subjects aged 2 to 11 were randomized to receive either desloratadine or placebo for a period of 17 days. A loading dose regimen was used in order to achieve DL steady state within 17 days. A total of 17 PMs and 20 normal metabolizers (NMs) were treated with desloratadine (1.25mg for subjects aged 2-5, and 2.5mg for subjects aged 6-11). A total of 3 PMs and 7 NMs were treated with placebo.
- Study P03016 was a multiple-dose safety study in which 42 subjects aged 2 to 11 were randomized to receive either desloratadine or placebo for a period of 29 days. A total of 15 PMs and 5 normal metabolizers (NMs) were treated with desloratadine (1.25mg for subjects aged 2-5, and 2.5mg for subjects aged 6-11). A total of 5 PMs and 17 NMs were treated with placebo.

The Applicant points out that, although Study 2818 identified 4 PMs who were 2 years of age, for various reasons no 2 year-old PMs received active drug in Study 3016. Therefore, the Applicant has submitted data from a previously conducted

single-dose DL PK study in 58 subjects aged 6 months to 2 years, in which 4 PMs were identified (Study P01341).

The third open-label PK study was a multicenter study performed in the US and Latin America (Study P03031). This study was intended to evaluate the prevalence of the poor metabolizer phenotype in children ages 2 to 11, and to identify subjects for enrollment in a subsequent multi-dose study (Study P02994). In Study P03031, 2033 subjects were phenotyped after receiving a single dose of loratadine 10mg. A total of 79 PMs were identified (27 aged 2-5 years, and 52 aged 6-11 years). Study P02992 was a PK and safety study in which subjects received loratadine 10mg or placebo once-daily for 36 days. The study enrolled 97 subjects who had participated in Study P03031. Among these, 48 were PMs who were randomized to receive DL (1.25 or 2.5mg) and 10 were PMs who were randomized to receive placebo.

The pharmacokinetic and safety data from these studies is described in detail in the Medical Officer Review of this submission (Dr. Richard Nicklas). The submission includes steady state pharmacokinetic data from a total of 32 pediatric poor metabolizers aged 2 to 11 years, as well as single dose pharmacokinetic data from 4 poor metabolizers aged 6 months to 2 years. The pharmacokinetic data suggest that the systemic exposure to desloratadine is approximately 6 times higher in pediatric patients who are poor metabolizers, as compared with normal metabolizers. This 6-fold increase is similar in magnitude to that seen in the adult population. Although the numbers of PMs included in the database is relatively small, there was no evidence of a safety concern associated with the increased systemic exposures seen in pediatric poor metabolizers who received the proposed dose of desloratadine. In this regard, particular attention was paid to potential effects on the ECG QT interval. The OCPB review team, along with a consultation from Dr. He Sun, analyzed data from a rigorously performed QT study and determined that there was no evidence of QT prolongation among poor metabolizers. Further details of this analysis may be found in Dr. Sayed Al Habet's OCPB Review.

Comment 19 in the October, 2002, Approvable letter encouraged the Applicant to determine the mechanism accounting for higher levels of drug exposure observed in some patients, and to assess the potential for drug-drug interactions that might be expected based on the explanatory mechanism. The Applicant reports that it has conducted extensive in vitro experiments in order to determine the enzyme(s) responsible for the conversion of DL to 3-OH DL. The nature and findings of these experiments are discussed in the OCPB review. Although these experiments did not identify the enzyme(s), the Applicant has been able to conclude that the formation of 3-OH DL is not catalyzed by any of the known CYP450 enzymes. The major route of elimination of DL in poor metabolizers is excretion of unchanged drug into urine and feces.

#### NDA 21-563

The May 14, 2003, AE letter for NDA 21-563 asked the applicant to provide a discussion of how caregivers will administer the proposed small volumes of syrup, and to make specific changes in the proposed labeling. In its response, the Applicant has made the

requested labeling changes, and has also included labeling language to that the age-appropriate dose of Clarinex Syrup should be administered with a commercially available measuring dropper that is appropriately calibrated.

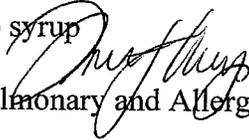
### **Recommendation**

The Applicant has adequately responded to the clinical deficiencies listed in the prior AE letters for both NDA 21-300 and NDA 21-563, as well as other relevant communications (see above). The clinical recommendation for both applications is therefore, Approval. The CMC team has also recommended Approval for these applications. It should be noted that the Division has previously determined that, for scientific reasons, the youngest ages at which seasonal allergic rhinitis and perennial allergic rhinitis may be diagnosed are 2 years of age and 6 months of age, respectively. This determination is reflected in the current labeling for another antihistamine, Zyrtec (cetirizine hydrochloride; Pfizer).

### **Labeling Issues**

As discussed in the Administrative section of this Review, the Applicant has submitted two NDAs for this product, Clarinex Syrup. The proposed labeling included in the current submission, which is harmonized with the currently approved label for the tablet and Reditab formulations, represents the proposed label submitted with NDA 21-563, with modifications to address the labeling comments in the May 14, 2003 AE letter (for NDA 21-563) and to address the new data relating to the poor metabolizer phenotype. In general, the proposed labeling is deemed acceptable. However, the Division recommended a few modifications to the currently proposed label. First, the Indication for seasonal allergic rhinitis should be  $\geq 2$  years of age, and the Indication for perennial allergic rhinitis should be  $\geq 6$  months of age (see discussion above). Second, the OCPB review team has suggested minor modifications to the Pharmacokinetics: Absorption section, and the Pediatric Subjects section. Third, the Pharmacokinetics: Metabolism section should state the numbers of subjects screened for metabolizer status, by age group. Finally, in this same section, the conclusions regarding the relative safety among poor metabolizers and normal metabolizers should be clarified by stating the specific numbers of poor metabolizers and normal metabolizers who received desloratadine in the prospective multiple dose studies, and by stating that, although not seen in these studies, an increased risk of exposure-related adverse events in patients who are poor metabolizers cannot be ruled out. On August 30, 2004, during a telephone conference with the Applicant, agreement was reached on these points.

**Division Director's Memorandum**

Date: Tuesday, October 02, 2001  
NDA: 21-300  
Sponsor: Schering Plough  
Proprietary Name: Clarinex (desloratadine) syrup  
From: Robert J. Meyer, MD,   
Director, Division of Pulmonary and Allergy Drug Products

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**Introduction:** This is the first action for NDA 21-300, an application for a new formulation of desloratadine, the major metabolite of loratadine. The PDUFA 10-month goal date is Oct. 8<sup>th</sup>, 2001. This product, being a syrup, is primarily intended for pediatric use and the program was based on previous showing of safety and efficacy in adults with the 5 mg. tablet, pediatric PK data with the syrup and clinical safety data in the population in question (patients ages 2 to 11 years of age).

**CMC:** There are a number of outstanding CMC issues, but the primary problem is GMP issues with multiple Schering facilities that preclude approval at this point, even if all other CMC and clinical issues had been addressed.

**Biopharmaceutics/Clinical:** Please see the primary reviews from the Biopharmaceutics and Medical reviewers for details. See, especially, Dr. Chowdhury's Medical Team Leader memo, with which I fully concur.

Essentially, there were no serious clinical safety signals identified in the limited data set submitted, but there are a significant number of children who, in the single-dose studies done to support this NDA, appear to be slow-metabolizers. It is not apparent that Schering has provided us either adequate data to identify the mechanism of this finding, the extent of exposure likely to result from multiple, repeated dosing, nor to identify patients at risk. It does appear that the number of such "outliers" in metabolism is higher in children than adults (close to 14% in children). The sponsor needs to better explain these findings, to put these in the context of any potential drug-drug interactions that might increase the number of patients with high levels of exposure, and the sponsor needs to characterize the exposures that result from multiple, repetitive dosing in apparent poor metabolizers and what the safety consequences of such levels are likely to be.

**Labeling:** We will ask the sponsor to update this proposed labeling to account for changes already agreed in prior reviews of other Clarinex NDAs, but final labeling cannot be arrived at until the PK/clinical issues and CMC issues are addressed by the sponsor.

**Conclusions:** This product cannot be approved currently, since we have significant outstanding CMC issues, EERs with "withhold" recommendations due to GMP issues and, just as importantly, lingering biopharmaceutics/clinical issues that are of significant concern.

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