CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-563

MEDICAL REVIEW

Clarinex (desloratadine) Syrup
Patients 6-23 months of age
NDA 21,563

Sponsor: Schering Corporation
Date of Submission: 4 December 2002
Medical Reviewer: Richard Nicklas MD
Date of Review: 14 May 2003

Table of Contents

Clinical Review for NDA 21,563

Executive Summary

I. Recommendations

A. Recommendation on Approvability:

The safety of Clarinex syrup in patients 6-23 months of age has been demonstrated. Efficacy of Clarinex has been demonstrated in older children and adults and can be extrapolated to patients 6-23 months of age. Approval of Clarinex syrup for patients 6-23 months of age can not be given until issues relating to poor metabolizers of desloratadine are resolved. Therefore, this NDA is clinically Approvable pending resolution of the poor metabolizer issue.

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

No phase 4 studies and/or risk management are necessary at this time.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program:

The sponsor has submitted data from two studies to support the safety of Clarinex syrup in patients 6-23 months of age for the treatment of allergic rhinitis and chronic urticaria: 1) study 1341, a pharmacokinetic study in 58 patients 6-23 months of age which was designed to establish the appropriate dose of desloratadine for administration to this patient population; and 2) study 1368, which was designed to establish the safety of Clarinex syrup in 131 patients 6-23 months of age, based on assessment of adverse events, vital signs and ECGs after repetitive drug administration for 15 days. These studies are linked to pharmacokinetic data in older children and adults and to an extensive safety database in older children and adults. Efficacy demonstrated in older children and adults can be extrapolated to patients 6-23 months of age because there is no reason to believe that either the clinical condition being studied or the pharmacokinetics/pharmacodynamics would be different in this age group than in older children or adults.

B. Efficacy;

Efficacy of desloratadine syrup was not evaluated in the studies submitted in this NDA, since the Division agreed that the efficacy demonstrated in older children and adults could be extrapolated to patients 6-23 months of age.

C. Safety:

The safety of Clarinex syrup was demonstrated in studies 1368 and 1341. There were no clinically significant differences in the adverse event profile for Clarinex syrup compared with placebo in these studies, although a greater incidence of fever, diarrhea and upper respiratory infections were seen, especially in patients 6-11 months of age. This finding is stated in the labeling for the entire age range of 6-23 months, but should be divided into the incidence of these adverse events in patients 6-11 months and 12-23 months of age. There was no significant change in vital signs or physical examination compared to baseline nor difference from the placebo control group in patients who received desloratadine in these studies. The ECGs done in these studies did not demonstrate any clinically significant difference compared to baseline or to the placebo control group. Therefore, the sponsor has demonstrated that Clarinex syrup is safe for administration to patients 6-23 months of age. There were no clinically significant change from baseline in laboratory tests in patients receiving desloratadine in study 1341.

D. Dosing:

The dose recommendation in the current Clarinex syrup labeling for patients 6-11 years of age is 2.5 mg and for patients 2-5 years of age is 1.25 mg, based on pharmacokinetic data that showed that the exposure (AUC) after desloratadine administration at these doses in these patient populations was comparable to that seen in adults who received a dose of 5 mg. of Clarinex syrup. In this submission, based on the data from pharmacokinetic study 1341 it was concluded that patients 6-11 months of age required a dose of 1.00 mg and patients 12-23 months of age required a dose of 1.25 mg. The Division agrees that it is reasonable for the sponsor to select a dose of 1.00 mg per day for patients 6-11 months of age and a dose of 1.25 mg per day for patients 12-23 months of age.

E. Special Populations:

There were no clinically significant gender or age differences in the pharmacokinetic or safety evaluation of Clarinex syrup.

POOR METABOLIZERS: There are poor metabolizers of desloratadine and this phenotype has previously been shown to be more common in African-American

patients. However, based on data submitted previously by the sponsor, there does not appear to be any greater incidence of adverse events or other safety concerns in patients who are poor metabolizers. However, the issue of safety in patients who are poor metabolizers of desloratadine has not yet been completely resolved. As a result, the sponsor has studies that are ongoing or planned in response to this issue as raised by the Division in regard to the review of NDA 21,300. There were 9 patients in study 1341 who were poor metabolizers of desloratadine.

In study 2781, patients are being phenotyped as poor or normal metabolizers of desloratadine. These are patients 2-11 years of age, who received treatment in safety studies 302 and 303 submitted under NDA 21,300. Patients who received loratadine, the parent compound for desloratadine, in study 98-566 are also being phenoyped as poor or normal metabolizers. Two screening studies, studies 2818 and 3031 are identifying poor and normal metabolizers in patients 2-11 years of age who will be enrolled into the PK and safety study 2798 to determine the extent of exposure of desloratadine in these populations.

There were 58 patients who received desloratadine in study 1341 and 131 patients who received desloratadine in study 1368. In study 1341, there were 30 females and 28 males. In study 1368, 56% were male and 44% were female. In study 1341, 19 were Caucasian and 39 were African-American. In study 1368, 23% of the patients were Caucasian, 9% were African-American, 2% were Asian and 65% were Hispanic.

The sponsor has, in this submission, 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 a pharmacokinetic study in patients 6-23 months of age. The latter two studies are part of this NDA submission. 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.

Clinical Review

I. Introduction and Background

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

Desloratadine (Clarinex), the major metabolite of loratadine (Claritin), possesses qualitatively similar pharmacodynamic activity to loratadine. Desloratadine is an H-1 receptor antagonist that can be administered orally. Desloratadine has less extensive first-pass metabolism and a longer plasma elimination half-life than loratadine. Desloratadine has been approved as a 5 mg tablet for seasonal allergic rhinitis (SAR) and for perennial allergic rhinitis PAR) in the United States. Desloratadine syrup has been approved for SAR and chronic urticaria in children 2 years of age and older in all 15 member countries of the EU. Patients are exposed to desloratadine from taking loratadine which has been available for treatment of SAR since 1988 and chronic urticaria since 1993. Clarinex syrup has been found approvable in the United States for children 2-5 years of age at a dose of 1.25 mg per day and for children 6-11 years of age at a dose of 2.5 mg per day.

As discussed below, approval for Clarinex syrup in patients 6-23 months of age has not been granted pending resolution of CMC and clinical issues. In terms of the latter, further information need to be provided by the sponsor addressing the issue of safety when Clarinex syrup is administered to poor metabolizers of desloratadine.

Desloratadine products

Product	IND/NDA number	submission/filing date	date approved
Tablet SAR/chronic urticaria adults/adoles	IND 55,364	9 March 1998	--
Syrup	IND 57,960	26 February 1999	--
2.5 mg/120 mg PSE tablet 12 hour SAR	IND 58,506	18 June 1999	--
5 mg/240 mg PSE tablet 24 hour SAR	IND 58,545	25 June 1999	--
[redacted]	[redacted]	20 August 1999	--
Reditabs (rapidly disintegrating)	IND 59,109	12 October 1999	--
5 mg/120 mg PSE tablet 24 hour SAR	IND 64,472	26 March 2002	--
5 mg tablet SAR adults/adolescents	NDA 21,165	20 October 1999	21 December 2001
5 mg tablet chronic urticaria, adults/adoles	NDA 21,297	30 August 2000	8 February 2002
Syrup 2-11 years	NDA 21,300	8 December 2000	Pending
5mg/PSE tablet 12 hour SAR	NDA 21,313	8 December 2000	Pending
Reditabs (rapidly disintigrating)	NDA 21,312	20 December 2000	26 June 2002
5 mg tablet AR – SAR, PAR, adults/adolescents	NDA21,363	16 April 2001	8 February 2002

B. State of Armamentarium for Indication(s) :

At the present time, the treatment of allergic rhinitis includes: 1) avoidance; 2) medication; and/or 3) allergen immunotherapy. 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.

C. Important Milestones in Product Development:

The NDA for desloratadine syrup (NDA 21,300) for use in patients 2-11 years of age was submitted on 8 December 2000 and was found to be approvable. On 21 December 2001, the 5 mg tablet formulation was approved in the US for seasonal allergic rhinitis in adolescents and adults. On 8 February 2002, the 5 mg tablet formulation was approved in the US for the treatment of perennial allergic rhinitis and chronic urticaria. The 5 mg tablet formulation of desloratadine has been approved for seasonal allergic rhinitis in 61 countries and for chronic urticaria in 32 countries. The rapidly disintegrating tablet formulation of desloratadine (Reditabs) was approved on 26 June 2002 for seasonal allergic rhinitis and chronic urticaria for patients 12 years of age and older. The safety of desloratadine syrup in 303 pediatric patients 2-11 years of age was evaluated in PK studies in healthy volunteers (studies 1125 and 1126) and repetitive dose studies of 15 days duration in patients with allergic rhinitis or chronic urticaria (Studies 302 and 303)(NDA 21,300). A dose of 1.25 mg per day for patients 2-5 years of age and a dose of 2.5 mg per day for patients 6-11 years of age was found to be appropriate based on these studies and comparison to the PK profile seen in adults who received 5 mg per day of desloratadine.

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.

On 4 February 2000, the sponsor asked for a Written Request for Pediatric Exclusivity for Clarinex syrup. A Written Request was sent by the Agency to the sponsor on 6 June 2000. There were 4 studies requested: 1) a safety study in patients 6-11 years of age; 2) a safety study in patient 2-5 years of age; 3) a single dose PK and safety study in patients 6-23 months of age; and 4) a repetitive dose safety study in patients 6-23 months of age. Studies 1 and 2 were included in NDA 21,300 when it was submitted for approval in patients 2-11 years of age on 8 December 2000. Studies 3 and 4 are part of this NDA submission.

D. Other Relevant Information:

This submission is a response to the Written Request from the DAPDP of 6 June 2000, amended on 19 October 2000, 5 December 2000, and 7 May 2001. Study 1 (P302) and study 2 (P303) of the Written Request were submitted under NDA 21,300 on 8 December 2000 as a supplement for the indication of SAR in patients 2-11 years of age. This supplement was reviewed and found to be approvable. Study 3 (1341), a clinical pharmacology study and study 4 (1368), a 15 day safety study in children 6 months to 2 years of age are included in this submission.

E. Important Issues with Pharmacologically Related Agents:

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.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews:

Chemistry will not approve this application because of unresolved concerns about the syrup formulation related to the sponsor's submission of NDA 21,300 for the use of the syrup formulation in children 2-11 years of age (see Chemistry Review). There are no pharmacology concerns that would prevent approval of this application (see Pharmacology Review). Biostatistics has noted the greater frequency of adverse events in patients 6-11 months of age (see comments below for study 1368), but has concluded that this application is approvable. Biopharmaceutics also has concluded that the application is approvable and determined that there was no significant difference when the data was analyzed for responders and non-responders.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics;

In order to obtain information about the appropriate dose of desloratadine syrup in patients less than 2 years of age, a single dose PK study (study 1341) was done in patients 6-23 months of age and the data compared with the data seen in adults who received a dose of 5 mg. The objective of study 1341 was to determine the apparent total body clearance of deslortadine syrup in order to compare exposure (Cmax, AUC) to that seen in adolescent and adult patients administered the recommended dose of 5 mg. In order to minimize blood drawing, population pharmacokinetics was performed in patients 6-23 months and compared to pharmacokinetics in adults. Patients in study 1341 had previously received antihistamines or were candidates for antihistamine therapy. The study was designed as a single dose, open, parallel, PK and safety study of 58 patients between 6-23 months of age who received either 0.625 or 1.25 mg of desloratadine syrup. PK studies in patients 2-11 years of age had previously indicated that the Tmax was 2-4 hours, mean plasma elimination half life was 16-24 hours and oral bioavailability was not affected by food in that age group. In study 1431, population PK evaluation in patients 6-23 months of age suggested, based on clearance, that 1 mg in patients 6-11 months of age and 1.25 mg of desloratadine in patients 12-23 months of age was required to produce systemic

exposure similar to that seen in adult patients (19-45 years of age) after a dose of 5 mg (study 213). Study 213 involved 30 patients 19-45 years of age in a randomized, open, single dose, three way crossover study. Patients received 5 mg of desloratadine either in the tablet formulation or in the syrup formulation in either a fasting or fed state. Individual plasma desloratadine concentration-time data from studies 1341 and 213 were modeled together. In a prior submission under NDA 21,300, the pharmacokinetic profile of desloratadine syrup was assessed in four studies in patients 2-11 years of age. These studies demonstrated that the AUC for desloratadine in patients 6-11 years of age who received 2.5 mg of desloratadine was comparable to that seen in patients 2-5 years of age who received 1.25 mg of desloratadine, as well as in adult patients who received 5 mg of desloratadine.

Previous clinical pharamacology studies have shown that desloratadine is substantially absorbed after oral administraton with a Tmax of 2-4 hours and a ½ life of approximately 27 hours. Exposure (AUC) to desloratadine, 3-OH desloratadine, and 3-OH desloratadine glucuronide after administration a 5 mg tablet of desloratadine was comparable to that observed after administration of a 10 mg loratadine tablet. PK data in adults has shown that the AUC for the 5 mg tablet of desloratadine is essentially the same as the AUC for the 10 mg loratadine tablet. The effect of food on the bioavailability of desloratadine is less than the effect of food on bioavailability of loratadine and there is a lower potential for PK interaction with drugs that inhibit cytochrome P450 3A4 after desloratadine administration than after loratadine administration.

B. Pharmacodynamics:

There were no pharmacodynamic studies included in this submission.

IV. Description of Clinical Data and Sources

A. Overall Data:

Studies 1341 (PK) and 1368 (repetitive dose safety study) were the only studies submitted by the sponsor for review.

B. Tablular Listing of the Clinical Studies:

Parameter	study 1368	study 1341
Number of patients	255	58
Age range	6-23 months	6-23 months
Study design	Randomized, placebo-controlled, parallel, double-blind, multicenter, age	Single dose, open, parallel, age-stratified PK and safety study

	stratified study	
Dose age 6-11 months	1 mg per day	0.625 mg
Dose age 12-23 months	1.25 mg per day	1.25 mg
Number of patientsd/age/dose of desloratadine	66 patients 6-11 months received 1 mg/day 65 patients 12-23 months received 1.25 mg/day	10 patients 6-11 months and 10 patients 12-23 months received 0.625 mg 19 patients in each age group received 1.25 mg
Number of placebo patients	124	None
Period of treatment	15 days	Single dose
Gender	56%M, 44%F received desloratadine; 47%M, 53%F received placebo	28 males 30 females
Ethnic background	23% Caucasian 65% Hispanic	19 Caucasian 39 African-American
Safety parameters	Adverse events, vital signs, ECGs	Adverse events, ECGs

C. Postmarketing Experience:

There is no post-marketing experience in this country for this formulation of desloratadine. Desloratadine syrup has been approved in the EU for treatment of SAR and chronic urticaria. By 27 September 2002, the 5 mg tablet had been approved in 61 countries (including the US) for allergic rhinitis and in 32 countries for chronic urticaria. Desloratadine syrup has been approved in the EU, Iceland, Norway, Mexico, New Zealand, and Estonia for allergic rhinitis and chronic urticaria in patients 2 years of age and older. As of 11 September 2002 there had been no spontaneous adverse events reported for desloratadine syrup. Spontaneous adverse events have been reported in 20 patients under the age of 12 years for the tablet formulation of desloratadine, none of which were considered serious. These included headache (3), somnolence (2), diarrhea (2), malaise (2), mydriasis (1), euphoric mood (1), dyspnea (2), pallor (1), facial edema (1), chest pain (1), dizziness (1), edema (1), urticaria (1), sneezing (1), rhinitis (1), rhinorrhea (1), weight increase (1), pemphigoid reaction (1), attention disturbance (1), memory impairment (1), confusion (1), fatigue (1), and arrhythmia (1).

D. Literature Review:

No literature review was preformed because the relevant issues were addressed in the studies submitted by the sponsor.

IV. Clinical Review Methods

A. How the Review was Conducted:

Study 1368, the key safety study performed in patients 6-23 months of age was reviewed first. The clinical summary was reviewed first, followed by a review of the line listings for this study. Following this, study 1341, a clinical pharmacology and safety study was reviewed, beginning with the clinical summary and subsequently more detailed data from the study. After this was done, the integrated summary of safety and the proposed changes in the labeling were reviewed. Special review was made of one site in study 1368 that had falsified data in another study and ECG data from [redacted] the first company enlisted by the sponsor to re-read the ECG data. The data from this study was compared to data obtained with this drug product in older children and adults.

B. Overview of Materials Consulted in Review:

The data submitted by the sponsor in the submission of 4 December 2002 as well as the data submitted under NDA 21,300 and the Written Request for pediatric studies were considered in the analysis of this review.

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

The sponsor's [redacted] audited studies according to written Standard Operating Procedures. No DSI Audit was performed.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards:

The studies submitted by the sponsor were generally performed in accordance with accepted ethical standards. However, On 11 June 2002, the FDA issued a Warning Letter on Leonard J. Caputo MD for clinical studies unrelated to this NDA. Dr Caputo was cited for submitting false information to the FDA or the sponsor and deliberately violating regulations governing the proper conduct of clinical studies involving investigational new drugs. These findings were noted in regard to studies on flunisolide and beclomethasone. Dr Caputo was one of the investigators in study 1368, the only repetitive dose safety study submitted for patients 6-23 months of age (v9, p54)(v14, p471). The sponsor states that data from Dr Caputo's site (site 52)(12 patients) was authenticated by the sponsor's through review of the monitor's visit reports and an in-depth, on-site audit of all study-related source documents at that site. No evidence of falsification of data was found. In addition, a reanalysis of the study was performed, excluding this site from the analysis. There was no evidence from the reanalysis of the data excluding site 52, that the data from this site had any impact on the study results.

US studies were conducted in compliance with IRB regulations and international studies were conducted in accordance with the principles of the Declaration of Helsinki. The sponsor's [redacted] group conducted audits of study 1368. Blood drawing in young children was minimized through the use of population pharmacokinetics.

E. Evaluation of Financial Disclosure:

There was no apparent conflict of interest based on the financial disclosure forms submitted by the sponsor.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions:

Efficacy was not evaluated by the sponsor since the Division had indicated to the sponsor that efficacy in this age group could be extrapolated from efficacy previously demonstrated in older patients.

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

There was no efficacy data to review in this submission. The efficacy of desloratadine has been established for allergic rhinitis and chronic urticaria in patients 2 years of age and older. The effectiveness of desloratadine in this patient population can be extrapolated to patients 6-23 months of age because the condition being treated and the pharmacokinetics and pharmacodynamics of the drug product would not be expected to be different in patients 6-23 months of age than in older children or adults.

C. Detailed Review of Trials by Indication:

There was no efficacy data to review in this submission.

D. Efficacy Conclusions:

There was no efficacy data to review in this submission.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions:

The data from studies 1368 do not suggest any safety concern in patients 6-23 months of age, based on adverse event reporting, vital signs, physical examination, laboratory values (study 1341 only) or ECGs. Therefore, desloratadine is safe for administration to patients 6-23 months of age.

B. Description of Patient Exposure:

By March 2002, studies done with desloratadine utilizing all dosage forms included 28 large, repetitive dose, double-blind controlled studies with treatment for 2-6 weeks, 9 small single dose studies, 3 small repetitive dose studies, and 53 clinical pharmacology studies. Three of the large, repetitive dose, double-blind controlled studies assessed the safety in patients 6 months to 11 years of age. More than 8000 patients were treated in these studies. This data was not reviewed for this NDA.

In study 1368, 66 patients 6-11 months of age received 1 mg of desloratadine per day and 65 patients 12-23 months of age received 1.25 mg of desloratadine per day for a period of 15 days. Of the patients who received desloratadine, 56% were male and 44% were female, 23% were Caucasian, 9% were black, 65% were Hispanic and 2% were Asian. Approximately 95% of the patients completed the study and approximately 86% received desloratadine for 14-15 days.

C. Methods and Specific Findings of Safety Review:

The safety review included review of studies 1368 and 1341. After an evaluation of the conduct of these studies with comment on any irregularities noted, data relating to the safety parameters included in the study was reviewed in detail, both in terms of mean changes and individual changes from baseline. For the specific findings in these studies, see the **Appendix** below which details the conduct and findings from these studies. In addition, the sponsor submitted post-marketing data which is discussed above.

D. Adequacy of Safety Testing:

Given the large safety database for older children with the syrup formulation in older children and the tablet formulation in adults, the database provided by studies 1368 and 1341 is adequate to evaluate the safety of desloratadine syrup in patients 6-23 months of age.

E. Summary of Critical Safety Findings and Limitations of Data;

The Division had previously agreed with the sponsor that safety data accumulated over a longer period of time would not have added any additional information

over that data that could be generated by post-marketing surveillance data, for a drug product that has not been associated with any specific safety concerns and for which there is data generated over a longer period of time in older children and adults, i.e. randomized controlled studies of 4-6 months duration. Longer safety studies of 6-12 month duration were not required for approval of the tablet formulation.

The safety data provided by the sponsor do not suggest any safety concerns related to adverse events, ECGs or other safety parameters that would prevent approval, pending resolution of CMC and clinical issues related to safety in poor metabolizers. However, the incidence of certain adverse events, e.g. fever, diarrhea, and upper respiratory infections, was greater in patients 6-23 months of age who received desloratadine, than in patients who received placebo. The difference between the two treatment groups was greatest in patients 6-11 months of age (see study reviews in the Appendix). The labeling will need to be changed to divide the listing of these adverse events into the incidence in patients 6-11 months of age and the incidence in patients 12-23 months of age.

VIII. Dosing, Regimen, and Administration Issues:

In NDA 21,300, a dose selection of 2.5 mg for 6-11 year old patients and 1.25 mg for patients 2-5 years of age was established based on PK data that showed that the exposure (AUC) to desloratadine was comparable to adults who received a dose of 5 mg. A PK study included in this submission shows that patients 6-11 months of age require a dose of 1.00 mg and patients 12-23 months of age require a dose of 1.25 mg to obtain exposure comparable to that observed in adults after a dose of 5 mg of desloratadine. Based on this data, it is reasonable for the sponsor to have selected a dose of 1.00 mg per day for patients 6-11 months of age and a dose of 1.25 mg for patients 11-23 months of age.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation: The study population in study 1368 consisted of 56% males and 44% females in the desloratadine treatment group and 47% males and 53% females in the placebo group. In study 1341, there were 30 females and 28 males. There were appropriate numbers of males and females enrolled in both studies and the sponsor did an intensive analysis of the data linking gender with age and ethnicity. The potential for a gender effect on the data generated under these two studies was adequately analyzed by the sponsor.

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

The treatment groups in study 1368 had approximately the same mean age, age range, with approximately the same number of patients in the younger age group (6 months to < 1 year of age) and the older age group (1 year to < 2 years of age). In terms of race/ethnic background, 23% in both treatment groups were Caucasian, 9% and 4% were African-American in the two groups and 65% and 68% were Hispanic. 2% were Asian. There were no clinically significant differences in adverse events, vital signs, physical examination or ECGs, based on gender, race or ethnicity.

C. Evaluation of Pediatric Program:

The sponsor has in this submission included a claim for pediatric exclusivity. 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 a PK study in patients 6-23 months of age. The latter two studies are part of this NDA submission. 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. The database submitted by the sponsor in this submission in conjunction with the database submitted to NDA 21,300 is adequate to meet the study requirements in the Written Request to the sponsor of 6 June 2000 and are, therefore, adequate to grant the sponsor pediatric exclusivity for this drug product. This was the consensus of the Pediatric Exclusivity Board at the meeting on this issue of 12 February 2003.

D. Comments on Data Available or Needed in Other Populations:

There is no other data available at this time in other populations. The labeling for older patients states that patients who have renal or hepatic impairment should receive a lower dose of desloratadine. In adult patients with liver or renal impairment, a starting dose of one 5 mg tablet every other day is recommended. It is unclear if this recommendation should be extended to patients 6-23 months of age. Further studies are needed in children with renal or hepatic impairment to determine if a lower dose of desloratadine is needed in this patient population.

X. Conclusions and Recommendations

A. Conclusions:

The safety of Clarinex Syrup in patients 6-23 months of age has been adequately demonstrated for patients who metabolize desloratadine normally. However, there are inadequate data, at this time, to assure the safety of Clarinex Syrup in poor

metabolizers. The efficacy of Clarinex Syrup in patients 6-23 months of age can be extrapolated from the established efficacy of desloratadine in older patients and by pharmacokinetic data demonstrating comparable bioavailability after the dose proposed for patients 6-23 months of age and the dose proposed for adults.

B. Recommendations:

The clinical recommendation is that Clarinex Syrup for the treatment of allergic rhinitis and chronic urticaria in patients 6-23 months of age is approvable, pending resolution of issues related to the safety of this drug product in patients who are poor metabolizers of desloratadine.

C. Comments to the sponsor:

1. Clinical labeling comments that should be sent to the sponsor:

a. Under the Adverse Reactions section, the listing of adverse events should be divided into those that were seen in patients 6-11 months of age and those that were seen in patients 12-23 months of age.
b. Throughout the labeling, patients less than 2 years of age should be referred to as 6-11 months of age or 12-23 months of age.
c. Under 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.
d. The title of table 5 should be changed to read, "Incidence of Adverse Events Reported by 2% or More of Allergic Rhinitis Patients in Placebo-Controlled, Multiple Dose Clinical Studies with the Tablet Formulation of Clarinex".

2. [redacted]

XI. Appendix

A. Proposed Labeling with comments:

The Applicant proposed the following labeling changes to the existing labeling for Clarinex.

1. [redacted]

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 1

B. Individual More Detailed Study Reviews

1. Study 1368:

a. number of patients: 255 patients at 29 sites * in the US, Latin America and South Africa were randomized; all patients were included in the safety analysis; 131 patients received desloratadine; 66 patients 6-11 months of age; 65 patients 12-23 months of age; 124 patients received placebo (62 patients 6-11 months of age; 62 patients 12-23 months of age).

*** NOTE:** ***One site (site 52), Leonard J. Caputo M.D. received a Warning Letter from the FDA for other studies done with flunisolide and beclomethasone because the site submitted false information and deliberately violated regulations governing proper conduct of clinical studies. Because of this, the data from this study was analyzed including and excluding Dr Caputo's site. There were 12 patients at the Caputo site, 7 of whom received desloratadine and 5 of whom received placebo. There were 7 African-Americans (out of a total of 17 African-Americans in the entire study). Analysis of the data excluding the Caputo site showed no significant change in the study results and no change in the conclusions about safety. Analysis of the data from the Caputo site alone showed no significant difference from the overall study results.***

b. age range: 6 months to 23 months of age

c. patient population: patients who were candidates for antihistamine treatment or who had received antihistamines in the past; the patient must have experienced at least one of the following symptoms; itching of the nose, sneezing, rhinorrhea, tearing, redness of the eyes, or itching of the skin; patients with allergic symptoms or a personal history of allergic rhinitis; in the desloratadine treatment group, 44% were female compared with 53% of the placebo group; 65% of the desloratadine group and 68% of the placebo

group were Hispanic; 23% of each group were Caucasian (v9, t9 p58).

d. **study design: placebo-controlled, randomized, parallel, double-blind, multicenter, repetitive dose study**
e. **drug administration: patients 6-11 months of age received 1 mg per day in the AM; patients 12-23 months of age received 1.25 mg per day in AM; using a pre-marked dropper; 0.5 mg/mL; 2 ml = 1 mg; 2.5 ml = 1.25 mg**
f. **periods of study: 1-14 day screening period followed by randomized treatment for 15 days with visits on days 8 (visit 3) and 15 (visit 4)**
g. **parameters evaluated: Efficacy was not evaluated; adverse events in daily diary was the primary outcome variable; ECGs at screening (visit 1) and/or baseline (visit 2) and at visits 3 (day 8) and 4 (day 15); on days 8 and 15, ECGs, were done 1-3 hours after drug administration (Tmax was 2.89-3.40 hours)*; vital signs and physical examination at screening, baseline and after 1 and 2 weeks of treatment**
h. **study objective: to assess the safety of desloratadine syrup compared to placebo in pediatric patients 6-23 months of age**
i. **statistical considerations: Adverse events and VS were summarized using descriptive statistics; ECG parameters were analyzed by ANOVA which extracted sources of variation due to treatment; treatment comparisons of desloratatadine and placebo were based on raw means; QTc was derived using the Fridericia and Bazett correction. The two placebo age groups were analyzed individually and pooled for all summaries and analyses, as were the two desloratadine age groups. All analyses were based on the intent-to-treat population. The two placebo groups and the two desloratadine groups were pooled for all summaries and analyses.**

NOTE:** ***In the process of the Applicant's quality assessment of the ——————————— had been contracted to perform a centralized re-read of all ECGs), significant data errors were found, suggesting that the ——————— was of suspect validity. When the

sponsor was unable to confirm the integrity of the database, combined with admission by ——— that they did not follow quality assurance and standard operating procedures, the sponsor contacted ——— to perform centralized manual re-read of ECGs after the database was unblinded. Tracking identifiers were used to maintain a blinded assessment of ECGs. A quality assurance procedure for the central manual ECG re-reads was performed by —— The sponsor can be criticized for not designing the study so that site evaluation of ECGs was done with a standardized approach. However, once it was clear to the sponsor that there was inconsistency in the site handling of ECGs, the sponsor was correct in obtaining a centralized manual re-read of the ECG data. It is unfortunate that the ——— manual re-read of the data was of suspect validity, but the sponsor was correct in then having the data manually re-read by —— There is no reason to believe that the manually re-read ECGs by — do not accurately reflect any changes seen on ECG determinations in this age group and are, therefore, acceptable as a valid safety assessment of desloratadine in patients 6-23 months of age (see review of data comparing results obtained from site readings with re-reading by both ———

j. <u>study results:</u>

1. **<u>Discontinuations</u>: 9 patients in the desloratadine group and 5 patients in the placebo group were discontinued from the study. There were 3 patients who discontinued because of adverse events – one desloratadine patient who developed moderate otitis media, considered unrelated to the study drug and 2 placebo patients who developed URIs. These events were mild-moderate and considered unlikely to be related to the study drug (v1, p22).**

2. **<u>Exposure</u>: All randomized patients except 2 in the desloratadine treatment group received at least one dose of study drug; 95% of patients completed the study, 86%**

received study drug for 14-15 days and mean duration of treatment was approximately 15 days (v9, t10, p63).

3. **Adverse Events: Overall, there were treatment-emergent adverse events in 67% of the desloratadine group and 59% of the placebo group. All adverse events were considered treatment-emergent adverse events and were defined as any adverse event that; 1) occurred for the first time on or after the first day of treatment; 2) began prior to treatment and increased in severity while on treatment; or 3) began within 30 days after the last dose of treatment.**

   a. THE MOST COMMONLY REPORTED ADVERSE EVENTS (i.e. those adverse events that were reported by 5% of more of patients in the study)(also see table below) were: 1) diarrhea – 18% and 10% of the desloratadine and placebo groups, respectively; 2) upper respiratory infection – 16% and 11% of the desloratadine and placebo groups, respectively (note: in addition there was a greater incidence of otitis media (5% vs 3%) pharyngitis (4% vs 1%) and bronchitis (4% vs 1%) in the desloratadine group); 3) fever – 15% and 7% of the desloratadine and placebo groups, respectively; 4) cough – 11% and 8% of the desloratadine and placebo groups, respectively; 5) irritability – 2% in each group (note: the incidence of insomnia, however, was 3% in the desloratadine group and none in the placebo group); and 6) somnolence – 5% and 8% of the desloratadine and placebo groups, respectively. The incidence of hyperkinesia was 2% in both groups (v1, p14).

Most Commonly Reported Adverse Events

Adverse event	desloratadine	placebo
Fever	14.5%	7.3%
Diarrhea	17.6%	9.7%

Otitis media	**4.6%**	**3.2%**
Pharyngitis	**3.8%**	**0.8%**
URI	**16.0%**	**11.3%**
Insomnia	**3.1%**	**None**
Bronchitis	**3.8%**	**0.8%**
Cough	**10.7%**	**8.1%**
Irritability	**7.6%**	**8.1%**
Somnolence	**5.3%**	**8.1%**

NOTE: ***There is a suggestion that desloratadine lowered the resistance to infection in this age group, especially as noted below, in patients 6-11 years of age. This is based on the greater incidence of fever (15% vs 7% in the placebo group) and upper and lower respiratory infections (56 patients in the desloratadine group [N=131]and 37 patients in the placebo group[n=124](v15, t4, p22). In terms of treatment-related treatment-emergent adverse events, there were 17 patients in the desloratadine group and 9 patients in the placebo group who had what were categorized as psychiatric disorders – aggressive reaction, agitation, anxiety, emotional labile, insomnia, irritability, and nervousness.***

b. SERIOUS AND SEVERE ADVERSE EVENTS:
There were no deaths or life-threatening events. There was one serious adverse event– an 11 month female in the placebo group who developed viral bronchiolitis, that was considered unrelated to the study drug (v1, p22). There was one severe adverse event, in a 7 month old female in the placebo group who developed dermatitis, considered unrelated to the study drug (v1, p19). There was one cardiovascular adverse evemt in a 21 month old Hispanic female in the desloratadine group, who, based on a cardiologist's interpretation of a machine–read ECG on day 8 of the study, was diagnosed with right ventricular overload, considered mild, unrelated to the study drug and a subsequent ECG on day 15 was read as

normal (v1, p19). Manual re-reads of the day 8 ECG by cardiologists at two separate independent central ECG CROs were read as normal (v15, p20).

c. TREATMENT-RELATED ADVERSE EVENTS: There were 26% of the desloratadine group who had treatment-related adverse events, compared to 22% of the placebo group. Adverse events that were considered possibly or probably related to treatment and occurred in 2% or greater of patients were:

1) irritability – desloratadine 7%, placebo 6%;
2) diarrhea – desloratadine 6%, placebo 2%;
3) somnolence – desloratadine 5%, placebo 7%;
4) anorexia– desloratadine 3%, placebo 2%;
5) increase in appetite – desloratadine 2%, placebo 2%;
6) insomnia – desloratadine 2%, placebo none; and
7) fever – desloratadine 3%, placebo 1% (v1, p20-21).

d. AGE, GENDER AND RACE DIFFERENCES IN ADVERSE EVENTS: See tables below with commentary following.

1) Age Differences in Selected Adverse Events (N in parentheses)

	6-11 months		12-23 months	
Adverse event	desloratadine(66)	placebo(62)	desloratadine(65)	placebo(62)
Anorexia	5%	2%	2%	3%
Fever	12%	2%	17%	13%
Diarrhea	20%	8%	15%	11%
Nausea	3%	None	None	None
Vomiting	6%	3%	2%	5%
Otitis media	6%	2%	3%	5%
URI	21%	13%	11%	10%
Somnolence	9%	8%	2%	8%
Irritability	12%	11%	3%	5%
Bronchitis	6%	None	2%	2%

Possibly clinically significant differences in adverse events between younger and older patients were noted for fever – 12% and 2% of patients 6-11 months of age who received desloratadine and placebo, respectively and 17% and 13% of patients 12-23 months of age who received desloratadine and placebo, respectively. Somnolence occurred in 9% of the younger group and 2% of the older group that received desloratadine. Diarrhea occurred most frequently in patients who received desloratadine (18% vs 10%), particularly in the younger group, 20% of the desloratadine group compared to 8% of the placebo group. Upper respiratory infections, as well, had a greater incidence in the younger group that received desloratadine – 21% compared to 13% of the placebo group and compared to 11% of the older group who received desloratadine. Otitis media, pharyngitis and bronchitis were also more common in patients 6-11 months of age who received desloratadine, 6%, 5% and 6%, respectively, compared to 2% of patients receiving placebo in regard to otitis media and pharyngitis and none in regard to bronchitis (v9, t12, p68-69). Irritability was also more frequent in younger patients in both treatment groups – 12% and 11% of the desloratadine and placebo groups, respectively, compared to older patients – 3% and 5% of the desloratadine and placebo groups, respectively (v1, 17-19).

NOTE: ***There is a suggestion that patients 6-11 months of age might be more susceptible to infections than patients 12-23 months of age while receiving desloratadine. The extensive database on desloratadine and loratadine does not indicate that this compound has any immuno-suppressive potential. Infections, particularly in younger children are common. The tendency toward a greater frequency of infections in patients 6-23 months of age who receive desloratadine than in those who receive placebo is unlikely to represent any effect from the drug.***

2) Gender Differences in Selected Adverse Events

	MALE		FEMALE	
Adverse event	**desloratadine**	**placebo**	**desloratadine**	**placebo**
Fever	**14%**	**10%**	**16%**	**5%**
Diarrhea	**16%**	**12%**	**19%**	**8%**
URI	**19%**	**10%**	**12%**	**12%**
Cough	**7%**	**10%**	**16%**	**6%**

A greater difference in adverse events was seen in male patients – 73% in the desloratadine group compared to 52% in the placebo group – and compared to females – 60% and 65%, respectively (v9, pgs 129-136).

NOTE: ***It is not clear if the differences noted above are clinically significant.***

3) Racial Differences in Selected Adverse Events

	Hispanic		Caucasian		African-American	
Adverse event	**desloratadine (85)**	**placebo (84)**	**desloratadine (30)**	**placebo (29)**	**desloratadine (12)**	**placebo (5)**
Anorexia	**5%**	**2%**	**None**	**3%**	**none**	**None**
Fever	**14%**	**8%**	**20%**	**3%**	**8%**	**None**
Diarrhea	**21%**	**11%**	**13%**	**7%**	**8%**	**None**
Otitis media	**2%**	**4%**	**10%**	**3%**	**8%**	**None**
URI	**12%**	**13%**	**23%**	**10%**	**25%**	**None**
somnolence	**7%**	**10%**	**3%**	**3%**	**none**	**None**

In Hispanic patients (n = 85 in the desloratadine group and n = 84 in the placebo group) there was a greater incidence of agitation, anxiety, emotional lability, insomnia, irritability, and nervousness as treatment-related adverse events (16) after desloratadine administration than was seen in this patient population after placebo (7)(v9, p162-163).

NOTE: ***Any potential for more frequent infections after administration of desloratadine, based on the data above,***

would appear to be primarily in Caucasian patients. As indicated above, it is unlikely that the differences seen in the desloratadine and the placebo groups is clinically significant.

4. **Vital Signs: Vital signs were assessed at baseline and after 1 and 2 weeks of treatment. No clinically significant mean changes in vital signs consistent with an effect of the drug were noted. There were 6 desloratadine patients and 13 placebo patients who had a 30% or greater change in heart rate. There were 8 desloratadine patients and 7 placebo patients who had a 30% or greater change in diastolic blood presssure and there were 4 desloratadine and 2 placebo patients who had a 30% or greater change in systolic blood pressure (v1, p23). There were no significant differences based on gender, age or race. There were no patients who had a diastolic BP > 90 mm Hg after treatment. There were 8 desloratadine patients and 3 placebo patients who had a systolic BP > 110 mm Hg after treatment, compared to 5 and 7 patients, respectively, at baseline. Of the 8 desloratadine patients who had a systolic BP > 110 mm Hg after treatment, 4 were 6-11 months of age and 4 were 12-23 months of age and 7 were male (v9, pgs 222-237). There were no clinically significant differences in pulse rate based on age, gender or race. There were no clinically significant differences in percent change from baseline in vital signs based on age, gender or race (v9, pgs 247-261).**

5. **ECGs: NOTE: *Subsequent to unblinding, significant site-to-site variability in the ECG data was noted. It was concluded that this was due to the diversity of ECG equipment used and to significant differences in methodology (manual-read vs machine-read). The ECG equipment varied from 12 channel to single channel instruments, all of which were different models. In addition, different sites used different methodology for manual interval determinations. It is unclear to this***

reviewer why the sponsor did not establish a standardized approach for the reading of ECGs for all sites, but this does not invalidate the conclusions reached after ECGs were read appropriately by [redacted] At any rate, as a result, the sponsor chose to rely on centralized ECG data to draw conclusions about the cardiac safety of desloratadine. This was an appropriate approach, given the variability in the reading of ECGs at different sites. A centralized manual re-reading of ECGs was first performed by [redacted] (see above). Because of the irregularities discovered at [redacted] it was necessary and reasonable for the sponsor to request that another organization [redacted] perform a manual re-read of the ECGs from each study site after the database had been unblinded, although the sponsor took precautions to ensure a blinded assessment by [redacted] of ECGs. Therefore, as the sponsor has done, conclusions about the data should be based on readings by [redacted] not the readings by [redacted] This data, as discussed below, although the sponsor's methods were less than ideal, does not raise any safety concerns about the administration of desloratadine to patients 6-23 months of age. This is supported, in terms of QTc interval, by the lack of any evidence of significant prolongation of the QTc interval in older children and adults.

a. <u>PROCEDURE</u>: ECGs were obtained at baseline/screening and within 1-3 hours after drug administration on days 8 and 15. Assessment was made by analysis of manually read ECGs performed centrally by [redacted]. QT was corrected using both Bazett's and Fridericia's correction.

b. <u>OVERALL READING OF ECGs</u>: The sponsor reports that there were 6 patients in the desloratadine group and 6 patients in the placebo group whose ECG was normal at baseline and was read as "abnormal, clinically significant" on day 8 or day 15 (v1, t8, p25)(v13, pgs295-301). Of these patients, 4 in the desloratadine group and 3 in the placebo group

developed sinus tachycardia (193, 184, 182, and 190 bpm in the desloratadine group and 187, 199, and 185 bpm in the placebo group) and 2 in the desloratadine group and 3 in the placebo group developed inverted T waves (v15, t17, p55). In addition, based on site evaluations (v13,pgs 303-313) there was a 7 month old Hispanic female who had an ECG interpreted as "migratory pacemaker block image of itis bundle that was considered clinically significant (v13, p187). Otherwise, there was no indication that there were any abnormalities noted at the study sites that were not also noted when the ECGs were centrally read. NOTE: *Children have a higher incidence of inverted t waves than adults, sometimes occurring at one visit but not another. Inverted t waves in leads V1-V3 are particularly common.*

c. VENTRICULAR RATE: Mean change from baseline in ventricular rate was – 0.89 bpm in the desloratadine group and – 3.78 bpm in the placebo group using site ECG data and – 1.84 bpm and – 4.27 bpm, respectively using ▬ ECG data (v9, t15, p78). No clinically significant changes from baseline or significant differences between the desloratadine and placebo groups were noted.

d. QTc INTERVAL: Based on centrally re-read ECGs, a greater difference between the desloratadine and placebo treatment groups in terms of mean change from baseline in QTc (F) and QTc (B) was seen in males (3.69 and 4.30 msec, respectively) than was seen in females (- 0.47 and 1.12 msec, respectively). There was also a greater difference in the Caucasian and African-American subgroups than in the Hispanic subgroup (v9, p91). Using Fridericia's correction, there was a mean increase from baseline of 5.8 msec in Caucasians and 7.7 msec in African-Americans compared to an increase of 0.86 msec in Hispanics (v15, t18, pgs 56-57)(see table below).

1) Site-read compared to centrally-read ECGs; Statistically significant mean differences ($p < 0.04$) were found in change from baseline to endpoint in QTc interval, using both Bazett's (5.71 msec in the desloratadine group and – 4.88 msec in the placebo group)(v9, t15, p79) and Fridericia's (5.35 msec in the deloratadine group and – 2.63 in the placebo group) correction, based on assessment of site-generated ECG data. Assessment of centrally re-read ECG data did not show any statistically significant mean change from baseline to any time point after treatment in any ECG parameter, including QTc interval with Bazett's or Fridericia's correction (v1, t9, p27-28), although the mean increase in QTc (F) in the desloratadine group was2.2 msec compared to an increase on 0.5 msec in the placebo group after treatment (v9, p279), an effect that was seen primarily in male African-American and Caucasian patients 12-23 months of age (v9, p280-282). The same pattern of response was seen in regard to QTc change based on Bazett's correction (v9, p 283-286). There were no patients in either treatment group who had a QTc interval > 440 msec after treatment (Fridericia correction or Bazett correction).

NOTE: ***it is unclear why there was so much difference in the site-read and the centrally-read ECG assessments and which assessment could have given a more accurate picture of the ECG effect of the study drug.***

Mean changes in QTc interval (msec) from baseline - endpoint (v10, p302)

	site-generated *				centrally re-read			
	Bazett's		Fridericia's		Bazett's		Fridericia's	
Population	Clarinex	placebo	Clarinex	placebo	Clarinex	placebo	Clarinex	placebo
Total	5.12	- 4.34	4.80	- 2.22	1.49	- 1.30	2.19	0.49
6-11 mo	9.44	- 4.68	8.31	- 2.27	1.54	- 0.42	1.94	1.18
12-23 mo	0.66	- 4.00	1.18	- 2.18	1.44	- 2.15	2.44	- 0.18
Males	3.44	- 2.40	3.83	- 1.11	2.51	- 1.79	3.46	- 0.23
Females	7.21	- 6.03	6.02	- 3.20	0.26	- 0.86	0.65	1.12
Hispanic	5.80	- 7.22	5.63	- 3.35	- 1.05	- 0.96	0.59	1.92
Caucasia	2.11	3.32	2.25	1.00	6.69	- 1.11	5.79	- 2.93
AfricanA	7.00	- 5.80	5.92	- 2.80	10.08	-13.80	7.67	- 9.60

- **The differences in the site-generated ECG readings between the desloratadine and placebo groups in regard to change from baseline in QTc interval using both the Fridericia and Bazett correction were statistically significant. However, the difference in the mean baseline values for the two treatment groups were at least ½ the amount of the difference after treatment, making interpretation difficult.**

Change from baseline in QTc interval based on type of ECG reading (v10, p399-400)

	QTc (F)		QTc (B)	
Type of reading	**desloratadine**	**placebo**	**desloratadine**	**placebo**
manual re-read of site manual read	**0.38 n = 58**	**- 0.52 n = 60**	**- 0.86 n = 58**	**- 3.03 n = 60**
manual re-read of site machine read	**3.74 n =68**	**1.47 n = 62**	**3.50 n = 68**	**0.39 n = 62**

Mean change from baseline to endpoint in QTc interval (F)(central re-read)

Subgroup	n	desloratadine	n	placebo
US sites	48	4.19 msec	43	0.56 msec
LAFE sites	78	0.96 msec	79	0.46 msec
Males	69	3.46 msec	57	- 0.23 msec
Females	57	0.65 msec	65	1.12 msec
Caucasian	29	5.79 msec	28	- 2.93 msec
African American	12	7.67 msec	5	- 9.60 msec
Hispanic	81	0.59 msec	83	1.92 msec

2) Gender and Race Differences: Greater mean difference in the QTc interval was noted in patients 12-23 months than in patients 6-11 months of age, 0.76 msec and 2.62 msec (Fridericia) and 1.96 msec and 3.59 msec (Bazett), respectively (v9, t16, p81). A greater difference in mean change from baseline in QTc (F) and QTc (B) was seen in males (3.69 and 4.30 msec, respectively) than

was seen in females (- 0.47 and 1.12 msec, respectively). There was also a greater difference in the Caucasian and Black subgroups than in the Hispanic subgroup (v9, p91).

3) Individual Patient Changes: No patients in either treatment group had a QTc interval (Fridericia) increase of 61 msec or more. There were 3 desloratadine patients and one placebo patient who had a prolongation of the QTc interval (Bazett) of 61 msec or greater, but all 4 patients had a QTc interval that was 440 msec or less (v1, pgs 29-30)(v9, t18, p87)(v15, t15, p52). One patient, a 9 month old Hispanic female, (patient 164) had a change in QTc(B) of 72 msec (20%, 424 msec on day 15) after receiving desloratadine (v9, p83). There were only a few patients in each treatment group and comparable numbers in the two groups who had an increase in QTc (F) or QTc (B) of 15-19% (v9, t17, p86).

4) Analysis of the data from site 52 (Caputo site)(v14, pgs473-514): Mean change in QTc interval was 12 msec after desloratadine administration using both Fridericia's and Bazett's correction and was - 14 and – 16 msec after placebo administration, using Fridericia's and Bazett's correction, respectively (v14, p510,511).

5) Reanalysis of the data excluding site 52 (Caputo site)(v14, pgs515-634): Excluding site 52, the mean change in QTc interval (F) was 1.6 msec after desloratadine and 1.1 msec after placebo, which represents less of a difference between desloratadine and placebo than was seen with inclusion of site 52. The greatest difference was seen in the Caucasian subset of the patient population who had a 7.1 msec mean increase after desloratadine and a – 1.9 msec mean decrease after placebo with Fridericia's correction and a 8.4 msec mean increase after desloratadine and a 0.5 msec mean increase after placebo using Bazett's correction. Using Bazett's correction, there was a 0.9 msec mean increase

in the QTc interval after desloratadine and a 0.7 msec mean decrease in the QTc interval after placebo.

6) Evaluation of ECG data read by [redacted] (v13 and v14): The central readings by [redacted] of the ECG data generated during the study did not suggest any significant difference in ECG findings, including QTc interval, either when calculated by [redacted] or by the sponsor using the [redacted] data, than was reported after evaluation by [redacted] v14, pgs335-356). One patient developed a QTc interval of 454 msec (B)(397 msec F) after desloratadine administration (v13, p233). There was one placebo patient who developed a QTc interval of 446 msec (B)(372 msec F)(v13, p252). There were 2 desloratadine patients who developed a change from baseline in QTc interval of 61 msec or more using the Fridericia correction and no placebo patients who had such a change. There was one desloratadine patient and no placebo patients who had such a change in QTc interval using Bazett's correction(v11, p669,671). These patients were all 12-23 months of age and all had a 20% or greater change from baseline. Using Bazett's correction, there was a decrease in the QTc interval of 2.55 msec after desloratadine and a decrease of 9.05 msec after placebo (v11, p601). The change in QTc interval for African-American patients (N = 12) was an increase of 10.17 msec after desloratadine and – 8.20 msec after placebo compared to an increase of 1.76 msec in Hispanics after administration of desloratadine and a decrease of 6.41 msec in this patient population after placebo using Bazetts correction (v11, p616). A greater difference between desloratadine and placebo in regard to change from baseline in QTc interval was seen using either correction in patients 12-23 months of age, compared to patients 6-11 months of age.

2. **Study 1341 entitled "Single Dose Pharmacokinetic Study of Desloratadine Syrup in Pediatric Subjects 6 Months to 2 Years of Age with Allergic Disorders". (see Biopharm Review)**

   Objective: to determine the apparent total body clearance of desloratadine syrup in pediatric patients 6-23 months of age in order to determine the dose that would produce comparable exposure to that seen in adolescent and adult patients given the recommended dose of 5 mg as the syrup formulation in the fasting state in study 213 (cross-study comparison).

   a. **number of patients: 58 (30 females, 28 males) stratified into two groups according to age, i.e. 6-11 months and 12-23 months)**
   b. **age range: 6-23 months of age; 20 patients 6-11 months, 38 patients 12-23 months of age**
   c. **patient population: patients who had previously received antihistamines or were candidates for antihistamine treatment**
   d. **study design: open, single dose, parallel PK and safety study**
   e. **drug administration: 0.625 or 1.25 mg (1.25 or 2.5 ml from a dosing syringe); 10 patients in each age group, i.e. 6-11 months and 12-23 months, received 0.625 mg and 19 patients in each age group received 1.25 mg.**
   f. **periods of study: patients confined to study center for 24 hours prior to drug administration and for 72 hours after treatment**
   g. **parameters evaluated: plasma levels obtained by population PK techniques at 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after drug administration; plasma desloratadine concentration-time data when desloratadine syrup was administered to adult patients under fasting conditions in a separate study were used for comparison; safety parameters included adverse events, vital signs done 24 and 72 hours after drug administration, physical examination done 72 hours after drug administration, laboratory tests done 48 and 72 hours after drug administration and ECGs done 3 and 72 hours after drug administration.**

h. Study results:

Cross-study comparison between this study in patients 6-23 months of age and the supporting adult study (v9, t1, p8)

Study #	study objective	study design	N	demographics	drug admin
1341	To determine bioavailability of desloratadine syrup in patients 6-23 months of age with allergic disorders	Single dose, open label, randomized stratified, parallel group, PK and safety study	58	6-23 months, 30 females, 28 males. 19 Caucasian, 39 African-American	Single doses, Syrup, 0.625 and 1.25 mg fasting for 2 hours
213	To determine bioavailability of desloratadine syrup in healthy adult volunteers	Randomized, open label, single dose, three-way crossover study	30	19-45 years 6 females, 24 males, all Caucasian	Single doses, syrup fasting and fed and tablet fasting, 5 mg

PK assessment of desloratadine with cross-study comparison

	6-11 months		12-23 months		adults
Parameter	0.625 mg	1.25 mg	0.625 mg	1.25 mg	5 mg
Mean Cmax (ng/mL)	1.20	2.22	1.01	2.11	1.94
Mean Tmax (hr)	3.40	2.89	3.27	2.93	3.22
Mean AUC (ng.hr/mL)	37.2	40.2	26.2	42.7	43.2

NOTE: ***The higher mean Cmax that was seen in patients 6-11 months of age than in either patients 12-23 months of age or adults at a dose of 5 mg supports the sponsor's proposal to use a lower dose, i.e. 1 mg rather than 1.25 mg in this age group. It should be noted, however, that the mean AUC is not substantially different when patients 6-11 months of age are given a dose of 1.25 mg than when they are given a dose of 0.625 mg or even when adults are given a dose of 5 mg.***

1) **<u>POOR METABOLIZERS</u>: There were 4 patients in the 12-23 month old age group who were poor metabolizers based on an AUC 3-OH desloratadine to AUC desloratadine ratio of < 10% (patients 43, 46,77, and 78). In addition, there were 2 patients in the 6-11 month old age group (patients 6 and 17) and 3 patients in the 12-23 month old age group (49, 52, 71), who had a ratio just outside the range that would classify them as a poor metabolizer (11-13%)(v1, p17). The sponsor did not evaluate the PK data in this study excluding poor metabolizers. There is great variability in the individual PK data and the confidence limits on the mean data are very wide (see Biopharm Review with analysis of data excluding poor metabolizers and patients just outside the range that would classify them as a poor metabolizer).**

2) **<u>ECGs</u>: There were 6 female patients, ages 6, 7, 11, 20 (2) and 23 months, who developed sinus tachycardia after treatment with desloratadine (100-180 bpm), not associated with any signs or symptoms. Five of these 6 patients received a dose of 0.625 mg.**

   There were 7 patients who had a normal ECG at baseline who had an abnormal ECG after treatment. Two of these patients developed sinus tachycardia 3 hours after administration of 0.625 mg. Three patients developed T wave changes 72 hours after drug administration (one patient received 0.625 mg and 2 patients received 1.25 mg) and two patients developed sinus tachycardia 72 hours after a dose of 1.25 mg (v15, t22, p64).

   NOTE: ***It is unlikely that the ECG changes seen 72 hours after drug administration reflected an effect of the drug. T wave changes and sinus tachycardia are not uncommon in patients of this age and an effect of the drug this late after drug administration without any***

prior change in the ECG also mitigates against these changes being a drug effect.

QTc interval: There were no patients with a QTc interval more than 440 msec or a change from baseline more than 60 msec using either Bazett's or Fridericia's correction. There were no clinically relevant differences in QTc interval based on gender or age (v1, p18). The greatest mean changes were seen using Bazett's correction for QTc interval – specifically a decrease of 4.3 msec in the 6-11 month group and an increase of 3.8 msec in the 12-23 month group after a dose of 0.625 mg and an increase of 6.3 msec in the 6-11 month group and a decrease of 4.2 msec in the 12-23 month group after a dose of 1.25 mg (see table below)(v15, t21, p62).

Mean Change in QTc interval

	0.625 mg		1.25 mg	
Age range	**Bazett's**	**Fridericia's**	**Bazett's**	**Fridericia's**
6-11 months	**- 4.3 msec**	**- 3.2 msec**	**6.3 msec**	**4.9 msec**
12-23 months	**3.8 msec**	**1.3 msec**	**- 4.2 msec**	**- 6.2 msec**

NOTE: ***As can be seen from the table above, in the younger patients a higher dose produced prolongation of the QTc interval not seen at the 0.625 mg dose. This effect was not seen, however, in patients 12-23 months of age, in whom the lower dose produced a prolongation of the QTc interval not seen with the 1.25 mg dose. It is difficult to draw any conclusions about increased safety of the 0.625 mg dose in patients 6-11 months of age, since it would be reasonable to believe that if this was a dose effect, it would also be seen in patients 12-23 months of age.***

3) **There were two patients, both in the 0.625 mg dose group who developed adverse events. All adverse events were described as treatment-emergent adverse events if: 1) the adverse event occurred for the first time on or after the first day of treatment; 2) the adverse event began prior to treatment but increased in severity while on treatment; or 3) the adverse event began within 30 days after treatment was stopped. A 23 month old patient developed loose stools, that were mild and considered possibly related to the study drug. A 10 month old patient had teething pain, which was mild and considered unrelated to the study drug. There were no serious or unexpected adverse events. (v1, p18).**

4) **There were no clinically significant changes in any laboratory parameter, with the possible exception of one 6 month old African-American female who had an SGOT of 48 IU/L at baseline which increased to 80 IU/L after administration of 0.625 mg of desloratadine.**

5) **Based on correction of total body clearance for surface area, the calculated dose for patients 6-11 months of age was 1.01 mg and for patients 12-23 months of age was 1.29 mg. Population PK analyses showed that to achieve exposure of desloratadine comparable to that seen after the administration of 5 mg in adults, patients 6-11 months required a dose of 1 mg and patients 12-23 months required a dose of 1.25 mg.**

CONCLUSIONS: The sponsor has selected a dose for patients 6-11 months of age based on comparison with data obtained in older patients, specifically adult patients 19-45 years of age, rather than based on study of that dose in this patient population. In this study, a dose of 0.625 and a dose of 1.25 mg were evaluated in patients 6-11 months of age. Based on the higher mean Cmax obtained after a dose of 1.25 mg in this age group (2.22 ng/mL) compared with patients 12-23 months of age (2.11 ng/mL) and adults (1.94

ng/mL), the sponsor concluded that a dose of 1.25 mg was inappropriate for this age group. As a result of this information, a dose of 1 mg per day was safely administered to patients 6-11 months of age for a period of 15 days in study 1368 and supports the selection of a 1 mg per day dose for patients 6-11 months of age. In addition, a dose of 0.625 mg produced a lower mean Cmax in patients 6-11 months of age (1.20 ng/mL) than the recommended dose for patients 12-23 months of age (2.11 ng/mL) or for adults (1.94 ng/mL). The mean AUC, however, that was obtained after a dose of 1.25 mg was slightly less (40.2 ng.hr/mL) than was seen after the recommended dose for patients 12-23 months of age (42.7 ng.hr/mL) and after the recommended dose for adults (43.2 ng.hr/mL). The sponsor has not submitted PK data for patients 6-11 months of age excluding poor metabolizers. Nevertheless, the dose selected by the sponsor for patients 6-11 months of age is reasonable based on the PK data from study 1341 and the safety data from study 1368 and is, therefore, acceptable.

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/s/

Richard Nicklas
5/14/03 11:20:56 AM
MEDICAL OFFICER

Eugene Sullivan
5/14/03 11:26:54 AM
MEDICAL OFFICER

DIVISION DIRECTOR'S MEMORANDUM

Date: May 14, 2003

To: NDA 21-563

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

Product: Clarinex (desloratadine) Syrup

Applicant: Schering-Plough Corporation

Administrative and Introduction

This memorandum summarizes the review of a pediatric supplement submitted by Schering in response to the Agency's pediatric study written request for desloratadine. The application was received on December 4, 2002, and the PDUFA action due date is June 4, 2003. The drug substance desloratadine is approved for marketing in the United States in two 5 mg oral formulations, a standard tablet, and an orally disintegrating tablet. Desloratadine is approved for use in allergic rhinitis (seasonal and perennial) and chronic idiopathic urticaria in patients 12 years of age and older a dose of 5 mg tablet once daily.

The pediatric study written request for desloratadine asked for two pharmacokinetic studies and two safety studies, one pair in subjects 2 to 11 years of age, and another pair in subjects 6 months to <2 years of age. In a previous application Schering submitted the results of studies covering the 2 to 11 year age group. Those studies were conducted with a syrup formulation. The Division took an approvable action on that application because of various deficiencies, including chemistry and manufacturing deficiencies, and safety concerns for some children who metabolize desloratadine slowly that results in a high exposure of desloratadine in those children. With this application, Schering submitted the results of a pharmacokinetic study and a safety study in children 6 months to <2 years of age. This completes the pediatric written request studies, and pediatric exclusivity for desloratadine was granted on February 12, 2003. This application does not address the deficiencies identified in previous review of desloratadine syrup application.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

Several CMC deficiencies were identified during previous review of desloratadine syrup application. All US manufacturing facilities related to this application also do not have an acceptable EER status. These are identified in Dr. Peri's review dated May 7, 2003. Schering is aware of these deficiencies and has not addressed them with this application.

Clinical Pharmacology and Biopharmaceutics, and Clinical Safety
This submission is comprised of two studies, one pharmacokinetic study, and one safety study. These studies are reviewed in detail in Dr. Lee's Clinical Pharmacology and Biopharmaceutics review, and in Dr. Nicklas's Medical Officer review. Dr. Sullivan also comments on these studies in his Medical Team Leader Memorandum. The reviewers have concluded that the pharmacokinetics and safety of desloratadine has been adequately assessed in children ages 6 months to <2 years and I concur with that assessment. Brief comments are made on the two studies below.

The pharmacokinetic study (Study 1341) was conducted in 58 children 6 months to <2 years of age to assess the desloratadine exposure following single-dose administration of the syrup formulation at two dose levels, 0.625 mg and 1.25 mg. Sparse sampling approach was utilized in this study and a population pharmacokinetic analysis was performed. The results were compared to the data from previous studies in children and adults. Based on the results of the study, Schering concluded that the optimum dose of desloratadine would be 1 mg for children ages 6-11 months, and 1.25 mg in children 12 months to <2 years. Dr. Lee of the Office or Clinical Pharmacology and Biopharmaceutics reviewed these data and concur with the Applicant's conclusion.

The safety study (Study 1368) was a randomized, multi-center, double-blind, placebo-controlled 15-day study conducted in 225 subjects ages 6 to 11 months who were considered to be candidates for antihistamine therapy or who had received antihistamines in the past. The dose of desloratadine was based on the results of the pharmacokinetic study. Subjects 6-11 months old received 1 mg once a day, and subjects 12 months to <2 years old received 1.25 mg once a day. Efficacy was not evaluated in this study. Desloratadine was well tolerated as assessed by recording of adverse events, vital signs, physical examination, and ECG. However, the ECG data were not particularly useful. The machines used for recording ECG was not standardized across centers, and the ECGs were not read in an ideal fashion. These are discussed in detail in Dr. Sullivan's memorandum. The final ECG reading did not reveal any safety signals. Cardiac safety of desloratadine has been previously extensively studied in adults and in older children. Thus, accurate ECG data, although desirable, is not absolutely essential to support the safety of desloratadine in this age group.

The two studies that Schering has conducted in this age group, the pharmacokinetic study to choose appropriate dose, and the safety study to support the safety of that dose are considered by this Division to be a reasonable program to support approval for a systemically active drug such as an antihistamine. The disease characteristics of allergic rhinitis and chronic idiopathic urticaria are similar in adults and children, and the response to therapy is also expected to be similar. Therefore, efficacy of desloratadine can be extrapolated from adults to children. However, seasonal allergic rhinitis is generally not diagnosed below the age of 2 years, therefore, when desloratadine is approved, the indication for perennial allergic rhinitis may be carried down to 6 months, but the indication for seasonal allergic rhinitis would be limited to ages 2 years and above.

Pharmacology and Toxicology
There are no outstanding preclinical issues. All preclinical pharmacology and toxicology studies were cross-referenced to IND 55364 and NDA 21165.

Data Quality, Integrity, and Financial Disclosure
No DSI audit of clinical study sites was requested or conducted for this application. Desloratadine is not a new molecular entity, and during the review process of this application no irregularities that would raise question on the data integrity were found. No ethical issues are present. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present. The applicant submitted an acceptable financial disclosure statement and statements of good clinical practice.

Pediatric Consideration
Desloratadine tablet is currently approved for use in allergic rhinitis (seasonal and perennial) down to the age of 12 months. Schering has developed a syrup formulation of desloratadine and has studied that formulation for the ages 6 months to <12 years. With this application, the pediatric program for desloratadine can be considered to be complete. At some time in future, when the outstanding deficiencies with desloratadine are resolved, desloratadine syrup can be approved down to the age of 6 months for chronic idiopathic urticaria and perennial allergic rhinitis. Seasonal allergic rhinitis is generally not considered to be present below 2 years of age.

Product Name
The proprietary name of Clarinex is approved and used by Schering for products containing desloratadine. This product name has been previously reviewed and approved by the Agency.

Labeling
Schering has proposed to incorporate the results of the pharmacokinetic study and safety studies in appropriate sections of the product label. Various disciplines have reviewed the proposed language of the label, and comments will be communicated to Schering in the action letter. Final labeling language will be worked out with Schering when the syrup formulation is ready for marketing approval.

The recommended dose of 1 mg and 1.25 mg would require 2 ml and 2.5 ml, respectively, of the formulation to be measured. This requires a precise discriminating measurement of small volumes. Schering will need to address how this instruction will be conveyed in a reasonable way so that the parents or caregiver can dose the children appropriately.

Recommendation and Action

The pharmacokinetic and safety studies did not identify any new safety signals for desloratadine in children down to the age of 6 months. The result of the pharmacokinetic and clinical safety studies can be incorporated into the product label. However, before the syrup formulation can be marketed in the United States, various deficiencies identified in previous review of the syrup formulation must be resolved. Therefore, the action on this application will be APPROVABLE.

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/s/

Badrul Chowdhury
5/14/03 03:37:25 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMORANDUM

Date: May 12, 2003
To: NDA 21-563
From: Eugene J. Sullivan, MD, FCCP
Acting Medical Team Leader
Division of Pulmonary and Allergy Drug Products (HFD-570)
Subject: Secondary medical review of NDA for Clarinex (desloratadine) Syrup for use in children aged 6 months to 2 years

Administrative

This NDA is submitted to support the approval of Clarinex (desloratadine) Syrup in children 6 months to 2 years of age. The PDUFA action due date on this application is June 4, 2003. The drug substance, desloratadine, has already been approved in two 5mg formulations (a standard tablet and a rapidly disintegrating tablet ["Reditab"]), for allergic rhinitis (seasonal and perennial) and chronic idiopathic urticaria in patients 12 years of age and older. The approved dose for this age range is 5mg daily.

The syrup formulation was the subject of NDA 21-300, which was submitted for the use of Clarinex Syrup in-patients aged 2 to 11 years. The proposed dose in NDA 21-300 was 2.5 mg in patients 6-11 years of age, and 1.25 mg 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 with the 5mg dose in adults and adolescents. Although the Division agreed with this approach, and agreed that the exposures were comparable, an Approvable action was taken. One specific issue precluded a clinical recommendation for approval. The data indicated that a subset of children exhibit very poor metabolism of desloratadine and are thus exposed to significantly greater levels of desloratadine. The Application did not contain sufficient evidence of safety associated with these higher exposures. In addition to this clinical concern, various CMC deficiencies were identified, which precluded approval. The Applicant is currently working to adequately address the clinical safety concern and the CMC deficiencies.

The two clinical studies included in this application were performed in partial fulfillment of a Written Request for Pediatric Studies, which was issued on June 6, 2000, and amended on October 19, 2000, December 5, 2000, and May 7, 2001. The Written Request specified 4 clinical studies: 1) a safety study in patients 6-11 years of age; 2) a safety study in patients 2-5 years of age; 3) a pharmacokinetic and safety study in patients aged 6-23 months; and 4) a safety study in patients aged 6-23 months. The first two studies were submitted in NDA 21-300. The latter two studies are submitted with this application. At its February 12, 2003 meeting, the Pediatric Exclusivity Board determined that pediatric exclusivity would be granted.

Chemistry, Manufacturing, and Controls

Clarinex syrup contains 0.5 mg/ml desloratadine, and 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, granulated sugar, natural and artificial flavor for bubble gum, and FDC Yellow #6 dye.

During the review of NDA 21-300, the Division CMC review team identified several deficiencies that precluded approval of the syrup formulation. These deficiencies were conveyed to the Applicant in the action letter. Because the Applicant has not yet responded to the action letter for NDA 21-300, a CMC review of the current application was not undertaken. The action letter for the current application will make reference to the deficiencies that were identified previously.

Pharmacology, Toxicology and Biopharmaceutics

This application did not contain any new pharm/tox data. The Division's pharmacolgy/ toxicology reviewer (Dr. Hao) reviewed the previously submitted pharm/tox data on this drug substance as well as the parent substance, loratadine, to verify that the proposed doses in the proposed population are adequately supported. Dr. Hao concluded that the existing preclinical data provide adequate support. Dr. Hao also verified that the labeling language describing the dose comparison between the proposed dose and the dose studied in the carcinogenicity studies was appropriate.

A Biopharmaceutics review was performed by Dr. Sue-Chih Lee. Her findings are discussed in the Clinical Studies section below.

Clinical Studies

The clinical program for this application was based on the assumption that the efficacy of desloratadine in the proposed population could be assumed if it could be established that the proposed clinical dose results in systemic exposure that is comparable to the exposure achieved with the approved dose (5mg daily) in adolescents and adults. This approach is reasonable and is consistent with the Agency's Guidance for Industry entitled "Allergic Rhinitis: Clinical Development Programs for Drug Products." Also, given comparable exposures, the relatively large safety database that has been accrued in older patients can be used as supportive safety data for this application.

Two clinical studies were submitted. The first study was a single dose pharmacokinetic study to establish the most appropriate dose(s) in this age group (Study 1341). The second study was a 15-day multiple dose study to establish the safety of the proposed doses (Study 1368).

Study 1341

Study 1341 was a randomized, parallel group, open label study in which 58 male and female patients aged 6-23 months were exposed to a single dose of desloratadine of either 0.625mg or 1.25mg following a 2-hour fast. Patients were stratified into two age groups,

6-11 months and 12-23 months. Sparse sampling and population pharmacokinetic techniques were used in order to minimize blood sampling. Plasma desloratadine concentration data from DL syrup administered to adult subjects under fasting conditions in a previous study (Protocol P01341) were used for comparison. The Applicant concluded that the data from this study suggested that the dose that would achieve exposures that most closely approximate the exposures in adults following a dose of 5mg differed in the two age groups. The optimum dose was calculated to be 1mg in the 6-11 month age group, and 1.25mg in the 12-23 month age group. These data were reviewed by the reviewer from the Office of Clinical Pharmacology and Biopharmaceutics, who concurred with the Applicant's conclusion. On the basis of these results, the Applicant undertook Study 1368 to examine the safety of these doses.

Study 1368

Study 1368 was a multi-center, multinational, randomized, double-blind, placebo controlled, parallel group, 15-day safety study in children aged 6-23 months. Subjects who were aged 6-11 months received desloratadine 1mg daily, and subjects who were aged 12-23 months received desloratadine 1.25mg daily. A total of 255 subjects, all of whom were considered candidates for antihistamine treatment or who had received antihistamines in the past, were enrolled. A total of 66 subjects were treated with desloratadine 1mg daily, 65 subjects were treated with desloratadine 1.25mg daily, and 124 subjects were treated with placebo.

Efficacy was not evaluated in Study 1368. Safety evaluations included the following: adverse events (captured in daily diaries), ECGs (performed at baseline and on Days 8 and 15, 1-3 hours after drug administration), and physical examination and vital signs (performed at baseline and on Days 8 and 15).

There were no deaths or life-threatening adverse events in any group, and there were no serious or severe adverse events in the active treatment groups. Common adverse events occurring more frequently in the desloratadine groups were: diarrhea (17.6% vs. 9.7%), fever (14.5% vs. 7.3%), upper respiratory infection (16.0% vs. 11.3%), cough (10.7% vs. 8.1%), otitis media (4.6% vs. 3.2%), pharyngitis (3.8% vs. 0.8%), bronchitis (3.8% vs. 0.8%), and insomnia (3.1% vs. none). Among these, the adverse events of diarrhea, fever, otitis media, upper respiratory infection, and bronchitis were particularly evident in the youngest age group. There were no significant findings in terms of physical examination or vital signs.

The ECG data from this study are problematic. The study was designed with insufficient attention to the quality of the ECG data, such that there was significant variability in terms of the ECG equipment used and the methodology used to measure the ECG intervals. Study sites used ECG equipment from 11 different manufacturers, and there were almost as many models as there were sites. The ECG equipment ranged in technology from 12-channel to single channel instruments. In order to measure the ECG intervals, some sites relied on machine-read measurements and others performed manual readings, either by counting squares on the printout or by using an ECG ruler. The

Applicant only became aware of these limitations after unblinding the database, at which time appreciable site-to-site variability in the data was observed. On the basis of that observation, the Applicant decided to rely on a centralized re-reading of the ECG data, which had been performed by [redacted]. However, in the process of QA/QC of the [redacted] the Applicant identified two obvious and significant data point errors. This called into question the adequacy of the QA/QC procedures in place at [redacted] subsequently acknowledged that they had not followed their QA/QC standard operating procedures and could not provide documentation of what QA/QC procedures had been performed. Based on this discovery, the Applicant contracted with [redacted] to perform a blinded re-read of the ECG data. Although the data from the [redacted] re-read did not suggest any ECG drug effects, including QTc interval, the quality of the data and the circumstances of its analysis preclude firm conclusions.

Efficacy Assessment

This application did not contain efficacy data. Desloratadine has been demonstrated to be effective in the treatment of allergic rhinitis and chronic idiopathic urticaria in adults and adolescents aged 12 years and older. The Division has previously determined that there is adequate rationale to allow extrapolation of established efficacy of antihistamines in adults and adolescents down to young children based on pharmacokinetic comparability. Study 1341 established that the proposed doses (1mg daily in children 6-11 months old, and 1.25mg daily in children 12-23 months old) result in exposures that are comparable to the exposures at the currently approved dose.

Safety Assessment

An extensive body of data regarding the safety of desloratadine as well as the parent molecule, loratadine, has previously been reviewed by the Division in the context of other applications. This prior data, which involved older patient populations, can be used to generally support the safety of desloratadine.

The two clinical studies submitted with this application more specifically address the safety of desloratadine in the proposed population. Although these data are considered adequate to support approval of this application, two issues should be noted. The first issue is that in Study 1368, certain adverse events were notably more common in the younger age subgroup (6-11 months). These adverse events include diarrhea, fever, otitis media, upper respiratory infection, and bronchitis. The Applicant has proposed labeling language that specifies the adverse event data for the entire population (6 –24 months). Given that the recommended dose differs between the two age subgroups, and that there was an apparent age effect in regard to the frequency of adverse events, the label should specify the adverse event data for the two age subgroups separately. The second issue is that the ECG data from Study 1368 are of very limited value. Although the final re-read by [redacted] did not suggest a safety signal, it is clear from the course of events that the data are flawed. There was inadequate standardization of the ECG procedures and there were two post-hoc analyses of the data. Therefore, while the data do not raise any specific concern, it should be acknowledged that firm conclusions could

not be derived from the data. However, extensive prior experience with the drug has not suggested that desloratadine is associated with any significant cardiac effects.

Recommendation

The data submitted allow reasonable extrapolation of the efficacy previously generated in older patients, and, with one exception, establish an acceptable safety profile. The one exception refers to the previously identified phenomenon of poor metabolism in a subset of children. This issue was identified during the review of NDA 21-300, and was one of the reasons for the Approvable action taken on that application. The Applicant is currently working to address the issue; however, because this issue is still outstanding, the clinical recommendation for the current application is for an Approvable action. In order to achieve a clinical recommendation for Approval, the Applicant will need to provide data establishing the safety of desloratadine in the subset of pediatric patients who exhibit poor metabolism. In addition to the clinical concern discussed above, outstanding CMC concerns, which preclude approval, remain.

Labeling Issues

The Applicant has proposed labeling language based on the data in this submission. This language was reviewed and preliminary comments will be sent to the Applicant in the action letter. The labeling issues identified by the Division include the need to express the adverse event data by age subgroup (6-11 months, and 12-23 months), and the need to include language referring to the absence of data in children with renal or hepatic impairment. Additional labeling revisions may be necessary once additional data regarding poor metabolizers is submitted and reviewed. Final labeling will be agreed upon once the syrup formulation is deemed acceptable for marketing approval.

The drug substance, desloratadine, has already been approved for allergic rhinitis (seasonal and perennial) and chronic idiopathic urticaria (CIU). The current application, along with NDA 21-300, is intended to support the use of Clarinex Syrup in younger children. The Division has previously taken a position that drugs to treat CIU and perennial allergic rhinitis may be approved down to 6 months of age. However, because the diagnosis of seasonal allergic rhinitis requires a recurrent pattern of seasonal symptoms, drugs to treat seasonal allergic rhinitis may be approved only down to 2 years of age. Therefore, once approved, the CIU and perennial allergic rhinitis indications will be carried down to 6 months of age, and the seasonal allergic rhinitis indication will be carried down to 2 years of age.

The proposed doses of desloratadine (1mg and 1.25mg) will require accurate measurement of very small volumes (2ml and 2.5ml). This submission did not address how this will best be accomplished. The Applicant will be informed that this issue must be addressed in future submissions.

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/s/

Eugene Sullivan
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