CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-563

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21-563
Submission Date:	12/04/2002
Brand Name:	Clarinex™ Syrup
Generic Name:	desloratadine
Dosage Form; Strength(s):	Syrup, 0.5 mg/mL
Route of Administration:	Oral
Reviewer:	Sue-Chih Lee, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph.D.
OCPB Division:	Division of Pharmaceutical Evaluation II
OND Division:	Division of Pulmonary & Allergy Drug Products (HFD-570)
Sponsor:	Schering-Plough
Submission Type :	Original application Pediatric Use (6 months to <2 years)
Indication:	Treatment of seasonal allergic rhinitis and chronic idiopathic urticaria
Proposed Dosing regimen:	6 mo.-1 yr: 1.00 mg once daily 1-2 yr: 1.25 mg once daily

1. EXECUTIVE SUMMARY

In this submission, the sponsor seeks approval of Clarinex® Syrup for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in pediatric patients aged 6 months to less than 2 years. This drug product is the subject of an "approvable" NDA (NDA 21-300), which seeks the same indication but is for pediatric patients aged 2-11 years. Clarinex® Tablets and syrup have been approved for use in adults and children 12 years and older with a dosing regimen of 5 mg once daily .

In support of this application, the sponsor submitted a pharmacokinetic study (Study # P01341) and clinical safety data from a 15 day, Phase III study in children aged 6 months to <2 years conducted in response to the Written Request dated June 6, 2000 and amended on October 19, and December 5, 2000, and May 7, 2001. Recently, the sponsor submitted the preliminary report of another clinical study that assessed the safety in poor metabolizers of desloratadine. The full report is expected to be submitted to the Agency soon.

PK study P01341 was conducted to assess desloratadine exposure in pediatric subjects 6 months to <2 years following single-dose administration of the syrup 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 sponsor determined desloratadine dose in the intended pediatric age group based on the oral clearance estimates obtained from the analysis so that exposure to desloratadine would be comparable to that in adults.

The dosage regimen proposed by the sponsor is 1 mg once daily for children 6 months to <1 year, and 1.25 mg once daily for children 1 year to <2 years. The proposed dosing regimen is acceptable. (Note: In NDA 21-300, the sponsor's proposed dosage regimen is 1.25 mg QD for children aged 2-5 years, and 2.5 mg QD for children aged 6-11 years.)

1.1 RECOMMENDATION

From the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics, the Human Pharmacokinetics and Biopharmaceutics section of the NDA is acceptable. The labeling comment for the DOSAGE and ADMINISTRATION section as shown on page 8 should be communicated to the sponsor.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation II

RD/FT Initialed by Emmanuel Fadiran, Ph.D. _____

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3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Sponsor's analysis: The sponsor conducted a population pharmacokinetic analysis using data from a pediatric PK study (#P01341) and adult data from Study P00213. A one-compartment model with first order absorption and first order elimination was used to characterize desloratadine PK. The population mean parameter estimates are presented in Table 1. Based on the population mean clearance estimates, the pediatric dose that would provide a similar exposure as that in adults following a 5-mg dose was determined to be 1.01 mg for pediatric patients aged 6 months to <1 year, and 1.29 mg in children 1 year to <2 years of age.

Table 1. Population Mean (±SE) PK Parameters of DL and Predicted Dose by Age Group

Age Group	V/F, L (%SE)	Ka, hr^{-1} (%SE)	CL/F, L/hr (%SE)	Predicted Dose[a] (mg)
6 Mo. to < 1 Yr	470 (15)	0.922 (0.12)	27.8 (35)	1.01 (0.66-1.37)
1 to <2 Yrs	499 (13)		35.5 (51)	1.29 (0.63-1.96)
Adults	2249 (23)		137 (58)	-
Intersubject Variability, %CV	32 (27)	36.6 (48)	69 (29)	-

[a] [a]Calculated as CL_{ped}/CL_{adult} * 5 mg

Reviewer's analysis: This reviewer repeated the sponsor's analysis with some modifications and similar results were obtained. The diagnostic plots indicated that the structural model could be improved. Examination of PK data from previous studies in adults and older children with dense sampling suggested that desloratadine follows more closely a two-compartment PK model. Therefore, this reviewer performed a population PK analysis using the two-compartment model. Available data for the syrup formulation from 6 studies were combined in the analysis. Body weight was found to be a significant factor for all clearance and volume terms in the model.

Poor metabolizers: The sponsor identified poor metabolizers of desloratadine based on the AUC ratio of the 3-OH metabolite compared to the parent compound. Subjects with a ratio of ≤0.1 are considered to be poor metabolizers. Subjects with a ratio of close to 0.1 (up to 0.13) were considered to be potential poor metabolizers. These subjects were lumped into one category

(designated as "slow metabolizers") in this reviewer's analysis. It was found that mean clearance for "slow metabolizers" was approximately 25% that of the extensive metabolizers.

Individual Bayesian estimates for PK parameters were used to compute AUC and Cmax for each subject. Both AUC and Cmax values were normalized to the proposed dose and compared to adult values following a 5-mg dose. In this study, the percentage of poor metabolizers in each age group may not represent the true picture in the general population. Therefore, the comparison between children and adult values were carried out with and without slow metabolizers.

Comparison of exposure measures between children and adults: For the 6 month to <1 year age group, the median Cmax and AUC at the proposed dose level (1 mg) were comparable to the adult values but the AUC in these children was more variable than in the adult group. For the 1-2 year age group, the AUC was generally lower than the adult values while Cmax in these children was somewhat higher than the adult values. This was true whether slow metabolizers were included or excluded from the analysis. Since no exposure- response relationship for efficacy or safety was established, it is not known whether dose in the 1-2 year age group can be increased to ensure efficacy without jeopardizing the safety. To consider both AUC and Cmax under these circumstances, the sponsor's proposed dose is deemed acceptable. This conclusion was reached whether a one-compartment model or a two compartment model was used in the population PK analysis. Apparently, the one-compartment approximation resulted in an acceptable error for the purpose here although it systematically underpredicted Cmax.

4. QUESTION BASED REVIEW

4.1 Pharmacokinetics

Q1. From the clinical pharmacology and biopharmaceutics standpoint, did the sponsor conduct all the required studies?

YES.

Although only one PK study (P01341) was provided in this submission, a food effect study for the syrup formulation was previously submitted to another NDA (21-300). High-fat meal had no effect on the bioavailability of desloratadine from the syrup formulation based on the review by Dr. Sandra Suarez-Sharp of DPEII. The to-be-marketed formulation was used in study P01341 and, therefore, there are no bioequivalence issues.

In vitro dissolution testing was not conducted because desloratadine is completely dissolved in the syrup formulation and as such there is no need to conduct a dissolution test for this drug product.

Q2. Was the assay method used in the pharmacokinetic study adequately validated?

YES.

An-HPLC/MS/MS method was employed for assay of desloratadine and its metabolite (5-OH desloratadine) in plasma samples. The method was adequately validated.

Table 2. Assay Validation Results for Desloratadine and the 3-OH Metabolite.

	Desloratadine	**5-OH Desloratadine**
Linearity:	0.025 -10.0 ng/mL	0.025 -10.0 ng/mL
	$r>0.996$	$r\geq0.998$
Accuracy (%bias):	$\leq 5.51\%$	$\leq 2.54\%$
Precision (%CV):	$\leq 7.09\%$	$\leq 8.47\%$
Specificity:	No interference observed with blank plasma	No interference observed with blank plasma

Q3. Did the sponsor characterize the pharmacokinetics of the parent compound and active metabolite (3-OH desloratadine) in children 6 months to <2 years of age?

YES for the parent compound, and PARTIALLY for the 3-OH metabolite.

Sparse pharmacokinetic data for desloratadine, but not for the 3-OH metabolite, was subject to a population PK analysis. Although the 3-OH metabolite is active, its potency and plasma concentrations are lower than those observed for the parent compound. Therefore, it is not critical to characterize the pharmacokinetics of the metabolite. The sponsor did assay plasma samples for the 3-OH metabolite to identify poor metabolizers and potential poor metabolizers of desloratadine and to roughly assess dose proportionality for the metabolite.

Q4. Is the proposed dosing regimen in children aged 6 months to <2 years supported by the pharmacokinetic data?

YES.

The sponsor's proposed dosage regimen is 1 mg in children 6 months to <1 year of age, and 1.25 mg in children 1 to <2 years of age. These regimens were determined based on the results of a population PK analysis with the objective of attaining similar desloratadine exposure in children as compared to adults following 5 mg once daily administration of the syrup. In the sponsor's analysis, a one-compartment model was used to describe desloratadine PK. To better characterize desloratadine PK, this reviewer conducted a population analysis using a two-compartment model. Available data for the syrup formulation from six studies were pooled in the analysis.

The individual Bayesian estimates for PK parameters obtained from the analysis were used to compute individual AUC and Cmax values expected at the proposed dose level (Table 3).

Table 3: Mean (±SD) PK parameter values based on individual Bayesian predictions from this reviewer's analysis (AUC and Cmax values are normalized to the proposed dose level for pediatric subjects)

	Mean (CV%)			Median		
Parameter[a]	**6 mo -<1yr Dose = 1.0 mg N=20**	**1 - <2 years Dose=1.25 mg N=38**	**Adults Dose=5 mg N=30**	**6 mo -<1yr Dose = 1.0 mg**	**1 - <2 years Dose=1.25 mg**	**Adults Dose=5 mg**
Cmax (ng/mL)	2.20 (37)	2.42 (36)	2.26 (54)	1.92	2.30	1.86
AUC(I) [ng.hr/mL]	68.1 (106)	72.3 (206) 49.5 (103)[a]	47.8 (75)	47.7	34.8	38.6
Ka (hr^{-1})	0.89 (25)	0.83 (25)	1.25 (39)	-	-	-
Lag Time, hr	0.37 (34)	0.42 (95)	0.27 (52)	-	-	-
CL/F (L/hr)	29 (70)	38.6 (54)	136.7 (46)	21.1	36.0	129.6
V_c/F	337 (33)	371 (34)	2059 (39)	-	-	-
V_p/F (L)	267 (65)	249 (33)	1348 (27)	-	-	-

[a]Subject #43 removed from the analysis because the concentration-time data for this subject showed disparity beyond what could be explained by normal analytical errors.

Both AUC and Cmax values are also presented in the Box plots below (Fig. 2) for easy comparison of desloratadine exposure among the three age groups. Desloratadine AUC in children aged 6 months to <1 year was more variable compared to the other two age groups, but the median AUC and Cmax at the proposed dose level were comparable to the adult values. For the 1 to <2 year age group, the AUC was generally lower than the adult value while Cmax for this group was somewhat higher than that for the adult group. Since exposure-response relationships for efficacy and safety have not been established, it is not known whether the dose for this age group can go higher than 1.25 mg to ensure efficacy without adversely affecting the safety. To consider both AUC and Cmax under this circumstance, the 1.25 mg dose appears reasonable for the 1 to <2 year age group.

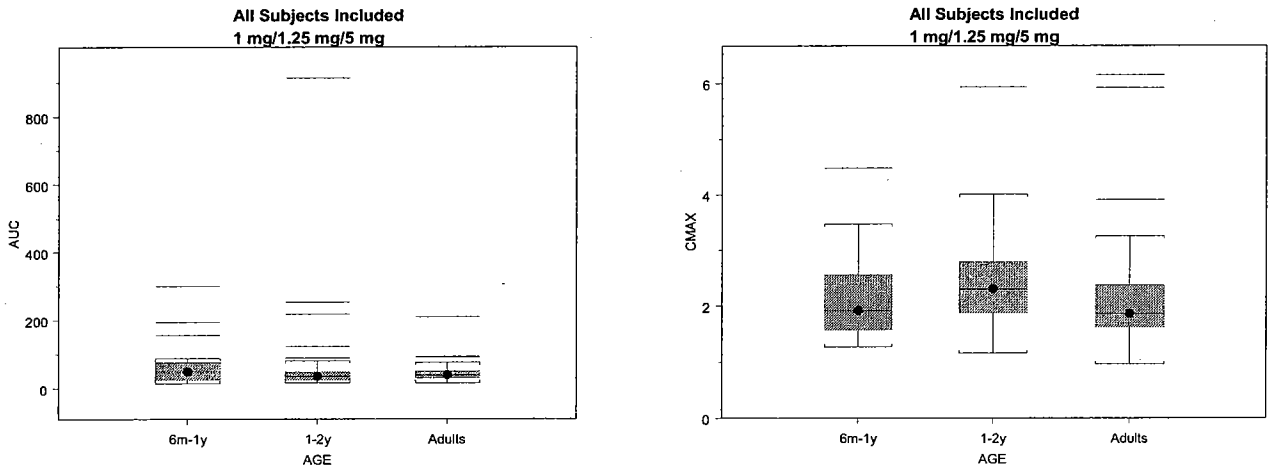
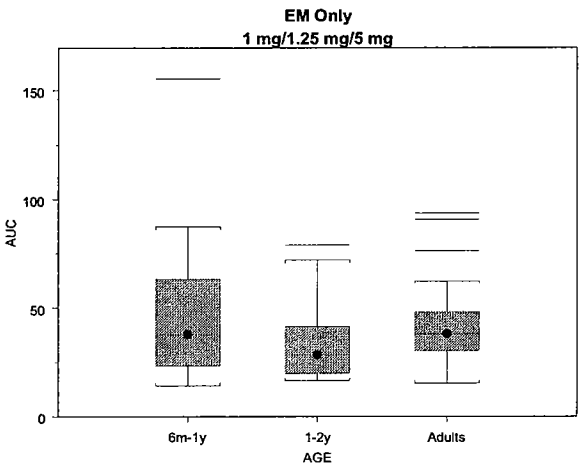
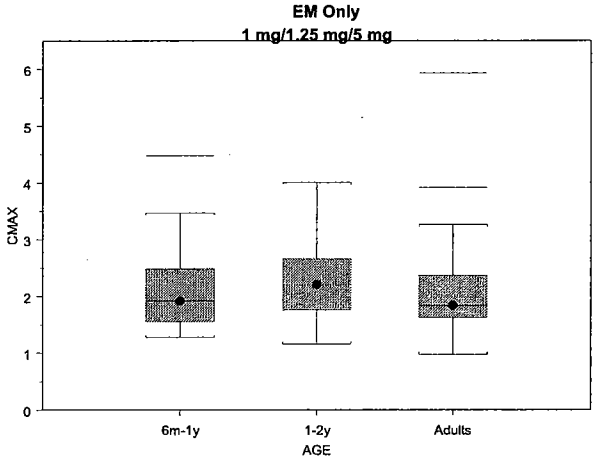


Figure 2. Box plot s comparing desloratadine AUC (left panel) and Cmax (right panel) in children 6 months to <1 year (1 mg dose), children 1 to <2 years (1.25 mg dose), and adults (5 mg dose)

In this study, the percentage of poor metabolizers in each age group may not be representative of the true population. By lumping poor metabolizers and potential poor metabolizers (designated as slow metabolizers, or SM) as one group in covariate analysis, it was found that the mean apparent clearance for slow metabolizers was only 25% that of the extensive metabolizers. Box plots of AUC and Cmax values for extensive metabolizers at the proposed dose level are presented for the three age groups (Figure 2). As previously observed, the AUC for the 1 to <2 yr group was generally lower than the adult values whereas the Cmax values for this group were higher than the adult values. Again, the 1.25 mg dose appears reasonable for children aged 1 to <2 years.

Figure 2. Box plot for extensive metabolizers comparing desloratadine AUC (upper panel) and Cmax (lower panel) in children 6 months to <1 year (1 mg dose), children 1 to <2 years (1.25 mg dose), and adults (5 mg dose)





Statistics for AUC	
AGE:6m-1y	
Min:	14.23
1st Qu.:	23.71
Median:	37.63
3rd Qu.:	62.66
Max:	155.39
N:	18
AGE:1-2y	
Min:	16.47
1st Qu.:	21.93
Median:	28.27
3rd Qu.:	40.09
Max:	78.97
N:	31
AGE:Adults	
Min:	15.43
1st Qu.:	30.10
Median:	38.05
3rd Qu.:	48.20
Max:	93.53
N:	29

Statistics for CMAX	
AGE:6m-1y	
Min:	1.28
1st Qu.:	1.56
Median:	1.92
3rd Qu.:	2.48
Max:	4.48
N:	18
AGE:1-2y	
Min:	1.16
1st Qu.:	1.82
Median:	2.20
3rd Qu.:	2.65
Max:	4.01
N:	31
AGE:Adults	
Min:	0.97
1st Qu.:	1.62
Median:	1.84
3rd Qu.:	2.37
Max:	5.93
N:	29

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6. APPENDICES

6.1 Sponsor's Proposed Package Insert

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6.2 Individual Study Review

Protocol P01341: SCH 34117: Single-Dose Pharmacokinetic Study of Desloratadine Syrup in Pediatric Subjects ≥6 Months to 2 Years of Age with Allergic Disorders

The study design of Protocol P01341 is summarized in Table 4.

Table 4: Protocol P01341 Summary

Investigator	[redacted]
Study Center	[redacted]
Study Period	17 JUL 2000 to 29 JUL 2000
Objective	To assess the oral clearance of desloratadine (DL) syrup in subjects ≥6 months to <2 years of age in order to determine the appropriate dosage of DL in such subjects. The appropriate dosage in pediatric subjects will have comparable concentrations and exposure of DL to that seen in adolescents and adults given 5 mg of DL.
Methodology	*Study design*: single-dose, randomized, stratified, parallel-group, open-label *Subjects*: 58 pediatric subjects (28 male and 30 female; 19 Caucasians & 39 Blacks) were enrolled and stratified into 2 groups according to their age (≥6 months to <1 year and ≥1 year to <2 years). *Treatments*: Each subject was randomized to either 0.625 mg (1.25 mL) or 1.25 mg (2.5 mL) of DL syrup. The study drug was given following a 2-hr fast. *Number of subjects:* Dose / 6 mo-1 yr / 1-2 yrs 0.625 mg / 10 / 19 1.25 mg / 10 / 19
Sampling	Within each treatment, the subjects were randomized to two different blood sampling schemes: A (1, 3, 6, 24, and 72 hrs postdose) B (2, 4, 8, 12, and 48 hrs postdose)
Inclusion Criteria	Male and female pediatric subjects between the age of ≥ 6 months to < 2 years and weighed between 7.7-15.5 kg who were a candidate for antihistamine therapy or had been treated with an antihistamine in the past. Subjects were to have normal or clinically acceptable physical examinations and ECGs. Routine laboratory tests had to be within normal limits for their respective age or clinically acceptable to the investigator/sponsor.
Test Product	Desloratadine syrup 0.5 mg/mL, oral, Batch No 53266-003-B
Assay	LC/MS/MS LLOQ: 0.025 ng/mL
Data Analysis	Population PK analysis was performed using data from this study and adult data from Protocol P00213 to generate the estimates of clearance (CL/F), volume of distribution (V/F), and other parameters. Cmax and AUC were estimated from Bayesian predictions for each individual.

Population PK Analysis

Data:
PK data for desloratadine were obtained from 2 studies: sparse data from the above study in pediatric subjects (Protocol #**P01341**) and rich data in adults from Protocol P00213. Altogether, there were 88 subjects with a total of 800 plasma samples. The sponsor conducted the population PK analysis using [redacted] Protocol P00213 was a single-dose, randomized

3-way crossover study in 30 healthy adult volunteers to determine the bioavailability of syrup formulation relative to the tablets and food effect on the syrup formulation. For this study, only the data for the syrup formulation under fasted conditions were used in the analysis.

Table 5: Description of Data

Protocol No.	Group	Age	Wt, kg	n	DL Dose (mg)	Number of DL Samples
P01341	1	≤6 mo - <1 yr (9.8±1.9 mo.)	9.60±1.20	10	0.625	50
	2	≤6 mo - <1 yr (9.7±1.4 mo.)	9.68±1.84	10	1.25	50
	3	1 - <2 yr (20.8±2.2 mo.)	12.0±1.45	19	0.625	95
	4	1 - <2 yr (19.9±3.1 mo.)	11.0±1.42	19	1.25	95
P00213	-	Adult (19-54 yrs)	-	30	5	510
Total	-	-	-	*88*	-	*800*

Poor metabolizers: Individual plasma DL and 3-OH DL (metabolite) concentration-time data were used to calculate the AUC from time 0 to the time of the final quantifiable sample using the linear trapezoidal method. Poor metabolizers were defined as those having an AUC ratio of 3-OH DL relative to DL of <10%. Based on this criterion, 4 subjects (#43, 46, 77 and 78) in the 1 year to <2 years age group were identified as poor metabolizers. In addition, two subjects (Subject Nos. 6 and 17) in the 6 months to <1 year age group and three subjects (Subject Nos. 49, 52, and 71) in the 1 year to <2 years age group had metabolite to parent ratios just outside the definition (<10%) of a poor metabolizer.

Model

The structural model was a one-compartment model with first order absorption and first order elimination without absorption lag time.

In the base model, CL/F, V/F, and Ka were assumed to be derived from a single distribution for all subjects regardless of their age. In the full model, CL/F and V/F were assumed to be different for each of the three age groups (6 months to <1 yr, 1 yr to <2 yr, and adults), ie, the individual parameter values are derived from the distribution for their respective age group. The population mean absorption rate constant (Ka) was based on adult data and fixed for all 3 age groups due to the absence of data in the absorption phase for the pediatric subjects. The intersubject variability for each PK parameter was modeled as an exponential error distribution. An exponential variance function ($\sigma^{2} \cdot e^{a|yij|}$) was used for the residual error model, where a is a constant and yij is predicted concentration for the ith subject at time j.

FOCE method was used in the model fitting. A statistically significant difference ($p<0.05$) was concluded for an added parameter if the change in the objective function (OBJF) was at least 3.9. Goodness-of-fit was assessed by examination of scatter plots of predicted versus observed concentrations with a line of unity and weighted residuals versus predicted concentrations.

Additional scatter plots of predicted (Bayesian) concentrations versus observed concentrations by age group were assessed. Based on the results, the full model was taken as the final model.

Results

Presented below are scatter plots of weighted residuals versus predicted concentrations and individual predicted (Bayesian) concentrations versus observed concentrations for the final model.

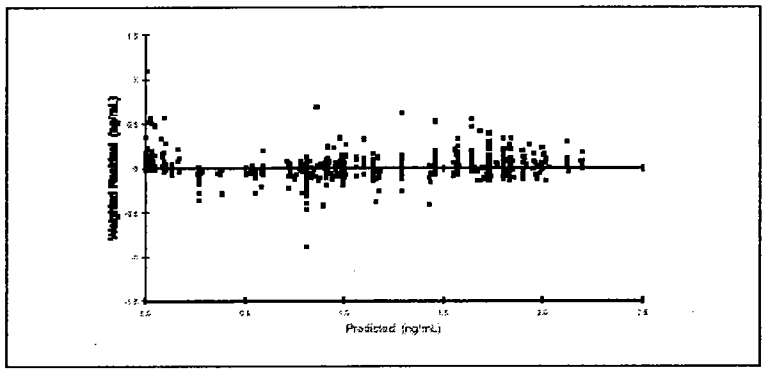


Figure 3: Weighted residuals versus Population predicted concentrations

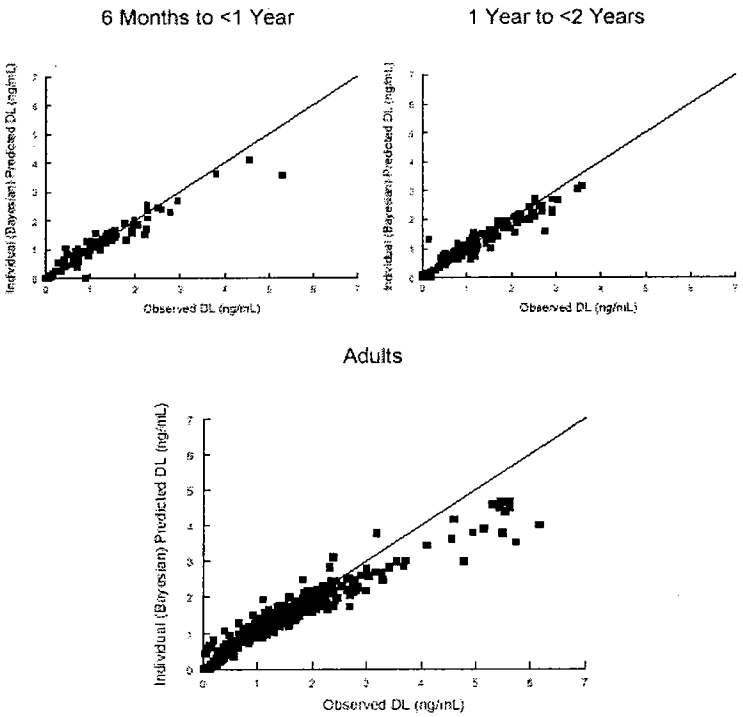


Figure 4. Individual Predicted Versus Observed DL Concentrations by Age Group

The population mean PK parameter estimates for desloratadine by age group as obtained from the population PK analysis are shown in the table below.

Table 6: Population Mean (±SE) PK Parameters of DL and Predicted Dose by Age Group

Age Group	V/F, L (%SE)	Ka, hr^{-1} (%SE)	CL/F, L/hr (%SE)	Predicted Dose (mg)
6 Mo. to < 1 Yr	470 (15)	0.922 (0.12)	27.8 (35)	1.01 (0.66-1.37)
1 to <2 Yrs	499 (13)		35.5 (51)	1.29 (0.63-1.96)
Adults	2249 (23)		137 (58)	-
Intersubject Variability, %CV	32 (27)	~~69 (29)~~[a] 36.6 (48)	~~37 (48)~~[a] 69 (29)	-
Residual Variability		~~σ^2 = 36;~~ [a] σ^2 = .00934 (36)	~~a = 16~~[a] a = 1.47 (16)	

[a]Correction made by this reviewer based on the sponsor's analysis output.

From the individual Bayesian estimates of PK parameters, individual AUC, Cmax and Tmax values were calculated. The following table presents the mean (%CV) and median parameter values for each age and dose group.

Table 7: Mean (%CV) and Median Bayesian Predicted DL Parameters by Age and Dose

Parameter[a]	6 mo. To <1 yr				1 yr to <2 yrs				Adult	
	0.625 mg		1.25 mg		0.625 mg		1.25 mg		5.00 mg	
	Mean (%CV)	Median	Mean (%CV)	Median	Mean (%CV)	Median	Mean (%CV)	Median	Mean (%CV)	Median
Cmax (ng/mL)	1.20 (29)	1.19	2.22 (39)	1.96	1.01 (28)	0.94	2.11 (27)	2.20	1.94 (42)	1.69
Tmax (hr)	3.40 (22)	3.30	2.89 (20)	2.68	3.27 (26)	3.05	2.93 (30)	2.81	3.22 (23)	3.11
AUC(I) (ng.hr/mL)	37.2 (69)	29.9	40.2 (65)	29.3	26.2 (118)	16.9	42.7 (88)	28.7	43.2 (81)	34.4
CL/F (L/hr)	26.4 (78)	21.0	43.0 (53)	42.8	39.1 (46)	37.0	46.9 (59)	43.6	155 (47)	146
CL/F/kg (L/hr/kg)[b]	2.7 (66)	2.3	4.7 (66)	3.9	3.3 (51)	3.2	3.9 (60)	3.4	2.1 (52)	1.8
CL/F/m^2 (L/hr/m^2)[c]	60.9 (71)	50.6	102.3 (61)	87.3	75.9 (49)	71.4	89.6 (60)	77.4	81.0 (49)	71.3
CL/F/m (L/hr/m)[d]	35.0 (70)	30.6	54.9 (55)	54.2	51.2 (51)	47.4	62.0 (63)	53.6	87.5 (47)	82.4

a: Based on model predicted individual parameter estimates.
b: Apparent total body clearance corrected for body weight.
c: Apparent total body clearance corrected for body surface area.
d: Apparent total body clearance corrected for height.

The sponsor computed corrected total body clearance by normalizing with body weight, body surface area or height and concluded that correction for body surface area resulted in more comparable values across the three age groups (see Table 7 and Figure 5). Additionally, similar apparent total body clearance values were obtained between male and female subjects within each of the pediatric age groups (Figure 6).

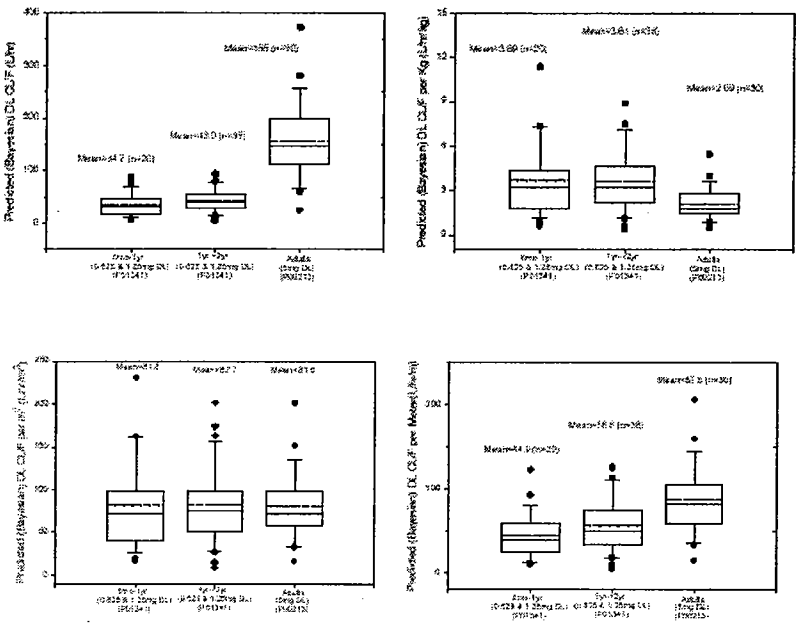


Figure 5: Individual predicted apparent total body clearance: comparison among three age groups

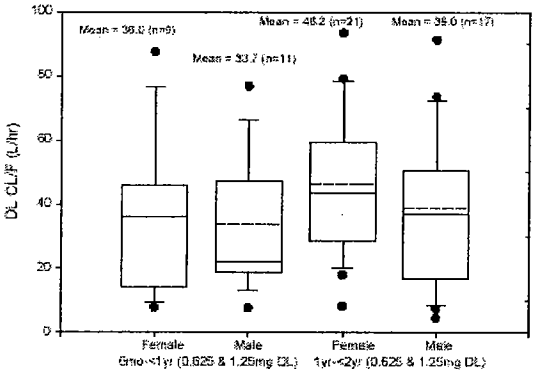


Figure 6: Individual Bayesian CL/F by Gender and Age Groups

The DL exposure at 0.625-mg dose level in both pediatric age groups was low relative to adults administered with 5 mg of DL as indicated by the mean Cmax and AUC ratios (pediatric/adult). (See Table 8.)

Table 8: AUC and Cmax Ratios* and the corresponding 90%CI

Parameter	6 mo -<1yr 0.625 mg Dose Group	6mo -<1yr 1.25 mg Dose Group	1 - <2 years 0.625 mg Dose Group	1- <2 years 1.25 mg Dose Group
AUC				
Point Estimate (90% CI)	0.82 (0.56-1.21)	0.93 (0.63-1.37)	0.52 (0.38-0.71)	0.90 (0.66-1.23)
Cmax				
Point Estimate (90% CI)	0.64 (0.52-0.77)	1.13 (0.93-1.38)	0.54 (0.46-0.63)	1.12 (0.95-1.30)

*Ratio: mean pediatric group value/mean adult value

Based on the CL estimate from the population PK analysis, the sponsor concluded that pediatric subjects aged 6 months to <1 year and 1 year to <2 years would require 1.00 mg and 1.25 mg of DL, respectively, in order to obtain DL exposure similar to that in adult subjects administered 5.00 mg of DL. The dose was calculated according to the following equation:

$$DL\ (mg)=(CL/F_{children} * 5\ mg)/CL/F_{adults}$$

The exposure at the proposed dose level for the two pediatric age groups were computed assuming dose proportionality. The mean and median parameter values for the two pediatric age groups and adults are listed in the table below. The sponsor considered that the Cmax and AUC values at the proposed dose levels in pediatric subjects (1 mg for the 6 mo-1yr age group, and 1.25 mg for the 1-2 yr age group) are comparable to that in adults following administration of 5 mg DL syrup.

Table 9: Mean (%CV) and median Bayesian PK parameter estimates by age group with AUC and Cmax values normalized to the proposed dose level

	Mean (CV%)			Median		
Parameter[a]	**6 mo -<1yr Dose = 1.0 mg**	**1 - <2 years Dose=1.25 mg**	**Adults**	**6 mo -<1yr Dose = 1.0 mg**	**1 - <2 years Dose=1.25 mg**	**Adults**
Cmax (ng/mL)	1.69 (49)[b] 1.85?	1.56 (46)[b] 2.07?	1.94 (42)	1.49[b]	1.41[b]	1.69
Tmax (hr)	3.16 (22)	3.10 (28)	3.22 (23)	3.12	2.94	3.11
AUC(I) [ng.hr/mL]	38.7 (65)[b] 45.8?	34.4 (101)[b] 47.6?	43.2 (81)	29.3[b]	19.0[b]	34.4
Ka (hr^{-1})	0.959 (18)	0.929 (17)	0.956 (29)	0.950	0.944	0.912
Ke (hr^{-1})	0.071 (55)	0.086 (64)	0.065 (35)	0.066	0.083	0.060
CL/F (L/hr)	34.7 (66)	43.0 (55)	155 (47)	30.1	40.3	146
CL/F/kg (L/hr/kg)	3.69 (72)	3.61 (57)	2.09 (52)	3.19	3.25	1.76
CL/F/m^2 (L/hr/m^2)	81.6 (69)	82.7 (56)	81.0 (49)	71.9	75.6	71.3
CL/F/m (L/hr/m)	44.9 (64)	56.6 (59)	87.5 (47)	40.2	50.5	82.4
V/F (L)	494 (32)	518 (29)	2373 (33)	473	479	2314

[a] Parameter for all subjects in the age group

[b] Reviewer's note: These numbers appear to be in error as they do not agree with calculations from Table 7 or from the individual parameter values.

Reviewer's Analysis:

(A) Reanalysis

The sponsor's analysis was repeated by this reviewer with some modifications:

- Software: NONMEM
- Method: FOCE with Interaction
- Ka: not fixed
- Residual error: proportional model

Compared to the sponsor's analysis, similar population mean PK parameter estimates were obtained but with better precision. The diagnostic plots were also similar to the sponsor's. Based on the apparent clearance estimate, the predicted dose was calculated to be 1.03 mg for children aged 6 months to <1 years and 1.43 mg for children 1 to <2 years (See Table 10).

Table 10: Population Mean (±%SE) PK Parameters of DL and Predicted Dose by Age Group

Age Groups	V/F, L (%SE)	Ka, hr^{-1} (%SE)	CL/F, L/hr (%SE)	Predicted Equiv. Dose[a]
6 Mo. to < 1 Yr	523 (8)	1.16 (7)	24.9 (18)	1.03 mg
1 to <2 Yrs	544 (5)		34.5 (12)	1.43 mg
Adults	2570 (7)		121 (10)	-
Intersubject Variability, %CV	33 (20)	31 (39)	68 (20)	-
Residual – Variability, %CV	24 (12)			

[a]Calculated as CL_{ped}/CL_{adult} * Adult Dose

To visualize the exposure at the sponsor's proposed dose, individual Cmax and AUC values were calculated from individual Bayesian parameter estimates and then normalized to the sponsor's proposed dose. The Mean (±SD) PK parameter values are presented in Table 11.

Table 11: Mean (±SD) PK parameter values calculated from individual Bayesian predictions

	Mean (CV%)			Median		
Parameter[a]	**6 mo -<1yr Dose = 1.0 mg**	**1 - <2 years Dose=1.25 mg**	**Adults**	**6 mo -<1yr Dose = 1.0 mg**	**1 - <2 years Dose=1.25 mg**	**Adults**
Cmax (ng/mL)	1.75 (35)	2.00 (28)	1.84 (48)	1.61	2.06	1.55
Tmax (hr)	2.88 (19)	2.71 (22)	2.94 (19)	-	-	-
AUC(I) [ng.hr/mL]	52.4 (80)	50.0 (119)	48.9 (77)	45.4	31.5	38.7
Ka (hr^{-1})	1.17 (12)	1.15 (9.4)	1.18 (23)	-	-	-
CL/F (L/hr)	32.2 (69)	41.9 (54.2)	136.7 (48)	22.1	40.0	129.4
V/F (L)	541 (29)	558 (27)	2715 (33)	-	-	-

Because of high variability in PK parameters within each age group (e.g., the CV for AUC in the 1 to <2 yr age group was 119%), box plots of AUC and Cmax normalized to the proposed dose are also presented for the three age groups (Figure 7). The AUC for the 1 to <2 yr group was lower compared to the adult values. However, Cmax for this group was higher than that for the adult group. Since exposure-response relationships for efficacy and safety have not been established, it is not known whether the dose for this age group can go higher than 1.25 mg to ensure efficacy without jeopardizing the safety. To consider both AUC and Cmax under this circumstance, the 1.25 mg dose appears reasonable.

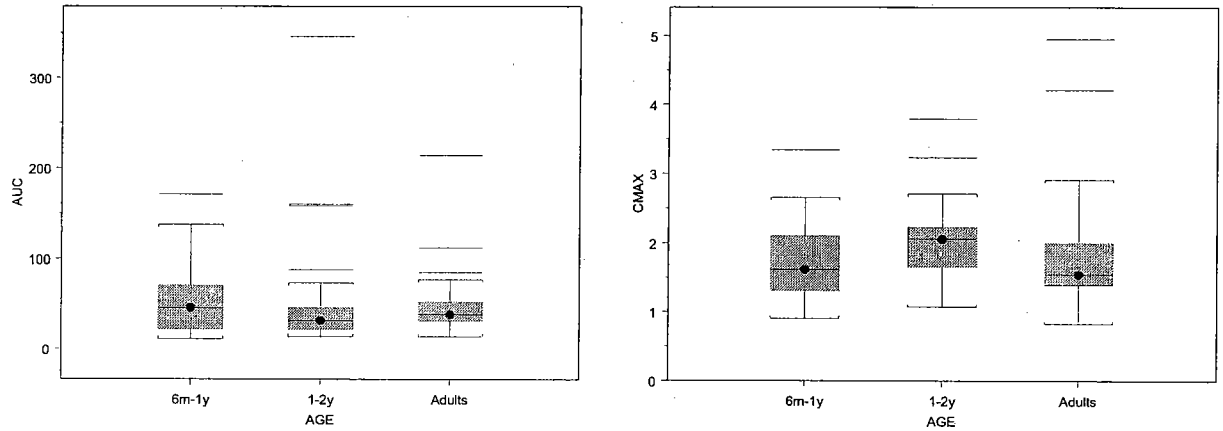


Figure 7: Box plots of normalized AUC and Cmax by age group

In this study, the percentage of poor metabolizers in each age group may not be representative of the true population. By lumping poor metabolizers and potential poor metabolizers as one group (designated as slow metabolizers, or SM) in covariate analysis, it was found that the mean apparent clearance for this group was only 21% that of the extensive metabolizers. The population mean (±%SE) apparent clearance estimate in extensive metabolizers were 28.7 (±14.9%) L/h for children 6 months to <1 year of age, 45.5 (±7.9%) L/h for children 1 year to <2 yearsd of age, and 128 (±8.1%) L/h for adults. Based on these clearance values, the predicted dose would be 1.12 mg for children 6 months to <1 year, and 1.78 mg for children aged 1 to <2 years.

Box plots of AUC and Cmax values normalized to the proposed dose are presented for the three age groups (Figure8). The AUC for the 1 to <2 yr group was lower compared to the adult values. However, Cmax for this group was higher than that for the adult group. As stated before, since exposure-response relationships for efficacy and safety have not been established, it is not known whether the dose for this age group should go higher than 1.25 mg for better efficacy without jeopardizing the safety. To consider both AUC and Cmax under the circumstance, again the 1.25 mg dose appears reasonable for children aged 1 to <2 years.
It should be noted that no genotyping was performed in this study and poor metabolizers were identified based on an AUC ratio (metabolite : parent compound) of ≤0.1.

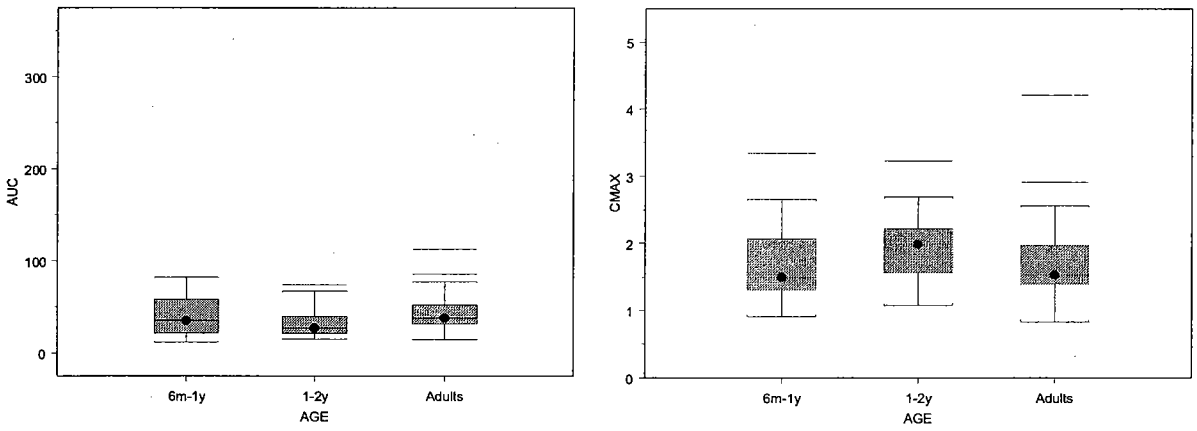


Figure 8: Box plots of normalized AUC and Cmax for extensive metabolizers (i.e., excluding poor metabolizers and potential poor metabolizers) by age group

(B) Further Analysis

In the above population PK analysis, a one-compartment model was used to characterize desloratadine PK. Figure 3 shows that the weighted residuals did not distribute evenly about zero over the predicted concentration range, indicating some deficiency in the structural model. PK data from previous studies with intensive sampling were examined which revealed that the two-compartment model is more appropriate. Therefore, further analysis with a 2-compartment

PK model was carried out using the FO method in NONMEM. All available data for the syrup formulation from 6 studies were combined in the analysis. The final model included weight as a covariate for all the volume and clearance parameters. Poor metabolizers and potential poor metabolizers were considered as one category (SM) separate from the extensive metabolizers (EM). SM was found to be a significant covariate for clearance.

Plots of weighted residulas versus predicted concentrations (Figure 9) and individual predicted concentration versus observed concentration (Figure 10) indicate improvement over the previous model.

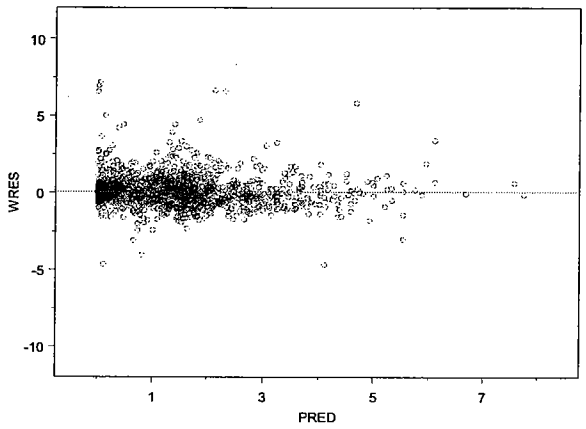


Figure 9: Diagnostic plot of weighted residuals versus predicted concentrations

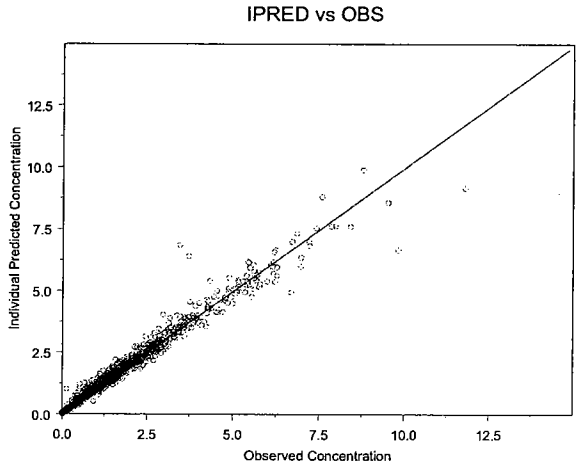


Figure 10. Plot of individual predicted concentration versus observed concentration

The individual Bayesian estimates of PK parameters obtained from the analysis were used to compute individual AUC and Cmax values expected at the proposed dose level (Table 10).

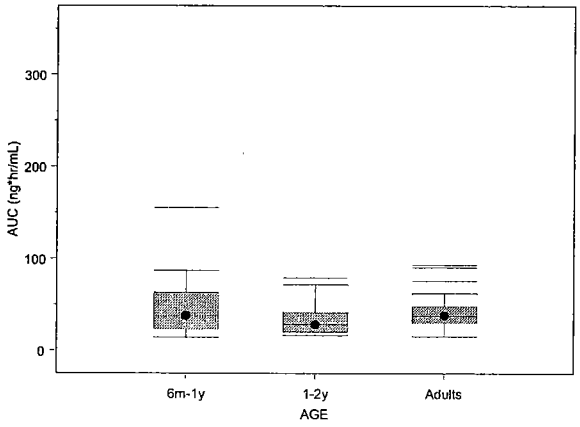
Table 10: Mean (±SD) PK parameter values based on individual Bayesian predictions
(AUC and Cmax values are normalized to the proposed dose level for pediatric subjects)

Parameter[a]	Mean (CV%)			Median		
	6 mo -<1yr Dose = 1.0 mg N=20	1 - <2 years Dose=1.25 mg N=38	Adults Dose=5 mg N=30	6 mo -<1yr Dose = 1.0 mg	1 - <2 years Dose=1.25 mg	Adults Dose=5 mg
Cmax (ng/mL)	2.20 (37)	2.42 (36)	2.26 (54)	1.92	2.30	1.86
AUC(I) [ng.hr/mL]	68.1 (106)	72.3 (206) 49.5 (103)[a]	47.8 (75)	47.7	34.8	38.6
Ka (hr^{-1})	0.89 (25)	0.83 (25)	1.25 (39)	-	-	-
Lag Time, hr	0.37 (34)	0.42 (95)	0.27 (52)	-	-	-
CL/F (L/hr)	29 (70)	38.6 (54)	136.7 (46)	21.1	36.0	129.6
V_c/F	337 (33)	371 (34)	2059 (39)	-	-	-
V_p/F (L)	267 (65)	249 (33)	1348 (27)	-	-	-

[a]Subject #43 removed from the analysis because the concentration-time data showed disparity.

There are discrepancies in AUC values for poor metabolizers between this analysis and the analysis using a one-compartment model. Subject #43 in 1-2 yr age group appears to have poor concentration data beyond what can be expected from normal analytical error. AUC values for extensive metabolizers were comparable to the previous analysis as shown in the box plot and statistics presented in Figure 11.

Figure 11: Box plot of normalized AUC for extensive metabolizers (i.e., excluding poor metabolizers and potential poor metabolizers) by age group.



Statistics for extensive metabolizers as shown in Figure 11:	Statistics for extensive metabolizers as shown in Figure 8, Left Panel:
Age group: 6mo-1yr	**Age group:6mo-1yr**
Min: 14.2	Min: 11.6
1st Qu.: 23.7	1st Qu.: 21.6
Median: 37.6	Median: 35.1
3rd Qu.: 62.7	3rd Qu.: 57.0
Max: 155.4	Max: 82.0
N: 18	N: 18
Age group: 1-2yr	**Age group:1-2yr**
Min: 16.5	Min: 14.3
1st Qu.: 21.9	1st Qu.: 21.4
Median: 28.3	Median: 26.9
3rd Qu.: 40.1	3rd Qu.: 39.2
Max: 79.0	Max: 73.8
N: 31	N: 31
Age group: Adults	**Age group: Adults**
Min: 15.4	Min: 14.3
1st Qu.: 30.1	1st Qu.: 31.2
Median: 38.0	Median: 37.6
3rd Qu.: 48.2	3rd Qu.: 51.8
Max: 93.5	Max: 112.4
N: 29	N: 29

Box plot for Cmax at the proposed dose in extensive metabolizers is presented in Figure 12. The plots for both AUC and Cmax indicate that the proposed dose for children aged 6 months to <2 years (1.00 mg for children aged 6 months to <1 year, and 1.25 mg for children aged 1 years to <2 years) is acceptable.

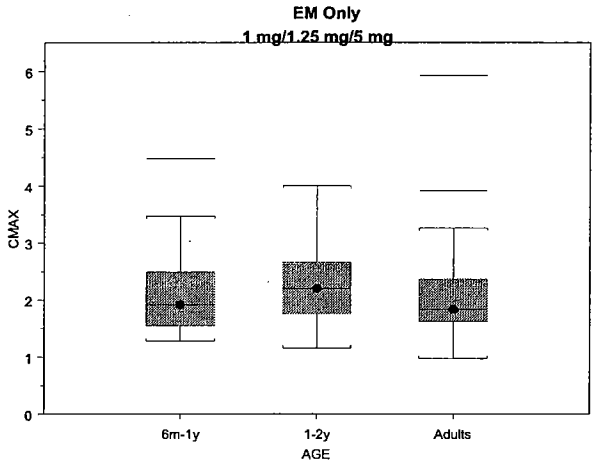
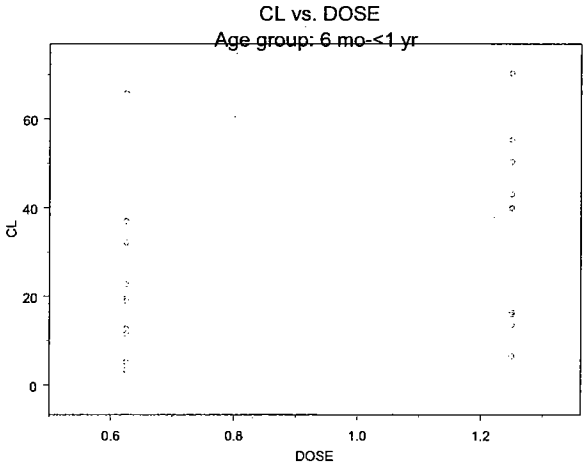


Figure 12: Box plot of normalized Cmax for extensive metabolizers by age group.

Reviewer's Comments:

1. It is noted that, within the 6-mo to <1-yr age group, mean desloratadine clearance was much lower for the 0.625-mg dose group than the 1.25-mg dose group (See Table 7). As the two dose groups had similar age and weight, the difference in mean clearance cannot be readily explained. It should be noted that both dose groups showed high variability in clearance values.



2. Apparently, the one-compartment approximation resulted in an acceptable error for the purpose here although it systematically underpredicted Cmax.

CONCLUSION:

The sponsor's proposed dosage regimen (1 mg once daily for children 6 months to <1 year and 1.25 mg once daily for children 1 year to <2 years) is acceptable.

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6.3 Cover Sheet and OCPB Filing/Review Form

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number	**21-563**	**Brand Name**	**Clarinex**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Desloratadine**
Medical Division	**Division of Pulmonary & Allergy Drug Products (HFD-570)**	**Drug Class**	**Histamine H1-receptor antagonist**
OCPB Reviewer	**Sandra Suarez-Sharp**	**Indication(s)**	**Treatment of seasonal allergic rhinitis and chronic idiopathic urticaria**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**Syrup**
Date of Submission	**12/04/2002**	**Dosing Regimen**	**Age 6 mo.-<1 yr: 1.00 mg qd Age: 1-<2 yr: 1.25 mg qd**
Estimated Due Date of OCPB Review	**Early May 2002**	**Route of Administration**	**Oral**
Medical Division Due Date	**May 19, 2003**	**Sponsor**	**Schering**
PDUFA Due Date	**June 4, 2003**	**Priority Classification**	**Standard**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:				
multiple dose:				
PATIENTS-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x			
Data sparse:	x			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
5.1.1.1.1.2.				

Filability and QBR comments

	"X" if yes	***5.1.1.1.1.2.1. comments***
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable. Request for electronic data files for population analysis
QBR questions (key issues to be considered)	**Does the PK data support the dosage regimen in children 6 months to <2 years of age?**	
Other comments or information not included above		

Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA 21-563, HFD-870 (Electronic Entry or Lee), HFD-570 (Zeccola), HFD-870 (Fadiran, Hunt, Malinowski), CDR (B. Murphy)

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/s/

Sue Chih Lee
5/12/03 02:25:56 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
5/13/03 12:56:29 PM
BIOPHARMACEUTICS
I concur