CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS SUMMARY

NDA	20-625 SE8-012 – Allegra® Capsules, Labeling supplement 20-872 SE8-011 – Allegra® Tablets, Labeling supplement 20-786 SE8-014 – Allegra-D® Tablets, Labeling supplement
Drug Substance	Fexofenadine HCl
Drug Product	Allegra®
Strengths	60 mg Capsule; 30, 60 and 180 mg Tablets
Route of Administration	Oral Capsules/Tablets
Sponsor	Aventis Pharmaceuticals
Type of submission	Pediatric exclusivity/Labeling Supplement with clinical Data
Date of submission	11/18/02
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.

1. EXECUTIVE SUMMARY

Fexofenadine HCl, the active ingredient of Allegra®, is a selective peripheral histamine H_1-receptor antagonist approved for the treatment of symptoms of seasonal allergic rhinitis (SAR) (60 mg BID or 180 mg QD) and chronic idiopathic urticaria (CIU) (60 mg BID) in patients 12 years and older. Allegra® is also marketed in the United States for the treatment of symptoms of SAR and CIU (30 mg BID) for children 6 to 11 years.

The current application was submitted as labeling supplement and Pediatric Exclusivity Determination request by including the following studies: one Phase I (M016455T/1123), two Phase III (M016455T/3001; M016455T/3002), and two bioavailability studies (PJPROO76; M016455T/1001).

Study T/1123 was a dose- ranging pharmacokinetic study in children from 6 months to <2 years of age using 15 and 30-mg doses of fexofenadine HCl (experimental formulations of fexofenadine). The mean C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$ and $t_{1/2}$ following 15 mg were 169 ng/mL, 1.1 hr, 767 ng•h/mL, 804 ng•h/mL, 6.2 hr, respectively. The mean C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$ and $t_{1/2}$ following 30 mg dose were 329 ng/mL, 1.1 hr, 1580 ng•h/mL, 1660 ng•h/mL, 7.4 hr, respectively. The mean C_{max}, AUC_{0-z}, and $AUC_{0-\infty}$ values observed in the 30-mg dose group were approximately twice of those in the 15-mg dose group with an average oral clearance (CLpo) of 22 L/h in both dose groups.

(b) (4)

[redacted]

(b) (4)

In addition, two PK studies were conducted to evaluate relative bioavailability of fexofenadine in food vehicles: Study PJPR0076 examined the bioavailability of the content of the fexofenadine marketed immediate-release capsule when co-administered with applesauce, and Study M016455T/1001 examined the bioavailability of fexofenadine when co-administered with other dosing vehicles including Gerber® rice cereal mixed with Similac® infant formula (GS formula). The co-administration of the 60 mg fexofenadine capsule formulation contents mixed with applesauce and GS formula did not affect the AUC but resulted 11.4 and 9.4% increase of C_{max} fexofendaine, respectively.

(b) (4)

Based on the submitted information, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds this submission acceptable.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Human Pharmacokinetics and Bioavailability section of the NDA and found that this submission is acceptable. (b) (4)

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

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/s/

Shinja Kim
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	20-625 SE8-012 – Allegra® Capsules, Labeling supplement 20-872 SE8-011 – Allegra® Tablets, Labeling supplement 20-786 SE8-014 – Allegra-D® Tablets, Labeling supplement 20-625 SE8-010 BL, Response to approvable letter 20-872 SE8-003 BL, Response to approvable letter
Drug Substance	Fexofenadine HCl
Drug Product	Allegra®
Strengths	60 mg Capsule; 30, 60 and 180 mg Tablets
Route of Administration	Oral Capsules/Tablets
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Team Leader	Emmanuel Fadiran, Ph.D.

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Study T/1123 was a dose- ranging pharmacokinetic study in children from 6 months to <2 years of age using 15 and 30-mg doses of fexofenadine HCl. The mean C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$ and $t_{1/2}$ following 15 mg were 169 ng/mL, 1.1 hr, 767 ng•h/mL, 804 ng•h/mL, 6.2 hr, respectively. The mean C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$ and $t_{1/2}$ following 30 mg dose were 329 ng/mL, 1.1 hr, 1580 ng•h/mL, 1660 ng•h/mL, 7.4 hr, respectively. The mean C_{max}, AUC_{0-z}, and $AUC_{0-\infty}$ values observed in the 30-mg dose group were approximately twice of those in the 15-mg dose group with an average oral clearance (CLpo) of 22 L/h in both dose groups.

(b) (4)

[redacted]

(b) (4)

In addition, two PK studies were conducted to evaluate relative bioavailability of fexofenadine in food vehicles: Study PJPR0076 examined the bioavailability of the content of the fexofenadine marketed immediate-release capsule when co-administered with applesauce, and Study M016455T/1001 examined the bioavailability of fexofenadine when co-administered with other dosing vehicles including Gerber® rice cereal mixed with Similac® infant formula (GS formula). The co-administration of the 60 mg fexofenadine capsule formulation contents mixed with applesauce and GS formula did not affect the AUC but resulted 11.4 and 9.4% increase of C_{max} fexofendaine, respectively.

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1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Human Pharmacokinetics and Bioavailability section of the NDA and found that this submission is acceptable. (b) (4) .

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

2. Table of Contents

3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Fexofenadine HCl is approved down to 2 years of age for the treatment of symptoms of SAR and CIU. The current submission seeks Pediatric exclusivity by including pediatric study reports in children 6 months to 2 years of age (M016455T/1123). In addition, two bioavailability studies (PJPROO76; M016455T/1001) were included in Section 6.

Study T/1123 was a Phase 1 dose- ranging PK study in children from 6 months to <2 years of age using 15-mg and 30-mg doses of fexofenadine HCl. The mean C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$ and $t_{1/2}$ following 15 mg were 169 ng/mL, 1.1 hr, 767 ng•h/mL, 804 ng•h/mL, 6.2 hr, respectively. The mean C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$ and $t_{1/2}$ following 30 mg dose were 329 ng/mL, 1.1 hr, 1580 ng•h/mL, 1660 ng•h/mL, 7.4 hr, respectively. The mean C_{max}, AUC_{0-z}, and $AUC_{0-\infty}$ values observed in the 30-mg dose group were approximately twice of those in the 15-mg dose group with an average oral clearance (CLpo) of 22 L/h in both dose groups.

(b) (4)

[redacted]

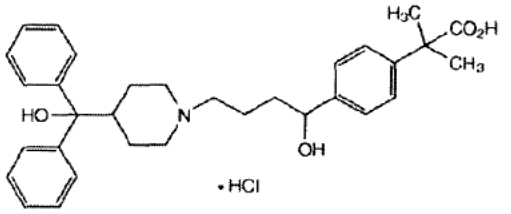
In addition, two PK studies were conducted to evaluate relative bioavailability: Study PJPR0076 examined the bioavailability of the content of the fexofenadine marketed immediate-release capsule when co-administered with applesauce, and M016455T/1001 examined the relative bioavailability of fexofenadine co-administered with 3 food delivery vehicles (Karo® syrup, Dannon® yogurt and Gerber® rice cereal mixed with Similac® infant formula). The co-administration of the 60 mg capsule formulation contents mixed with applesauce resulted

bioequivalent $AUC_{0-\infty}$ (90% CI = 92.3-119.4%) but higher C_{max} (94-132%) on the PK of fexofenadine in adults (PJPR0076). The relative bioavailability of 60 mg fexofenadine [redacted] (b) (4) power administered in Karo® Light syrup, Dannon® vanilla yogurt and Gerber® rice cereal prepared with Similac with Iron® were 115.3 %, 104.7 %, and 95.7 %, respectively compared to the reference fexofenadine capsule ((M016455T/1001).

4. Question Based Review

4.1. What are the general attributes of fexofenadine?

Chemistry: Allegra has a molecular weight of 538.13, and formulated as a capsule (60 mg) or tablet (30, 60 and 180 mg) for oral administration. It has the following chemical structure:



Indications and Dosage: Allegra is indicated for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 6 years of age and older. The recommended dose of Allegra is 60 mg twice daily for adults and ≥12 years of age and 30 mg twice daily for children 6-11 for both indications.

Pharmacokinetics in Pediatrics: Fexofenadine PK between pediatric patients from 6-12 years of age and healthy adult subjects were compared by pooling pharmacokinetic parameters from 4 healthy adult subject studies and one pediatric study. In comparing PK parameters between populations, AUC and C_{max} were 56% and 84% greater, respectively, with 40% lower CLpo in pediatric patients. The exposure of fexofenadine also has been studied in children 2-5 years of age but not in children younger than 2 years of age. This submission will provide the information in this population.

4.2. Is the Pediatric study conducted in children 6 months to < 2 years of age according to the "Pediatric Written Request"? What are the characteristics PK parameters in this children population following 15 and 30 mg fexofenadine?

Yes, Study T/1123 in children 6 months to < 2 years of age was conducted according to the Pediatric Written Request. In this study, fexofenadine was administered as [redacted] (b) (4) powder, by opening up one capsule of 15 mg or 30 mg and mixing in applesauce before administration. The mean plasma concentration-time profiles are shown in Figure 1, and descriptive statistics for PK parameters are presented in Table 1.

Figure 1. Mean fexofenadine plasma concentration-time profiles following 15 or 30 mg fexofenadine in subjects between 6 months to 2 years old

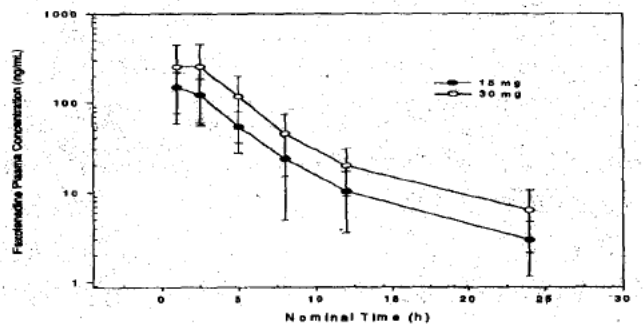


Table 1

Descriptive statistics of fexofenadine pharmacokinetic parameters after administration of a single dose of 15 or 30 mg fexofenadine HCl to 6-month to 2-year-old subjects (Study T/1123)

Parameter (unit)	Treatment	Mean ± SD [a]	CV% [b]	N	Min [c]	Max [d]
C_{max} (ng/mL)	15 mg	168.69 ± 69.99	41.5	21	35.90	334.46
	30 mg	328.95 ± 224.30	68.2	23	81.47	925.97
t_{max} (h)	15 mg	1.10 [e]	–[e]	21	1.00	5.00
	30 mg	1.10 [e]	–[e]	23	1.00	5.00
$AUC_{(0-z)}$ (ng·h/mL)	15 mg	767.05 ± 324.40	42.3	21	231.30	1435.42
	30 mg	1579.51 ± 914.51	57.9	22	550.60	4087.10
λ_z (h^{-1})	15 mg	0.120 ± 0.032	26.5	20	0.073	0.178
	30 mg	0.119 ± 0.044	36.7	23	0.027	0.186
$t_{1/2}$ (h)	15 mg	6.19 ± 1.65	26.6	20	3.90	9.51
	30 mg	7.38 ± 5.12	69.4	23	3.73	25.91
$AUC_{(0-\infty)}$ (ng·h/mL)	15 mg	804.29 ± 340.06	42.3	19	245.01	1497.64
	30 mg	1660.31 ± 909.60	54.8	22	588.07	4233.65
CL_{po} (L/h)	15 mg	21.70 ± 12.47	57.5	19	9.36	57.22
	30 mg	21.94 ± 11.73	53.4	22	6.62	47.68

[a]SD = standard deviation [b]CV = coefficient of variation [c]min = minimum
[d]max = maximum [e]t_{max} is presented as median without CV

As seen in Table 1, the fexofenadine mean C_{max}, AUC_{0-z}, and $AUC_{0-\infty}$ values observed in the 30-mg dose group were approximately twice of those in the 15-mg dose group with an average oral clearance (CLpo) of 22 L/h in both dose groups, indicating that the PK is linear in this dose range. In addition, the correlation between demographics and oral clearance (CLpo) using a two-sided test was evaluated. This analysis indicated that there was significant ($\alpha = 0.05$) correlation observed between CLpo and demographic factors (i.e., age, weight, height, etc.).

(b) (4)

(b) (4) , a Population PK analysis was performed. The population PK analysis for adults was based on the data from 269 treatment doses from 136 adult subjects, while pediatric population PK analysis was based on 90 treatment doses from 77 pediatric patients. The modeling revealed that age and body weight are significant predictors of variability in fexofenadine pharmacokinetics in pediatrics. The results are summarized in Table 2 and Figure 2 based on the final model. The sponsor combined all of

the adults and pediatrics data for population PK modeling, and the results from the sponsor's final model produced are similar to those obtained by the reviewer (Table 2).

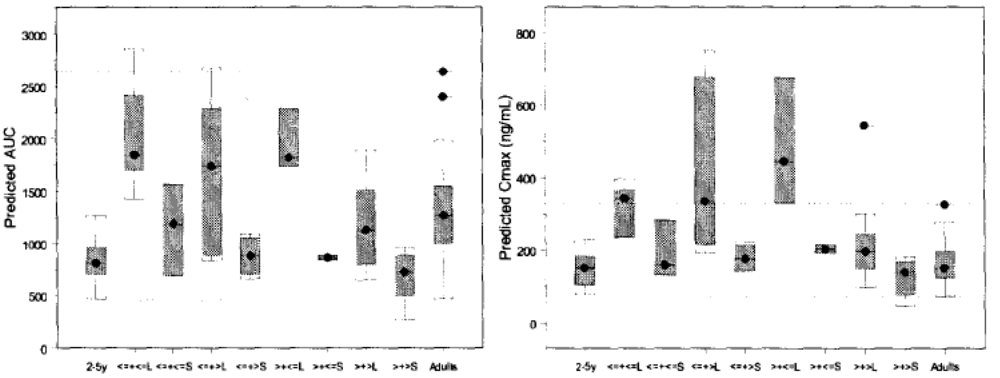
Table 2. Summary of fexofenadine PK parameter estimates by age group from the final model (reviewer's analysis)

	15 mg		30 mg		60 mg	
	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)
≤1yr+≤10.5kg[3]	**1150±437**	**191±80**	2050±581	315±75	-	-
≤1yr+>10.5kg[2]	**882±206**	**180±41**	2210±670	543±295	-	-
>1yr+≤10.5kg[4]	**862±33**	**203±17**	1950±300	483±176	-	-
>1yr+>10.5kg[1]	671±257	127±54	**1180±400**	**214±115**	-	-
2 - 5 yrs[5]	-	-	845±218	145±44	-	-
7 – 12 yrs[6]	-	-	1060±284	157±62	2110±585	308±127
Adults[7]	-	-	-	-	1290±414	165±54

[1]n= 10 and 13 for 15 and 30 mg, respectively; [2]n= 4 and 2 for 15 and 30 mg, respectively;
[3]n= 3 and 5 for 15 and 30 mg, respectively; [4]n= 2 and 3 for 15 and 30 mg, respectively;
[5]n= 21; [6]n= 14 and 13 for 30 and 60 mg, respectively; [7]n= 269

Figures 2 shows the box plots that illustrate the distribution of AUC and C_{max} for 6 months-<2 years and 2-5 years of age in reference to adults after 60 mg fexofenadine: L and S denote for administered dose of 30 and 15 mg, respectively. <=+<=, <=+> and >+> denote for children 6 months to ≤1 year of age and weighing ≤10.5 kg, children 6 months to ≤1 year of age and weighing >10.5 kg and children 6 months to >1 year of age and weighing >10.5 kg, respectively.

Figure 2. AUC and C_{max} as function of age group for fexofenadine dose



Administration of 30 mg fexofenadine to 7 to 12 years of age produced exposures (predicted C_{max} and $AUC_{0-\infty}$) comparable to those seen with a dose of 60 mg administered to adults. Administration of 30 mg dose to children 2 to 5 years of age produced exposures lower, but within the range, than those seen with a dose of 60 mg administered to adults. In children 6 months to <2 years of age, the following doses produced exposures comparable to those seen with a dose of 60 mg administered to adults: administration of 15 mg fexofenadine to children 6 months to ≤1 year and weighing ≤10.5 kg or >10.5 kg (i.e., regardless of body weight) or >1 year

of age with body weight ≤10.5 kg produced exposures similar to those seen with a dose of 60 mg administered to adults, while administration of 30 mg produced similar estimates of exposures for children >1 year of age and weighing >10.5 kg in comparison to 60 mg dose in adults. Noted that there were three outliers and their C_{max} values were 751, 676 and 543 ng/mL (median = 202.4 ng/mL). The age and weight of these children were 1 year and 10.9 kg, 1.5 years and 10.2 kg and 1.75 years and 11.8 kg, respectively.

The predicted CLpo values based on the final population model for adults, children 7-12 and 2-5 years of age are 51.9, 30.3 and 37.9 L/h, respectively. The predicted CLpo in children 6 months to >1 year of age with body weight ≤10.5 kg and >10.5 kg are 16.3 and 27.8 L/h, respectively. The predicted CLpo in children 6 months to ≤1 year of age with body weight ≤10.5 kg and >10.5 kg are 15.2 and 16.6 L/h, respectively. This indicates that the individual apparent oral clearance estimates of fexofenadine were on average 42% and 27% lower in children 7 to 12 years (n=14) and 2 to 5 years (n=21), respectively compared to adults. The individual clearance estimates of fexofenadine were on average 69% and 46% lower than in adults for children 6 months to >1 year of age with body weight ≤10.5 kg (n=5) and >10.5 kg (n=23), respectively. The individual clearance estimates of fexofenadine were on average 68% and 71% lower than in adults for children 6 months to ≤1 year of age with body weight >10.5 kg (n=6) and ≤10.5 kg (n=8), respectively.

In conclusion, age and body weight are significant predictors of variability in fexofenadine pharmacokinetics in pediatrics. (b) (4)

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4.4. Was bioequivalence established when the content of fexofenadine capsule was mixed with food delivery vehicles compared to intact fexofenadine capsule?

No. BA/BE of the contents of the fexofenadine mixed in with food delivery vehicles (compared to the intact fexofenadine capsule) was evaluated in 2 studies employing healthy adult male volunteers (Studies PJPR0076 and M016455T/1001). As shown in Table 4, BE was not established except the treatment A; however, the differences seen after treatments C and F (administration method used in clinical trails) are considered clinically insignificant.

Table 4. Point estimates and 90% confidence intervals (reference = intact fexofenadine capsule)

PJPR0076				
	$AUC_{0-\infty}$ (ng•h/mL)		C_{max} (ng/mL)	
Treatment	Ratio (%)	90% CI	Ratio (%)	90% CI
A	97.5	85.9-110.6	104.5	88.4-123.4
B	78.2	68.9-88.8	73.1	61.9-86.4
C	105	92.3-119.4	111.4	94.0-132.0
M016455T/1001				
D	115.3	103.6-128.3	132.9	114.8-153.9
E	104.7	94-116.6	121.8	105.1-141.1
F	95.7	85.8-106.6	109.4	94.3-127.1

A=((b) (4); B= (b) (4) C=marketed IR capsules in applesauce
D=Karo®light syrup; E=Dannon® vanilla yogurt; F=Gerber® rice cereal with Similac® with Iron

(b) (4)

4.6. Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes, fexofenadine was quantified by the validated LC-MS/MS assay method. Sample clean up was achieved by protein precipitation. The validated method has a standard curve range of 0.5 to 100 ng/mL using 50 µL of plasma. The performance of the assay during study sample analysis was acceptable as evidenced by QC sample precision and accuracy within ± 15%.

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APPENDICES

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Protocol M016455T/1123

Study Type: PK & Tolerability of single increasing dose in pediatrics.

Title: A Multicenter Study of Single Escalating Dose Safety and Phannacokineties of Oral Fexofenadine Hydrochloride in Children from 6 Months to 2 Years of Age

Clinical Investigators: Multicenter

Objectives:

Primary: To characterize the pharmacokinetics of fexofenadine following a single oral dose of 15 mg or 30 mg fexofenadine in children from 6 months to 2 years of age.

Secondary: To characterize the safety and tolerability of 15 mg or 30 mg fexofenadine in children from 6 months to 2 years of age.

Design:

This study was a multicenter, open-label, single rising dose pharmacokinetic trial in children from 6 months to 2 years of age. Two panels of sequential, escalating dose groups received a single oral dose of study medication. Dose escalation proceeded following review of safety data from the preceding dose panel.

Population: Children 6 months to <2 years of age who were candidates for antihistamine therapy or who had tolerated a therapeutic course of antihistamine within the preceding 6 months without adverse effects were eligible for study participation. Forty-eight subjects were enrolled to obtain 36 completed subjects overall with 18 completed subjects per dose group. There were to be 6 completed subjects per dose group in the age range of 6 months to <1 year with approximate representation of children of various ages across the age range of 6 months to <1 year. The age distribution ratio of children in the 6 month to <1 year range to children in the 1 to 2 year range was 1:2.

Treatments: Fexofenadine was administered as (b) (4) powder, by opening up one capsule of 15 mg (KN2000001) or 30 mg (KN1999032), mixing in applesauce followed by 4 oz water.

Sampling times: Blood samples were collected prior to dosing and at 1, 2.5, 5, 8, 12 and 24 hours postdose.

Criteria for evaluation:

PK: C_{max}, t_{max}, $AUC_{(0-z)}$, $AUC_{(0-\infty)}$, $t_{1/2}$ and CLpo

Safety: Age-appropriate physical exams, vital signs, 12-lead electrocardiograms, clinical laboratories and adverse events.

Analytical Methodology:

Assay Method: LC/MS/MS

Limit of detection: LOQ of 0.5 ngmL with linear range of 0.5 to 100 ng/mL

Accuracy and Precision: Satisfactory; precision (%CV) and accuracy were 7.7-13.8% and 98.8-101.8%, respectively.

Statistical procedures: Fexofenadine plasma concentrations were analyzed using noncompartmental techniques. PK parameters were summarized descriptively.

Results:

Study subjects and conduct: Demographic summary statistics in subjects with complete PK data is shown in the table below;

Characteristics	Statistics	Dose group 15 mg	Dose group 30 mg	Overall
Age (months)	Mean (SD)	13.9 (4.5)	15.8 (4.9)	14.9 (4.7)
Age (group)				
6-8 months	N	2	2	4
9-11 months	N	4	4	8
12-<24 months	N	13	17	30
Height (cm)	Mean (SD)	77.9 (4.8)	79.1 (6.8)	78.6 (5.9)
weight (kg)	Mean (SD)	11.2 (1.2)	11.0 (2.1)	11.1 (1.7)

Pharmacokinetics: Descriptive statistics for PK parameters are presented in Table 1, and $AUC_{0-\infty}$ and C_{max} values per age/weight are provided in Table 2. Table 3 shows the results of the evaluation of the correlation between demographics and oral clearance (CLpo) using a two-sided test. Mean plasma concentration-time profiles are shown in Figure 1.

Table 1

Descriptive statistics of fexofenadine pharmacokinetic parameters after administration of a single dose of 15 or 30 mg fexofenadine HCl to 6-month to 2-year-old subjects (Study T/1123)

Parameter (unit)	Treatment	Mean ± SD [a]	CV% [b]	N	Min [c]	Max [d]
C_{max} (ng/mL)	15 mg	168.69 ± 69.99	41.5	21	35.90	334.46
	30 mg	328.95 ± 224.30	68.2	23	81.47	925.97
t_{max} (h)	15 mg	1.10 [e]	--[e]	21	1.00	5.00
	30 mg	1.10 [e]	--[e]	23	1.00	5.00
$AUC_{(0-z)}$ (ng·h/mL)	15 mg	767.05 ± 324.40	42.3	21	231.30	1435.42
	30 mg	1579.51 ± 914.51	57.9	22	550.60	4087.10
λ_z (h^{-1})	15 mg	0.120 ± 0.032	26.5	20	0.073	0.178
	30 mg	0.119 ± 0.044	36.7	23	0.027	0.186
$t_{1/2}$ (h)	15 mg	6.19 ± 1.65	26.6	20	3.90	9.51
	30 mg	7.38 ± 5.12	69.4	23	3.73	25.91
$AUC_{(0-\infty)}$ (ng·h/mL)	15 mg	804.29 ± 340.06	42.3	19	245.01	1497.64
	30 mg	1660.31 ± 909.60	54.8	22	588.07	4233.65
CL_{po} (L/h)	15 mg	21.70 ± 12.47	57.5	19	9.36	57.22
	30 mg	21.94 ± 11.73	53.4	22	6.62	47.68

[a]SD = standard deviation [b]CV = coefficient of variation [c]min = minimum
[d]max = maximum [e]t_{max} is presented as median without CV

Figure 1. Mean fexofenadine plasma concentration-time profiles following 15 or 30 mg fexofenadine in subjects between 6 months to 2 years old

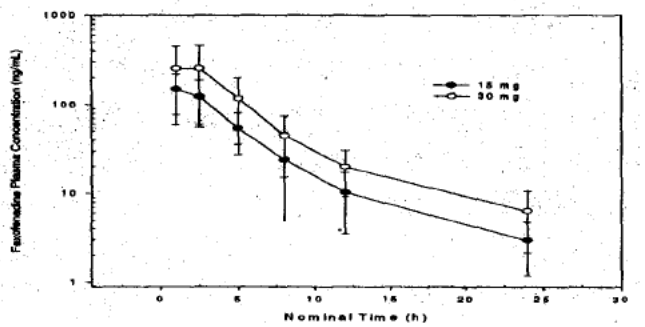


Table 2. $AUC_{0-\infty}$ and C_{max} following 15 and 30 mg fexofenadine per age/weight

Age (months)	Weight(kg) mean	Gp[1]	Gp[2]	C_{max} (ng/mL) 15 mg	C_{max} (ng/mL) 30 mg[3]	AUC_{inf} (ng•h/mL) 15 mg	AUC_{inf} (ng•h/mL) 30 mg[3]
6-8	8.7	9.1	8.3	148.7 (n = 2)	205.0 (n = 2)	1036.3 (n = 2)	1193.3 (n = 2)
9-11	10	10.8	9.1	195.9 (n = 4)	150.6 (n = 4)	796.8 (n = 4)	747.9 (n = 4)
12-<24	11.7	11.6	11.8	166.0 (n = 13)	163.9 (n = 17)	770.9 (n = 13)	908.6 (n = 17)
Overall mean	10.1	10.5	9.7	**170.2** (n = 19)	**173.2** (n = 23)	**868** (n = 19)	**909.6** (n = 23)

[1]subjects received 15 mg [2]subjects received 30 mg [3]Normalized to 15 mg

Table 3

95% confidence intervals for the estimated slope of covariates from regression analyses of CL_{po} and demographics and correlation coefficient for each dose group

		CL_{po} (L/h)			
Demographics	Treatment	Slope	P-value	95% Confidence Interval on Slope	Correlation Coefficient
Age (months)	15 mg (N=19)	0.65	0.3347	(-0.73, 2.02)	0.2341
	30 mg (N=22)	1.31	0.0089	(0.37, 2.25)	0.5440[b]
	Overall (N=41)	0.99	0.0106	(0.24, 1.74)	0.3950[b]
Weight (kg)	15 mg (N=19)	4.83	0.0443	(0.14, 9.51)	0.4660[a]
	30 mg (N=22)	3.47	0.0021	(1.42, 5.53)	0.6188[c]
	Overall (N=41)	3.77	0.0003	(1.87, 5.66)	0.5421[c]
Height (cm)	15 mg (N=19)	0.50	0.4356	(-0.81, 1.80)	0.1901
	30 mg (N=22)	1.05	0.0030	(0.40, 1.69)	0.6032[c]
	Overall (N=41)	0.87	0.0049	(0.28, 1.47)	0.4314[c]
Body surface area (m^2)	15 mg (N=19)	136.20	0.0761	(-15.92, 288.31)	0.4165
	30 mg (N=22)	113.95	0.0016	(48.75, 179.15)	0.6318[c]
	Overall (N=41)	119.0	0.0003	(58.13, 179.87)	0.5350[c]

[a] The power of rejecting H0, r=0 is 67% based on Cohen's power table
[b] The power of rejecting H0, r=0 is between 80% and 90% based on Cohen's power table
[c] The power of rejecting H0, r=0 is at least 90% based on Cohen's power table

Summary:

- Fexofenadine exhibits approximately linear pharmacokinetics (15 and 30 mg) in children 6 months to < 2 years of age based on overall subjects (see Table 1 and 2).
- Conclusions from Table 3:
  - There was no significant ($\alpha = 0.05$) correlation observed between CLpo, and age, height, and body surface area for subjects who received a single oral dose of 15 mg fexofenadine.
  - For subjects who received 30 mg fexofenadine, a significant and positive correlation was observed between CLpo, and age, weight, height, and body surface area.
  - When the two dose groups were combined, a significant and positive correlation was observed between CLpo, and age, weight, height, and body surface area. The highest correlation was observed between CLpo, and weight in two dose groups combined.

Comment: (b) (4) who manufactured the capsules used in this study tested for content uniformity and composite assay (potency), and the results are acceptable (per the reviewing chemist).

Population pharmacokinetics (Report B2002PPK0279)

Title: Fexodenadine population pharmacokinetic parameters in adult healthy volunteers and pediatric patients 6 months to 12 years of age.

Objectives:

- To estimate the population pharmacokinetics of fexofenadine in adults and children 6 months to 12 years of age.
- To identify demographic factors which explain the variability in fexofenadine
- To provide a dosing recommendation for fexofenadine in children 6 months to 12 years of age.

Table 1. Population PK analysis was performed using the following studies:

Study design summary of studies included in population pharmacokinetic analysis (Population pharmacokinetic Study T/1123)

Study	Design	Type	Dose(s)	Plasma Sample Times (h)	Single/Multiple Doses	Population
PJPR0015	Crossover	BE	90 mg	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, and 36	Single	Adult
PJPR0025	Crossover	BA	120 mg	0, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18, 24, 30, 36, and 48	Single	Adult
PJPR0026	Crossover	FE	60 mg	0, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48	Single	Adult
PJPR0029	Crossover	BE/FE	120 mg	0, 1, 1.5, 2, 2.5, 3, 4, 8, 12, 18, 24, 30, 36, and 48	Single	Adult
PJPR0037	Crossover	PK/PD	30 mg 60 mg	0, 1, 2, 3, 6, 8, 24, and 48	Single	Pediatrics (6 to 12 years)
PJPR0094	Crossover	BE	60 mg	0, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48	Single	Adult
I/1114	Parallel	PK	30 mg	First dose: 0, 1, 2, 3, 4, 6, 8, 12, and 24 Last dose: Group I: 0 and 2 Group II: 0 and 4	Single/Multiple	Pediatrics (2 through 5 years)
T/1123	Parallel	SED	15 mg 30 mg	0, 1, 2.5, 5, 8, 12, and 24	Single	Pediatrics (6 months to <2 years)

BE = bioequivalence; BA = bioavailability; FE = food effect; PK = pharmacokinetic; PD = pharmacodynamic; SED = single escalating dose.

All the data were derived after single-dose administration except in 2- through 5-year-olds where the pharmacokinetics were assessed after a single dose and following twice-daily dosing for 4-7 days. The PK parameter data base included data from 269 treatment doses from 136 adult subjects, and 90 treatment doses from 77 pediatric patients. Adult subjects ranged in age from 18 to 45 years, in weight from 58.1 to 101.7 kg, and in height from 165.1 to 195.6 cm. Pediatric patients ranged in age from 6 months to 12 years, in weight from 7.8 to 51.5 kg, and in height from 34 to 156 cm. The data base included 26 female (all less than 8 years old) and 187 male participants. In protocol M016455T/1123, 48 subjects received the study medication out of which 41 had all the scheduled PK samples collected and the parameters computed.

Formulations: Data included in this analysis are from studies in adults and children 6 to 12 years where fexofenadine HCl was administered in capsule formulation, except in study PJPR0094 which used tablet formulation (tablets are bioequivalent to capsules). For children aged 6 months through 5 years, fexofenadine HCl was administered by mixing capsule contents ((b) (4) powder) in applesauce.

Modeling process: Data were analyzed via non-linear mixed-effects modeling with the NONMEM software. Population PK models were developed using an iterative process in an attempt to define the best (most useful) model for the data.

Evaluation of Models and Covariates: A simple structural model without covariates was evaluated for C_{max} and CLpo to determine appropriateness as a base model for adults and pediatrics. Covariate-parameter (e.g., age, gender, weight, etc.) relationships were explored for C_{max} and CLpo: covariates were added to base model using a stepwise forward addition method based on the associated decrease in objective function value (OBJ) and its statistical significance. A decrease in standard error, inter-individual variance of the pharmacokinetic parameters and residual error were also considered as model selection criteria.

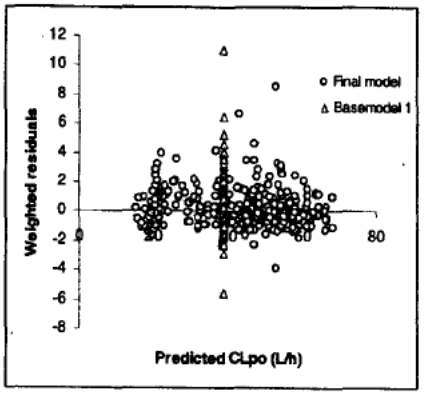
Results

Sponsor's Model: The sponsor combined all of the adults and pediatrics data for the Population PK modeling. Database consisted of a total 359 PK parameter observations from 213 subjects in 8 studies. The final population model for describing the CLpo and C_{max} are given below, and the diagnostic plots are shown in the figures below

$$CLpo_i = 46.8 \bullet \left(\frac{WGT_i}{W_{std}}\right)^{0.75} \bullet e^{(-0.0212 \bullet (Agei - 26))}$$

$$C\max_i = 211 \bullet \left(\frac{WGT_i}{W_{std}}\right)^{-0.611}$$

Figure 1. Diagnostic plots for base and final model for CLpo



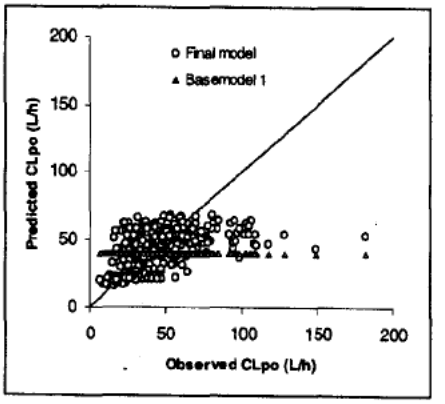


Figure 2. Diagnostic plots for base and final model for C_{max}

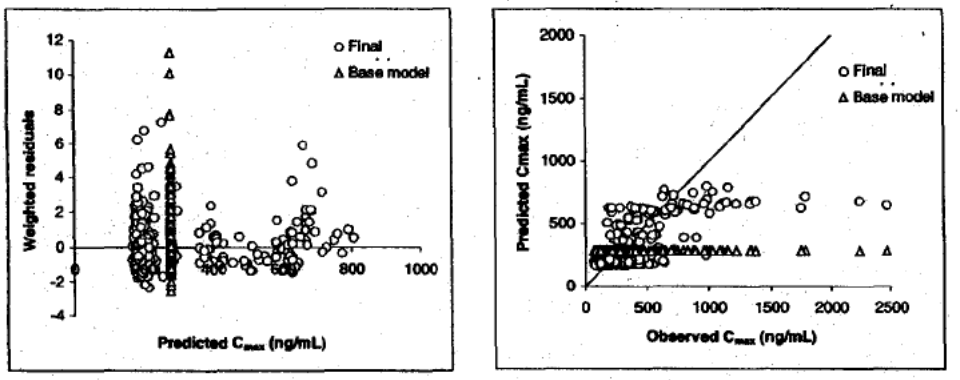


Table 2. Summary of fexofenadine PK parameter estimates from the (sponsor's) final model

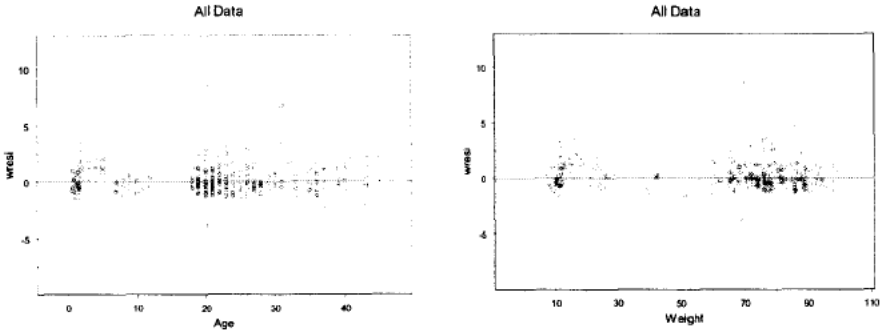
	n	15 mg		30 mg		60 mg	
		AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)
6 months - <2 yrs							
Weight ≤10.5 kg	*	1080±332	185±51	2140±546	361±122	-	-
Weight >10.5 kg	**	761±247	136±44	1460±708	253±150	-	-
2 - 5 yrs	21	-	-	930±234	154±39	-	-
7 – 12 yrs	***	-	-	1060±220	153±56	2110±561	303±115
Adults	269	-	-	-	-	1290±424	165±56

*based on 5 and 8 subjects for 15 and 30 mg dose, respectively;
**based on 14 and 15 subjects for 15 and 30 mg dose, respectively;
***based on 14 and 13 subjects for 30 and 60 mg dose, respectively;

The predicted CLpo based on the final model for adults, children 7-12 and 2-5 years of age are 52.2, 30.2 and 34.3 L/h, respectively. The predicted CLpo based on the final model in children 6 months to <2 years of age with body weight ≤10.5 kg and >10.5 kg are 14.9 and 23.6 L/h, respectively. Accordingly, the individual apparent oral clearance estimates of fexofenadine were on average 42% and 34% lower in children 7 to 12 years (n=14) and 2 to 5 years (n=21), respectively, compared to adults. In the 6 months to <2 year age group, when stratified by a body weight of 10.5 kg, the individual clearance estimates were on average 71% and 55% lower than in adults for the ≤10.5 kg (n=13) and >10.5 kg (n=29) groups, respectively.

Reviewer's Model: Since the database for adults is about 2-fold larger than that of pediatrics', it caused artificial bias to the data for pediatrics ((Figure 3). Therefore, this reviewer analyzed the data by separating the data set per adults and pediatrics, and modeled each population (i.e., adults and pediatric population) separately.

Figure 3. Weighted residuals vs age or weight (includ adults and pediatrics)



Data sets: A total of 90 fexofenadine PK parameter observations from 77 subjects in 3 studies were pooled for the population analysis for pediatrics, while a total of 269 PK parameter observations from 136 subjects in 5 studies were pooled for the adults population analysis.

Covariates: Based on the magnitude of decrease in OBJ, the covariates were ranked in the order age>weight>height>dose>gender>race with age being the most significant in pediatrics, while dose>age>height>weight>gender≅ race in adults. However, adding weight to the age power model for pediatrics or age to the dose model for adults, *i.e.*, a step-wise forward addition, did not improve the models significantly (at the significance level of $p<0.05$).

Table 3 and 4 summarizes the results of the base and final models for pediatrics and adults, respectively. Diagnostic plots for CLpo and C_{max} from the final model for pediatrics are shown in Figure 4 and those for adults are shown in Figure 5.

Table 3. Parameter estimates from models for Pediatrics – CLpo and C_{max}

	CL_{PO}	
Parameter	Base model	Final model
Model	$P_i = \theta_{tv}$	$P_i = \theta_1 \bullet (e^{(-\theta 2 \bullet Age)} - e^{(\theta 3 \bullet Age)})$
Estimate (SEE)[1]	θ_{tv}=24.4 (6%)	θ_1=683(46%), θ_2=0.187(5%), θ_3=0.218(11%)
IIV %CV (SEEv)[2]	47% (17%)	36% (21%)
Residual %CV(SEEv)[3]	15% (28%)	14.4 (NA)[5]
OBJ[4]	527	489.2
	C_{MAX}	
Parameter	Base model	Final model
Model	$P_i = \theta_{tv}$	$P_i = \theta_1 \bullet (Age/age_{std})^{\bullet \theta 2}$
Estimate (SEE)[1]	θ_{tv}=534 (7%)	θ_1 = 431(4%), θ_2 = -0.375(17%)
IIV %CV (SEEv)[2]	58% (16%)	48% (21%)
Residual %CV(SEEv)[3]	22% (32%)	23% (36%)
OBJ[4]	1122.8	1098.7

[1]Parameter estimate (SEE = Standard error of the estimate)
[2]Inter-individual variability %CV (SEE of variance)
[3]Residual variability %CV (SEE of variance)
[4]NONMEM objective function [4]Not applicable (additive error model)

Table 4. Parameter estimates from models for Adults – CLpo and C_{max}

	CL_{PO}	
Parameter	Base model	Final model
Model	$P_i = \theta_{tv}$	$P_i = \theta_1 \bullet (Dose/dose_{std})^{\bullet\theta 2}$
Estimate (SEE)[1]	θ_{tv}=50.6 (3%)	θ_1= 48.5 (3%), θ_2= -0.452 (23%)
IIV %CV (SEEv)[2]	34% (13%)	31% (15%)
Residual %CV(SEEv)[3]	19% (14%)	19% (14%)
OBJ[4]	1741.2	1722.3
	C_{MAX}	
Parameter	Base model	Final model
Model	$P_i = \theta_{tv}$	$P_i = \theta_1 \bullet (Dose/dose_{std})^{\bullet\theta 2}$
Estimate (SEE)[1]	θ_{tv}=199 (3%)	θ_1 = 210 (3%), θ_2 = -0.502 (22%)
IIV %CV (SEEv)[2]	34% (15%)	30% (18%)
Residual %CV(SEEv)[3]	26% (22%)	26% (17%)
OBJ[4]	2634.5	2613.4

[1]Parameter estimate (SEE = Standard error of the estimate)
[2]Inter-individual variability %CV (SEE of variance)
[3]Residual variability %CV (SEE of variance)
[4]NONMEM objective function

The plots of predicted CLpo and C_{max} versus weighted residual (wresi) indicated that there is systematic bias, however, the goodness-of-fit were demonstrated for the plots of predicted *vs.* observed for CLpo and C_{max}.

Figure 4. Diagnostic plots for CLpo (left) and C_{max} for pediatrics (final model).

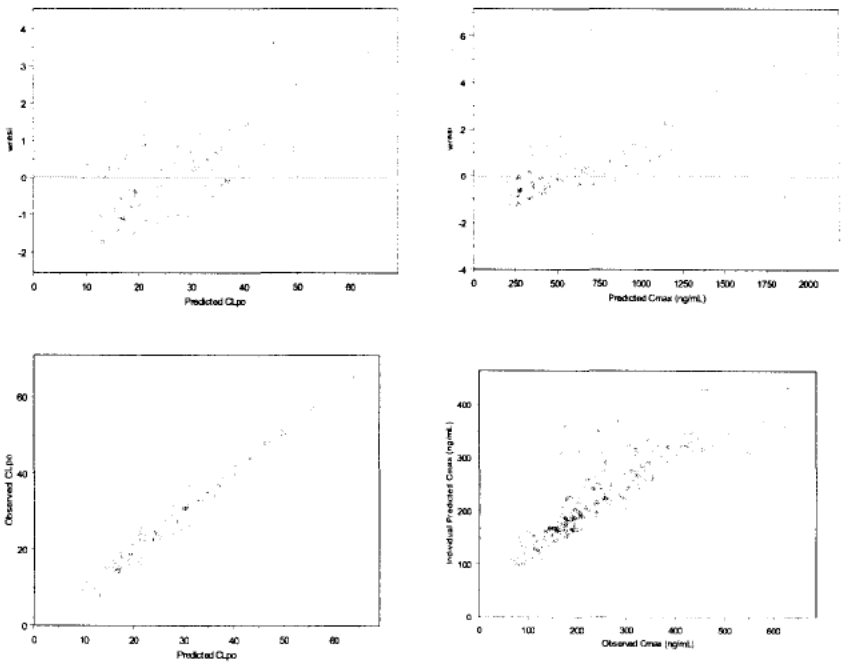
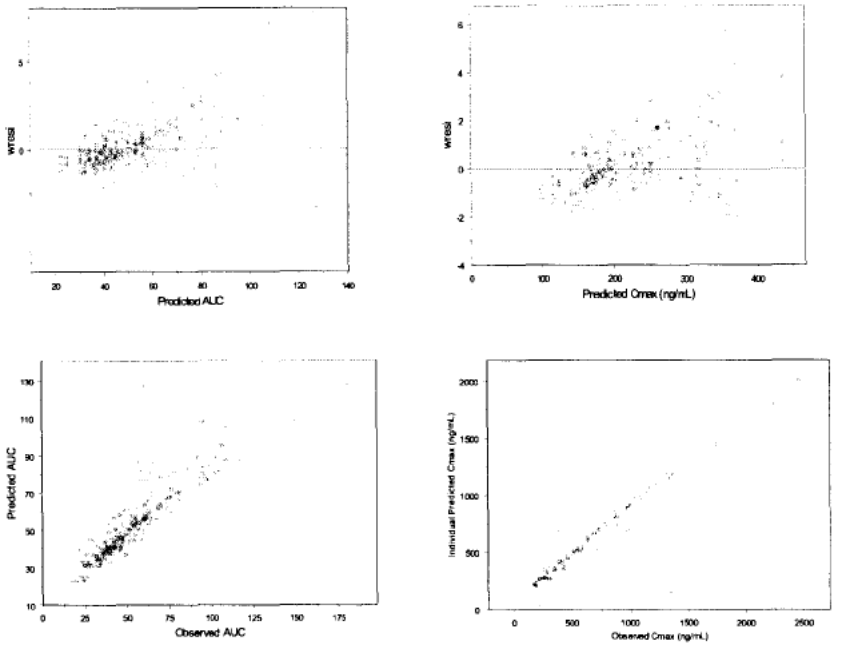


Figure 5. Diagnostic plots for CLpo (left) and C_{max} for adults (final model).



The mean (±STD) PK parameter estimates subdivided per age and weight for 6 months to < 2 years of age group from the final model is shown in Table 5.

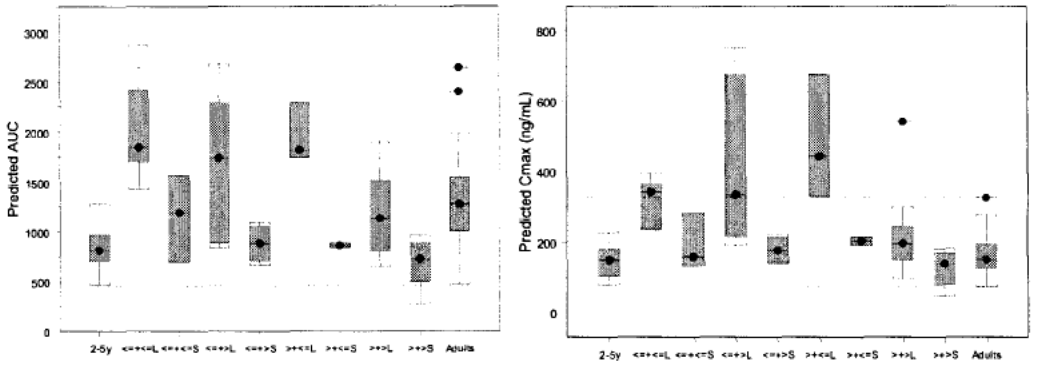
Table 5. Summary of fexofenadine PK parameter estimates from the final model

	15 mg		30 mg		60 mg	
	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)
≤1yr+≤10.5kg[3]	**1150±437**	**191±80**	2050±581	315±75	-	-
≤1yr+>10.5kg[2]	**882±206**	**180±41**	2210±670	543±295	-	-
>1yr+≤10.5kg[4]	**862±33**	**203±17**	1950±300	483±176	-	-
>1yr+>10.5kg[1]	671±257	127±54	**1180±400**	**214±115**	-	-
2 - 5 yrs[5]	-	-	845±218	145±44	-	-
7 – 12 yrs[6]	-	-	1060±284	157±62	2110±585	308±127
Adults[7]	-	-	-	-	1290±414	165±54

[1]n= 10 and 13 for 15 and 30 mg, respectively; [2]n= 4 and 2 for 15 and 30 mg, respectively;
[3]n= 3 and 5 for 15 and 30 mg, respectively; [4]n= 2 and 3 for 15 and 30 mg, respectively;
[5]n= 21; [6]n= 14 and 13 for 30 and 60 mg, respectively; [7]n= 269

Figures 6 shows the box plots that illustrate the distribution of AUC and C_{max} for 6 months-<2 years and 2-5 years of age in reference to adults after 60 mg fexofenadine: L and S denote for administered dose of 30 and 15 mg, respectively. <=+<=, <=+> and >+> denote for children 6 months to ≤1 year of age and weighing ≤10.5 kg, children 6 months to ≤1 year of age and weighing >10.5 kg and children 6 months to >1 year of age and weighing >10.5 kg, respectively.

Figure 6. AUC and C_{max} as function of age-weight group



Administration of 30 mg fexofenadine to 7 to 12 years of age produced exposures (predicted C_{max} and $AUC_{0-\infty}$) comparable to those seen with a dose of 60 mg administered to adults. Administration of 30 mg dose administered to children 2 to 5 years of age produced exposures lower, but within the range, than those seen with a dose of 60 mg administered to adults. In children 6 months to <2 years of age, the following doses produced exposures comparable to those seen with a dose of 60 mg administered to adults: administration of 15 mg fexofenadine to children 6 months to ≤1 year and weighing ≤10.5 kg or >10.5 kg (i.e., regardless of body weight) or >1 year of age with body weight ≤10.5 kg produced exposures similar to those seen with a dose of 60 mg administered to adults, while administration of 30 mg produced similar estimates of exposures for children >1 year of age and weighing >10.5 kg in comparison to 60 mg dose in adults. Noted that there were three outliers for C_{max} values of 751, 676 and 543 ng/mL (median = 202.4 ng/mL). The age and weight of these children were 1 year and 10.9 kg, 1.5 years and 10.2 kg and 1.75 years and 11.8 kg, respectively.

(b) (4)

In terms of CLpo, instead of AUC, the predicted CLpo by the final model for adults, children 7-12 and 2-5 years of age are 51.9, 30.3 and 37.9 L/h, respectively. The predicted CLpo in children 6 months to >1 year of age with body weight ≤10.5 kg and >10.5 kg are 16.3 and 27.8 L/h, respectively. The predicted CLpo in children 6 months to ≤1 year of age with body weight ≤10.5 kg and >10.5 kg are 15.2 and 16.6 L/h, respectively. This indicates that the individual apparent oral clearance estimates of fexofenadine were on average 42% and 27% lower in children 7 to 12 years (n=14) and 2 to 5 years (n=21), respectively compared to adults. The individual clearance estimates of fexofenadine were on average 69% and 46% lower than in adults for children 6 months to >1 year of age with body weight ≤10.5 kg (n=5) and >10.5 kg (n=23), respectively. The individual clearance estimates of fexofenadine were on average 68% and 71% lower than in adults for children 6 months to ≤1 year of age with body weight >10.5 kg (n=6) and ≤10.5 kg (n=8), respectively.

The mean (±STD) PK parameter estimates subdivided per weight for 6 months to <2 years of age along with other age group from the final model is shown in Table 6 (Table 5 for comparison):

Table 6. Summary of fexofenadine PK parameter estimates from the final model

		15 mg		30 mg		60 mg	
	n	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)
6 months - <2 yrs							
Weight ≤10.5 kg	*	1040±347	196±57	2010±471	378±140	-	-
Weight >10.5 kg	**	731±251	142±53	1310±548	258±176	-	-
2 - 5 yrs	21	-	-	845±218	145±44	-	-
7 – 12 yrs	***	-	-	1060±284	157±62	2110±585	308±127
Adults	269	-	-	-	-	1290±414	165±54

*based on 5 and 8 subjects for 15 and 30 mg dose, respectively;
**based on 14 and 15 subjects for 15 and 30 mg dose, respectively;
***based on 14 and 13 subjects for 30 and 60 mg dose, respectively.

Conclusions:

- Age and body weight are significant predictors of variability in fexofenadine pharmacokinetics in pediatrics.

(b) (4)

Protocol PJPR0076

Study Type: BA of fexofenadine oral single dose.

Title: Bioavailability of Fexofenadine Hydrochloride Capsules Coadministered with Applesauce and of Prototype Formulations for Pediatric Use.

Investigator and Location: (b) (4)

Objectives:

- To determine the bioavailability of the fexofenadine (b) (4) relative to the marketed immediate-release capsule.
- To determine the bioavailability of the fexofenadine marketed immediate-release capsule when coadministered with applesauce.

Formulation:

Table 1. Manufacturing History of the Fexofenadine HCl Formulations

Trmt	Lot Number	Formula Number	Release Date	Dosage Form	Strength	Batch Size	Comments
A	RH9631	(b) (4)	9/24/96	(b) (4)	60 mg	(b) (4)	(b) (4)
B	RH9636		10/11/96		60 mg		
C, D	RK9532		12/18/95	capsule	60 mg		

A: Fexofenadine HCl (2 x 60 mg) (b) (4) (Lot RH9631) given as a single dose
B: Fexofenadine HCl (2 x 60 mg) (b) (4) (Lot RH9636, capsule contents) given as a single dose
C: Fexofenadine HCl (2 x 60 mg) marketed IR capsules (Lot RK9532, capsule contents) in 10 ml applesauce given as a single dose
D: Fexofenadine HCl (2 x 60 mg) marketed IR capsules (Lot RK9532) given as a single dose

Study Design:

The study was conducted using an open-label, four-period, four-treatment, randomized, complete crossover single-dose design. Twenty-two healthy male volunteers between 19 and 39 years of age received the following treatments.

Treatment A: Fexofenadine (2 x 60 mg) (b) (4)
Treatment B: Fexofenadine (2 x 60 mg) (b) (4)
Treatment C: Fexofenadine (2 x 60 mg) marketed immediate-release capsules (capsule contents) in 10 mL applesauce
Treatment D: Fexofenadine (2 x 60 mg) marketed immediate-release capsules

All subjects fasted overnight. All treatments were separated by a washout period of 6 days. Serial blood samples were collected for fexofenadine analyses during a 48-hour period after each treatment.

Sampling times: Blood samples were collected at t = predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after the dose

Analytical Methodology:
Assay Method: LCMS/MS
Assay Sensitivity: Range 1.0 – 100 ng/mL
Accuracy and Precision: Satisfactory; precision (%CV) and accuracy were 8.1-13.7% and 90.8-100.5%, respectively.

Criteria for evaluation:
PK: C_{max}, t_{max}, AUC_{0-z}, $AUC_{0-\infty}$, and $t_{1/2}$
Safety: Laboratory tests, ECGs and adverse events.

Statistical methods: Fexofenadine plasma concentrations were analyzedd by noncompartmental methods. Treatment comparisons were evaluated with an analysis of the natural log transformed data. An analysis of variance, with terms for sequence, subject within sequence, treatment and period, was done for each parameter from which 90% confidence intervals for the ratio of treatment means were obtained.

Results:

Figure 1 presents the mean plasma concentration versus time profiles for all treatments. Mean plasma fexofenadine PK parameters for each treatment and pairwise treatment comparisons are presented in Table 1.

Figure 1. Mean fexofenadine plasma concentration versus time profiles of single oral dose of fexofenadine 120 mg using different formulations

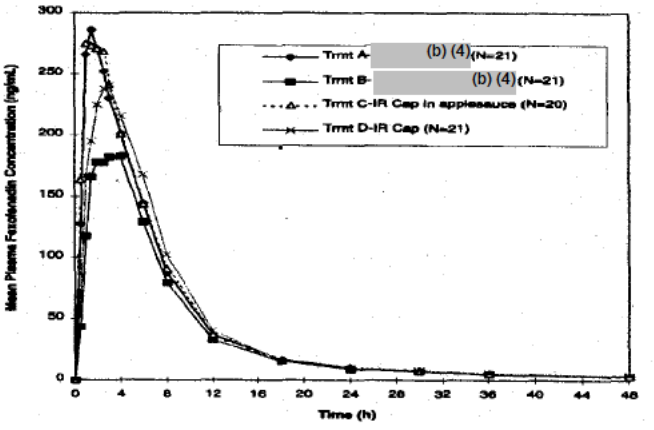


Table 1. Treatment Comparisons for key Plasma fexofenadine PK Parameters

Table 3. Treatment Comparisons for Key Plasma Fexofenadine Pharmacokinetic Parameters

Parameter	Treatment	Mean	%CV	Adjusted Mean*	Pairwise Comparisons		
					Pair	Ratio (%)†	90% CI on Ratio†
AUC(0-∞) (h•ng/mL)	A	2152.17	41.77	2039.27	A/D	97.47	(85.9, 110.6)
	B	1735.81	44.20	1636.90	B/D	78.24	(68.9, 88.8)
	C	2207.63	29.22	2195.65	C/D	104.95	(92.3, 119.4)
	D	2172.36	36.32	2092.17	-	-	-
C_{max} (ng/mL)	A	312.46	41.07	293.75	A/D	104.46	(88.4, 123.4)
	B	223.85	49.76	205.60	B/D	73.12	(61.9, 86.4)
	C	314.05	28.89	313.15	C/D	111.36	(94.0, 132.0)
	D	300.02	42.95	281.20	-	-	-
t_{max} (h)	A	1.81	43.23	1.70	A/D	76.44	(61.0, 95.8)
	B	2.79	30.87	2.67	B/D	120.07	(95.7, 150.6)
	C	1.65	44.08	1.50	C/D	67.64	(53.8, 85.1)
	D	2.57	58.43	2.22	-	-	-

A: Fexofenadine HCl (2 x 60 mg) (b) (4) (Lot RH9631) given as a single dose to fasted subjects (n=21)
B: Fexofenadine HCl (2 x 60 mg) (b) (4) (Lot RH9636, (b) (4) given as a single dose to fasted subjects (n=21)
C: Fexofenadine HCl (2 x 60 mg) marketed IR capsules (Lot RK9532, capsule contents) in 10 ml applesauce given as a single dose to fasted subjects (n=20)
D: Fexofenadine HCl (2 x 60 mg) marketed IR capsules (Lot RK9532) given as a single dose to fasted subjects (n=21)
* Adjusted mean is the least square mean transformed to the original scale from the analysis of log transformed data.
† Ratio (%) and 90% confidence interval (CI) on ratio were calculated from results of ANOVA on log transformed data.

Summary:

- (b) (4) is bioequivalent to the marketed IR capsule formulation based on $AUC_{0-\infty}$ and C_{max}.
- IR capsule contents emptied into 10 mL applesauce is bioequivalent to the marketed IR capsule formulation with respect to $AUC_{0-\infty}$ but not C_{max}.
- The (b) (4) formulation is not bioequivalent to the marketed IR capsule formulation.

Protocol M016455T/1001

Study Type: BA of fexofenadine 60 mg oral single dose

Title: An open label, bioavailability study of fexofenadine HCl 60 mg capsules administered orally in food delivery vehicles in fasting healthy adult male subjects.

Investigator(s), study site(s): (b) (4)

Objective: To characterize the relative bioavailability of 60 mg fexofenadine administered in food delivery vehicles compared to a 60 mg fexofenadine oral reference capsule.

Design: The study was a randomized, open-label, single-dose, four-way, complete crossover design in 24 subjects (20 completed). There was washout period of at least 6 days between doses. The study consisted of four periods, during which each subject received all treatments under fasted conditions. Fexofenadine HCl 60 mg capsule (Batch # 1035369) was administered as a (b) (4) powder in delivery vehicles as follows:

Treatment A: A single oral dose of 60 mg fexofenadine (b) (4) powder administered in 10 mL of Karo® Light syrup followed by 230 mL of water,
Treatment B: A single oral dose of 60 mg fexofenadine (b) (4) powder administered in 10 mL of Dannon® vanilla yogurt (low fat) followed by 230 mL of water,
Treatment C: A single oral dose of 60 mg fexofenadine (b) (4) powder administered in 10 mL of Gerber® rice cereal prepared with Similac with Iron® followed by 230 mL of water,
Treatment D: A single oral dose of 60 mg fexofenadine capsule administered with 240 mL water (reference treatment).

Sampling times: Blood samples were collected at t = prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36 and 48 hours post dose.

Analytical Methodology:
Assay Method: LCMS/MS
Assay Sensitivity: Range 1.0 – 150 ng/mL
Accuracy and Precision: Satisfactory; precision (%CV) and accuracy were 4.0-13.7% and 94.8-99.6%, respectively.

Criteria for evaluation:
PK: C_{max}, t_{max}, AUC_{0-z}, $AUC_{0-\infty}$, $t_{1/2}$ and CLpo
Safety: Laboratory tests, ECGs, physical exams, and adverse events.

Statistical methods: Comparisons between treatments were evaluated with an analysis of the natural log-transformed data. ANOVA with term for sequence, subject within sequence, period and treatment was performed for each parameter, from which 90% confidence intervals for the ratio of treatment means were obtained. Treatments A, B, and C were considered equivalent to Treatment D if the 90% confidence interval for the treatment ratio fell within 70% to 143%. The primary statistical comparison was to be based on C_{max} and $AUC_{0-\infty}$.

Results:

Summary of descriptive statistics of the PK parameters as well as the comparison between treatments are presented in the tables below:

Summary of fexofenadine pharmacokinetic parameter descriptive statistics

Treatment	AUC(0-∞) [a] (h*ng/mL)	C_{max} [a] (ng*mL)	t1/2 [a] (h)	t_{max} [b] (h)
A	1075 (27.3)	162 (32.6)	11.7 (48.9)	1.5 (1.0-3.0)
B	1039 (51.0)	153 (43.8)	11.8 (28.6)	1.5 (1.0-4.0)
C	915 (28.8)	139 (41.3)	11.2 (21.4)	1.5 (0.5-3.0)
D	952 (32.4)	124 (33.7)	11.4 (34.0)	2.0 (1.0-6.0)

[a] Reported values represent mean and (%CV)
[b] Reported as median values and (ranges)
A= 60 mg of fexofenadine (b) (4) powder administered in 10 mL of Karo® Light Syrup
B= 60 mg of fexofenadine (b) (4) powder administered in 10 mL of Dannon® vanilla yogurt (low fat)
C= 60 mg of fexofenadine (b) (4) powder administered in 10 mL of Gerber® rice cereal prepared with Similac with Iron®
D= 60 mg fexofenadine reference capsule

Summary of treatment comparisons for plasma pharmacokinetic parameters

Parameter	Treatment[a]	Adjusted Mean	%CV	Treatment comparison	Ratio %	90% Confidence interval on ratio %	p-value
AUC(0-∞) (ng*h/mL)	A	1045.25	27.33	A/D	115.29	103.63, 128.26 [b]	0.0296
	B	948.95	50.96	B/D	104.67	93.95, 116.61 [b]	0.4832
	C	867.19	28.81	C/D	95.65	85.83, 106.59 [b]	0.4050
	D	906.63	32.45				
C_{max} (ng/mL)	A	155.25	32.65	A/D	132.92	114.83, 153.85	0.0019
	B	142.24	43.78	B/D	121.78	105.12, 141.08 [b]	0.0289
	C	127.82	41.26	C/D	109.43	94.25, 127.06 [b]	0.3176
	D	116.80	33.69				

[a] A= 60 mg fexofenadine (b) (4) powder administered in 10 mL of Karo® Light Syrup; B= 60 mg fexofenadine (b) (4) powder administered in 10 mL of Dannon® vanilla yogurt (low fat); C= 60 mg fexofenadine (b) (4) powder administered in 10 mL of Gerber® rice cereal prepared with Similac with Iron®; D= 60 mg fexofenadine reference capsule
[b] Values within the 70% to 143% criterion

The relative bioavailability of 60 mg fexofenadine (b) (4) power administered in three food delivery vehicles (Treatments A, B and C) were 115.3 %, 104.7 %, and 95.7 %, respectively, relative to the 60 mg reference capsule (Treatment D); $AUC_{0-\infty}$ after Treatments B and C met BE criteria (i.e., 80-125%), but not after Treatment A. C_{max} following all 3 Treatments were higher (out side range of BE range) compared to the reference fexofenadine capsule (Treatment D).

Conclusions:

60 mg fexofenadine (b) (4) power administered in three food delivery vehicles (Treatments A, B and C) were not BE to the 60 mg reference capsule (Treatment D).

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-625 20-872 20-786**	**Brand Name**	**Allegra Capsules Allegra Tablets Allegra-D**
OCPB Division (I, II, III)	**DPE-II**	**Generic Name**	**Fexofenadine HCl**
Medical Division	**HFD-570**	**Drug Class**	**H_1-receptor antagonist**
OCPB Reviewer	**Shinja Kim**	**Indication(s)**	**Seasonal allergic rhinitis Chronic idiopathic urticaria**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**Capsules/tablets**
		Dosing Regimen	**60 mg bid or 180 mg qd for adults. 30 mg bid for 6-11 years of age**
Date of Submission	**11/18/02**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**3/18/03**	**Sponsor**	**Aventis Pharaceuticals**
PDUFA Due Date	**5/08/03**	**Priority Classification**	**P**
Division Due Date	**4/24/03**		

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:	x	1	1	Single PK study using 15 and 30 mg in 6 months to 2 years of age
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	1	1	Data from 8 studies
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		2	2	
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		4	4	3 PK study and a population PK analysis

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	x	**The sponsor was requested to provide for the following:** • Electronic format of NONMEM (all) data sets and (all) control NONMEM output files for Population PK analysis (Report #B2002PPK0279)
Comments sent to firm ?		
QBR questions (key issues to be considered)	• **Is pediatric study conducted according to the 'Pediatric Written Request'?** • (b) (4)	

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/s/

Shinja Kim
4/24/03 08:07:56 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
4/24/03 11:39:35 AM
BIOPHARMACEUTICS
I concur