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The Utility of Mixed-Effects Covariate Analysis in Rapid Selection of Doses in Pediatric Subjects: A Case Study with Fexofenadine Hydrochloride

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ABSTRACT: Fexofenadine hydrochloride is a non-sedating antihistamine that is used in the treatment of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. A pooled analysis of pharmacokinetic data from children 6 months to 12 years of age and adults was conducted to identify the dose(s) in children that produce exposures comparable to those in adults for the treatment of seasonal allergic rhinitis. The pharmacokinetic parameter database included peak and overall exposure data from 269 treatment exposures from 136 adult subjects, and 90 treatment exposures from 77 pediatric allergic rhinitis patients. The data were pooled and analysed using NONMEM software, version 5.0. A covariate model based on body weight and age and a power function model based on body weight were identified as appropriate models to describe the variability in fexofenadine oral clearance and peak concentration, respectively. Individual oral clearance estimates were on average 44%, 36% and 61% lower in children 6 to 12 years ($n = 14$), 2 to 5 years ($n = 21$), and 6 months to 2 years ($n = 42$), respectively, compared with adults. Trial simulations ($n = 100$) were carried out based on the final pharmacostatistical models and parameter estimates to identify the appropriate dose(s) in children relative to the marketed dose of 60 mg fexofenadine hydrochloride in adults. The trials were designed as crossover studies in 18 subjects comprising various potential dosing regimens with and without weight stratification. Pharmacokinetic parameter variability was assumed to have a log-normal distribution. Individual weights and ages were simulated using mean (SD) estimates derived from the studies used in this analysis and proportional measurement/model mis-specification errors derived from the analysis were incorporated into the simulation. The results indicated that a 30 mg dose of fexofenadine hydrochloride administered to children 1 to 12 years of age and weighing >10.5 kg and a 15 mg dose administered to children 6 months and older and weighing $\leqslant$10.5 kg produces exposures similar to those seen with the 60 mg dose in adults. Copyright © 2004 John Wiley & Sons, Ltd.

Key words: fexofenadine hydrochloride; pediatric population; pharmacokinetics; simulation; NONMEM; allergic rhinitis

Introduction

Fexofenadine hydrochloride (HCl) is currently approved in the United States (US) for adults and children 6 years of age and older as Allegra™ for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU) [1–8]. Placebo-controlled studies in adults have shown that fexofenadine is significantly superior to placebo in reducing SAR symptoms [3,9]. Fexofenadine HCl was well tolerated in all Phase I and clinical safety and efficacy trials with no evidence of dose-dependent increases in adverse events

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[3–4]. The most common adverse event observed with fexofenadine was headache, which occurred with similar frequency in patients treated with placebo. The currently approved doses/regimens of fexofenadine HCl in SAR are 60 mg BID and 180 mg QD for adults and 30 mg BID for children 6 to 12 years of age.

The pharmacokinetics of fexofenadine has been recently studied in children of ages 2 to 5 years and 6 months to 2 years (data on file). In children 2 to 5 years, the single and multiple dose pharmacokinetics of 30 mg fexofenadine HCl were evaluated and in children 6 months to 2 years, single doses of 15 and 30 mg were evaluated in anticipation of body-size-related increases in exposure. The clinical pharmacology aspect of these studies will be published separately. The relatively rich nature of blood samples collected across the pediatric population has allowed the pharmacokinetic parameters to be derived using noncompartmental techniques. However, comparison of pharmacokinetic metrics across the patient population is difficult because of the observed variability in exposure and the influence of age/body size-related factors on the pharmacokinetic behavior of fexofenadine.

Conventional approaches have typically involved initiation of compartmental analysis of the plasma concentration data followed by covariate analysis. In this study, pharmacokinetic parameters (C_{max} and CL_{po}) that were previously derived using noncompartmental analysis were used directly for covariate analysis to aid in the selection of doses for the pediatric population. This approach was made possible because fexofenadine pharmacokinetics was well characterized in the studies used for the pooled analysis with robust sampling times. The approach undertaken here represents the generation of robust data in support of dose selection while minimizing the time required to complete the analysis when using the conventional approach.

The present analysis was thus undertaken to examine the factors that contribute to the pharmacokinetic behavior of fexofenadine in children and adults using a mixed-effects modeling approach. The focus of the analysis was on estimating the typical population parameters and inter-individual variability in adults and children and investigating the relationship between patient demographics and exposure using mathematical models. The rationale for determining fexofenadine dose(s) based on achieving exposure(s) similar to those proven to be safe and efficacious in adults for treating SAR is derived from the expectation that the mechanism and pharmacology of fexofenadine as an H1 antagonist in children is substantially similar to that in adults.

Methods

Study design and analysis population

The study protocols used for the present analysis were single- or multiple-dose studies involving a variety of doses, parallel-group or crossover study designs, with and without repeated treatment administration. Pharmacokinetic data were obtained from bioavailability, bioequivalence and food-effect studies in healthy adult volunteers, a pharmacokinetic/pharmacodynamic study in children 6 to 12 years of age, a multiple-dose pharmacokinetic study in children 2 to 5 years of age and a multi-center, single escalating dose safety and pharmacokinetic study in children 6 months to 2 years of age (data on file). All the data were derived after single-dose administration except in 2- to 5-year-olds where the pharmacokinetics was assessed after single and twice-daily dosing for 4 to 7 days. Table 1 summarizes the details of the study designs, sampling collection times, doses, and analysis populations (data on file).

Ethics and administration

All the studies were conducted in accordance with good clinical practice (GCP) as required by the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice, 1 May 1996, and standard operating procedures for clinical investigation and documentation in force at Aventis Pharmaceuticals worldwide. Compliance with these requirements also constituted conformity with the ethical principles of the Declaration of Helsinki. The clinical study protocols, informed consent documents, and other

Table 1. Summary of studies included in the modeling analysis

Study	Design	Type	Dose(s)	Plasma sample times (h)	Single/multiple doses	Population
1	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
2	Crossover	BA	120 mg	0, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18, 24, 30, 36 and 48	Single	Adult
3	Crossover	FE	80 mg	0, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 28, 30, 36 and 48	Single	Adult
4	Crossover	BE/FE	120 mg	0, 1,1.5, 2, 2.5, 3, 4, 8, 12, 18, 24, 30, 36 and 48	Single	Adult
5	Crossover	PK/PD	30 mg 60 mg	0, 1, 2, 3, 6, 8, 24 and 48	Single	Pediatrics 6–12 years
6	Crossover	BE	60 mg	0, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 28, 30, 36 and 48	Single	Adult
7	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 1	Single/Multiple	Pediatrics (2–5 years)
8	Parallel	SED	15 mg 30 mg	0, 1, 2.5, 5, 8, 12 and 24	Single	Pediatrics (6 months–<2 years)

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

appropriate study-related documents were reviewed and approved by independent ethics committees (IEC)/institutional review boards (IRB).

Test formulations

Pharmacokinetic data were primarily obtained using fexofenadine HCl administered in capsule form. The granulation formula was identical in each of the capsule formulations. For studies in children 2 to 5 years and 6 months to 2 years of age, fexofenadine HCl granulation powder was supplied in capsules and was administered by emptying the contents onto applesauce. It has been previously demonstrated that the immediate release capsule contents emptied onto 10 ml applesauce produces similar exposures as the marketed capsule administered intact. In addition, tablet data from a bioequivalence study in healthy volunteers was included as tablets were demonstrated to be bioequivalent to capsules.

Bioanalytical methods

Plasma samples collected from studies in adult healthy volunteers and in children 6 to 12 years were analysed for fexofenadine at Kansas City Analytical Services Inc., and those collected in smaller children were analysed at Quintiles, Inc., Kansas City, MO. Cross-validation of the two high performance liquid chromatography/tandem mass spectrometry methods from the two centers indicated that the assays are essentially the same. However, due to blood volume constraints, a more sensitive assay was developed and used for the group of smallest children (0.5 ng/ml lower limit of quantification [LOQ] from 50 µl plasma) than those used for adults and older children (2 ng/ml LOQ from 100 µl plasma for 2- to 5-year-olds and 1 ng/ml LOQ from 0.5 ml plasma or greater for 6- to 12-year-olds and adults).

Pharmacokinetic parameter data

A data set containing key variables, such as protocol number, patient identification number, demographics (weight, age, height, gender and race), dose information and pharmacokinetic (PK) parameters such as peak concentration (C_{max}), area under the plasma concentration-time curve over infinity (*AUC*), oral clearance (*CL*), terminal half-life ($t_{1/2}$) was compiled. The data set included one record for each subject per treatment observation from each of the eight protocols grouped together by subject identifier (ID) and was assembled according to the typical data format requirements for $PRED [10]. Parameter data reported in the individual study

reports based on noncompartmental analysis were used for the present analysis. For the study in children 2 to 5 years, as sparse samples were collected at steady state, clearance estimates based on nonlinear mixed-effects modeling of single dose and steady state data were utilized for the present analysis.

Data analysis

The pharmacokinetic parameters (C_{max} and CL_{po}) were analysed via non-linear mixed-effects modeling with the NONMEM software, version V level 1.1, NM-TRAN version III level 1.0 on Windows NT using $PRED [10]. The analysis was performed on an IBM Thinkpad T21, Mobile Intel® Pentium® III 800 MHz, 392 Mb RAM. The first-order conditional estimation method with eta-epsilon interaction (FOCE/Interaction) was employed. Parameter data from all the subjects (adults and pediatrics) were simultaneously fitted to obtain the final population model. Population PK models were developed using an iterative process in an attempt to define the best (most useful) model for the data.

Model building

A simple structural model was evaluated to determine the appropriateness as base model for C_{max} and CL_{po} with inter-individual variability modeled as exponential error model as given below

$$P_i = \theta_{tv} e^{\eta_i}$$

where P_i is the value of the parameter of the individual, θ_{tv} is the typical value (tv) of this parameter in the population, and η is a variable accounting for the inter-individual variability (IIV), which is assumed to be normally distributed with mean zero and variance ω^2.

The random residual variability in pharmacokinetic parameter was estimated using a proportional error model as shown below

$$Y_{ij} = P_i(1 + \varepsilon_{ij})$$

where Y_{ij} denotes the observed value of the parameter (jth observation (e.g. for crossover treatment) for the ith individual) and P_i denotes the model predicted value of the parameter, and ε_{ij} is the random residual error in the PK parameter, which is assumed to be normally distributed with mean zero and variance σ^2.

The parameter values were then standardized for a body weight of 70 kg using an allometric model (base model 2)

$$P_i = \theta_{tv}\left(\frac{WGT_i}{W_{std}}\right)^{PWR}$$

where P_i is the parameter in the ith individual, WGT_i is the weight in the ith individual and θ_{tv} is the parameter in an individual with a standard body weight [W_{std}] of 70 kg. The power exponent [PWR] was either fixed to the known allometric exponent of 0.75 for CL_{po} or estimated as a parameter for C_{max} [11]. In addition, the analysis was repeated using a W_{std} of 10 kg (an arbitrarily selected value from the sample population), in order to ensure robustness of the estimate irrespective of the choice of W_{std} in relation to the actual weights in the sample. The required NONMEM specific PRED subroutines were written for these various models.

After identification of the appropriate weight-based model, other (age, gender, body surface area, height, race and fexofenadine HCl dose) covariate-parameter relationships were explored for C_{max} and CL_{po}. Diagnostic plots, parameter estimates and the minimum value of the objective function were used to guide model building and assess goodness-of-fit. The likelihood ratio test was used to compare hierarchical models. Covariates were added to base model 2 using a stepwise forward addition method with a significance level of $p < 0.001$ (change in objective function value of 10.88 for 1 degree of freedom) because of the multiple comparisons inherent in this method. Upon identification of significant covariates, the full population covariate model was refined using a stepwise backwards deletion method with a significance level of $p < 0.001$. Inter-occasion variability was not evaluated since most of the subjects had only one observation per treatment/dose.

Results

The demographics for the subjects included in this analysis are summarized in Table 2. The relationship between demographics and expo-

Table 2. Demographics of the analysis population

Protocol* (number of subjects treated)	Population	Age (y) Mean (± SD) Range	Height (cm) Mean (± SD) Range	Weight (kg) Mean (± SD) Range	Body surface Area (m^2) Mean (± SD) Range	Gender #Males #Females	Race #Caucasians #Non-Caucasians
Study 1	Normal	26.6(± 7.2)	182.1(± 5.2)	80.1(± 9.0)	2.019(± 0.134)	20	19 Caucasian
($n = 20$)	subjects	19–45	172.7–190.5	65.7–95.0	1.784–2.235	Males	1 Non-Caucasian
Study 2	Normal	28.3(± 7.5)	179.7(± 5.9)	79.3(± 9.5)	1.996(± 0.145)	23	18 Caucasian
($n = 23$)	subjects	19–43	170.2−193.0	59.4–99.9	1.684–2.307	Males	5 Non-Caucasian
Study 3	Normal	25.2(± 6.3)	179.3(± 7.3)	79.2(± 12.9)	1.990(± 0.194)	24	23 Caucasian
($n = 24$)	subjects	18–41	165.1–191.8	58.1–101.7	1.685–2.335	Males	1 Non-Caucasian
Study 4	Normal	27.4(± 6.5)	181.3(± 7.1)	76.6(± 9.2)	1.969(± 0.147)	23	19 Caucasian
($n = 23$)	subjects	20–43	167.6–193.0	60.3–89.6	1.728–2.193	Males	4 Non-Caucasian
Study 5	Normal	22.8(± 5.4)	180.2(± 6.6)	77.9(± 8.4)	1.983(± 0.124)	48	46 Caucasian
($n = 48$)	subjects	18–45	167.6–195.6	61.1–98.0	1.732–2.304	Males	2 Non-Caucasian
Study 6	Pediatric	9.1(± 1.8)	134.1(± 12.6)	32.1(± 9.3)	1.103(± 0.204)	13 Males	13 Caucasian
($n = 14$)	patients	7–12	118.0–156.0	21.8–51.5	0.861–1.508	1 Female	1 Non-Caucasian
Study 7	Pediatric	3.5(± 1.2)	98.1(± 17.6)	16.3(± 3.4)	0.683(± 0.120)	12 Males	l0 Caucasian
($n = 21$)	patients	2–5	34–125	11.8–23.7	0.371–0.905	11 Females	11 Non-Caucasian
Study 8	Pediatric	1.3(± 0.4)	78.6(± 5.8)	11.1(± 1.7)	0.511(± 0.053)	26 Males	23 Caucasian
($n = 42$)	patients	0.5–1.8	65.3–89.9	7.8–17.7	0.400–0.690	16 Females	19 Non-Caucasian

sure is illustrated in Figure 1. 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 cm 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.

Mixed-effects analysis and covariate effects

The principles of allometry were applied in the covariate analysis described here. Allometric scaling takes the form of a power function with a dependent variable (e.g. clearance) and an independent variable (e.g. body weight). Considerable data in the literature indicate that body size can be linked with physiological, structural and time variables [13]. In particular, pharmacokinetic parameters have been known to scale predictably across species via allometry. The parameter values in this analysis were standardized for a body weight of 70 kg using an allometric model. In this analysis, the power exponent [PWR] was either fixed to the known allometric exponent of 0.75 for CL_{po} [16] or estimated as a parameter for C_{max}. Holford and co-workers have incorporated the use of '1/4 power models' directly as a covariate in their models [11]. West *et al.* [14,15] have mathematically demonstrated the 3/4 power principle for metabolic rates.

Based on the results from base model, where a single value of a parameter was estimated for the entire population (6 months of age to adults), the population oral clearance was estimated to be 38.9 l/h with an inter-individual variability (%CV) of 52%. The application of the allometric model resulted in significant reductions in the NONMEM objective function ($p < 0.001$) and inter-individual variability with marked improvement in diagnostic plots (Figures 2 and 3). With the allometric model, oral clearance standardized to a 70 kg subject was estimated to be 55.9 l/h. Changing W_{std} from 70 kg to 10 kg gave a population clearance estimate of 13 l/h, which was proportional to that predicted using 70 kg. There were no other differences in the estimates of variability or standard errors, confirming the robustness of the model parameters irrespective of the choice of W_{std}. Evaluation of the PWR exponent (as opposed to the fixed parameter value of 0.75) resulted in an estimate of 0.443 with significantly lower values for the NONMEM objective function (OBJ) and inter-individual variability compared with base and allometric models. This indicated that factors in addition to the allometric weight model might be important predictors of CL_{po}. Similar reductions in OBJ were observed when the power function model was applied to body surface area.

Based on the results from base model, where a single value of a parameter was estimated for the entire population (6 months of age to adults), the population C_{max} (data normalized to 80 mg) was estimated to be 279 ng/ml with an inter-individual variability of 65%. The introduction of a weight based power function resulted in significant reductions in the NONMEM objective function ($p < 0.001$) and inter-individual variability with marked improvement in diagnostic plots. With the power function model, C_{max} standardized to a 70 kg subject was estimated to be 211 ng/ml for the 80 mg dose. Changing W_{std} from 70 kg to 10 kg gave a population C_{max} estimate of 692 ng/ml, which was proportional to that predicted using 70 kg. There were no other differences in the estimates of variability or standard errors, confirming the robustness of the model parameters irrespective of the choice of W_{std}. The PWR exponent was estimated to be −0.611.

Exploration of covariate-parameter relationships indicates that there is a high degree of correlation between the covariates (Figure 1). Table 3 summarizes the results of the step-wise forward addition of covariates to the allometric model to describe CL_{po}. The inclusion of age, height, gender, race, and dose to the allometric 3/4 model resulted in significant reductions in OBJ ($p < 0.001$) and inter-individual variance. Based on the magnitude of decrease in OBJ, the covariates were ranked in the order age>height>dose>gender>race with age being the most significant. When the remaining covariates were added in a step-wise manner to the age and weight-based model, there were no further reductions in OBJ that were significant at the $p < 0.001$ level. To confirm the findings, the two

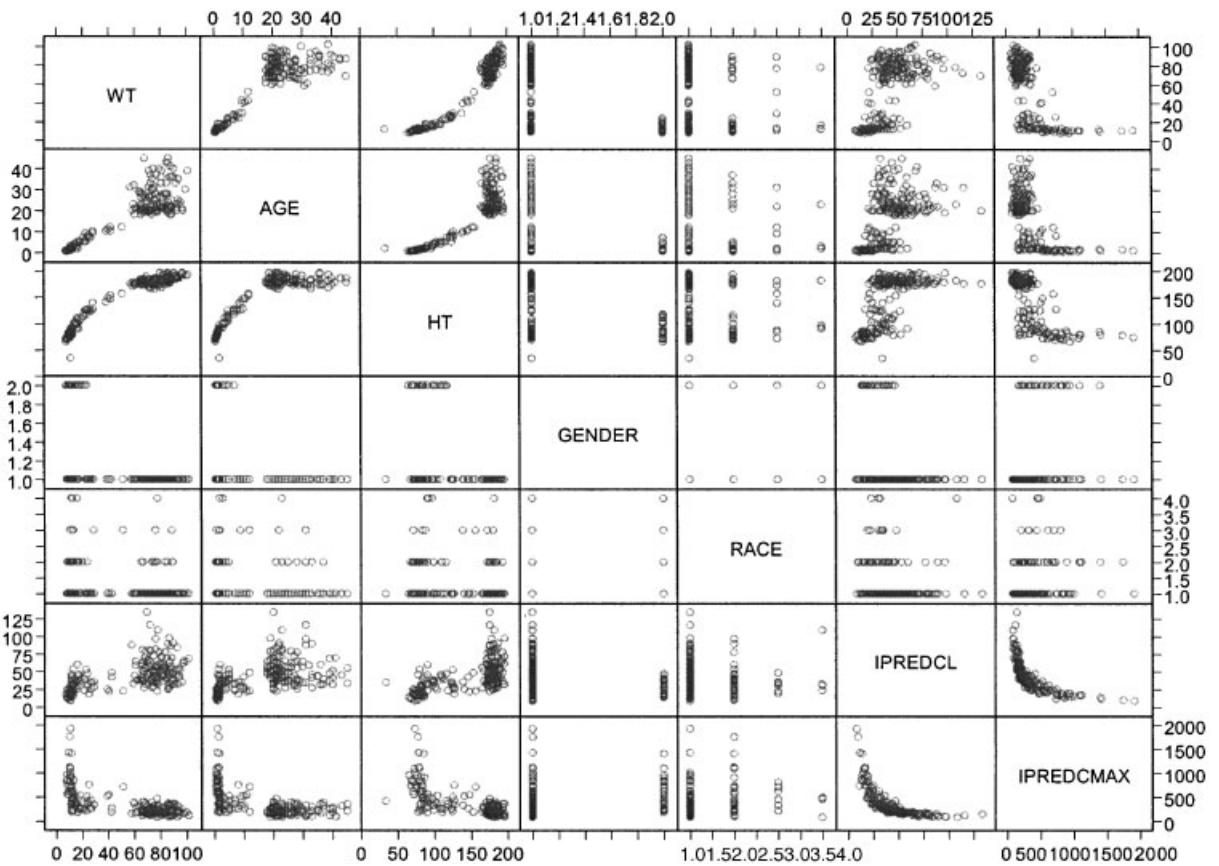

Figure 1. Scatterplot matrix of patient demographics and individual predicted CL_{po} and C_{max} (Abbreviations: WT, weight; HT, height; IPREDCL, individual predicted CL_{po}; IPREDCMAX, individual predicted C_{max})

Table 3. Stepwise addition of covariates for CL_{po}

Model no. (*.ctl) (*.out)	Covariate added	Model reference 1: $CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75}$	Delta OBJ	Decrease in IIV (%)	Comment
103	Age	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75} e^{[(Age_i-26)PWR_2]}$	71.237	30%	Significant reduction in OBJ ($p<0.001$)
1031	Height	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75}\left(\frac{HGT_i}{180}\right)^{PWR_2}$	70.312	32%	Significant reduction in OBJ ($p<0.001$)
1032	Dose	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75}\left(\frac{Dose_{ij}}{80}\right)^{PWR_2}$	57.919	36%	Significant reduction in OBJ ($p<0.001$)
1033	Gender	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75}(1+Sex^*\theta)$	22.785	11%	Significant reduction in OBJ ($p<0.001$)
		Sex=0 for male; =1 for female			
1034	Race	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75}(1+Rac^*\theta)$	15.689	8%	Significant reduction in OBJ ($p<0.001$)
		Rac=0 for Caucasian; =1 for non-Caucasian			
Model no. (*.ctl) (*.out)	Covariate added	Model reference 2: $CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75} e^{[(Age_i-26)PWR_2]}$	Delta OBJ	% decrease in IIV	Comment
1041	Height	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75} e^{[(Age_i-26)PWR_2]}\left(\frac{HGT_i}{180}\right)^{PWR_3}$	4.243	3%	Not significant
1042	Dose	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75} e^{[(Age_i-26)PWR_2]}\left(\frac{Dose_{ij}}{80}\right)^{PWR_3}$	3.694	6%	Not significant
1043	Race	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75} e^{[(Age_i-26)PWR_2]}(1+Rac\ \theta)$	2.56	1%	Not significant
		Rac=0 for Caucasian; =1 for non-Caucasian			
1044	Gender	$CL_{po_i}=\theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75} e^{[(Age_i-26)PWR_2]}(1+Sex\ \theta)$	1.929	1%	Not significant
		Sex=0 for male; =1 for female			

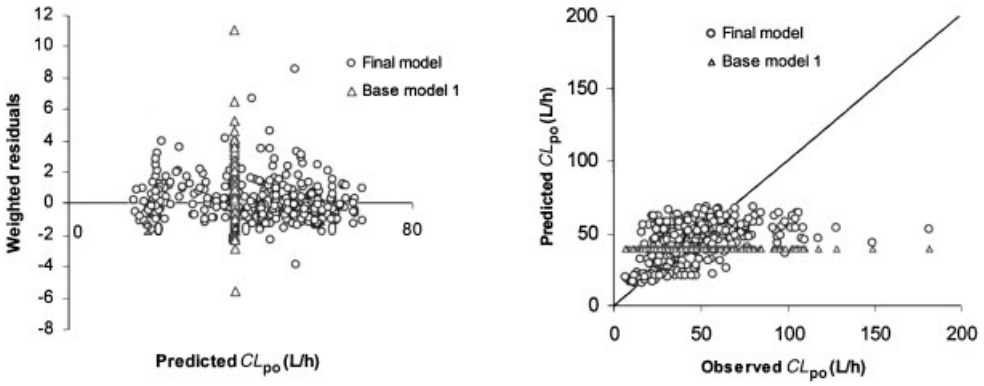

Figure 2. Diagnostic plots for base and final models for CL_{po}

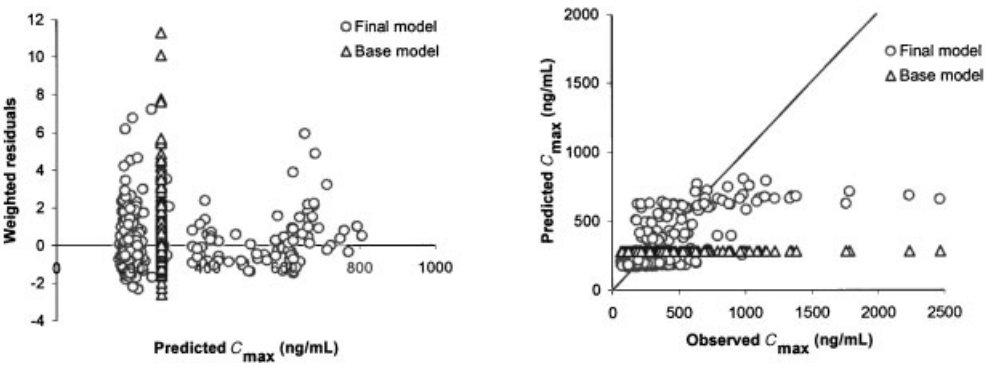

Figure 3. Diagnostic plots for base and final models for C_{max}

covariates were dropped from the full model in a step-wise manner. Dropping age from the full model resulted in an increase in OBJ of 71.237 ($p<0.001$) and dropping weight from the full model resulted in an increase in OBJ of 50.339 ($p<0.001$), with approximately 30% increase in inter-individual variance estimates in both cases, thereby confirming that they are indeed significant predictors of fexofenadine oral clearance. Table 4 summarizes the results of the step-wise forward addition of covariates to the power function model to describe C_{max}. For C_{max}, the inclusion of age, height, gender, race, and dose to base model 2 resulted in no significant reductions in OBJ ($p<0.001$) or inter-individual variance. The final population model for describing the oral clearance and the peak concentration of fexofenadine is presented in Table 5.

The mean (%CV) pharmacokinetic parameter estimates from NONMEM's posterior individual estimates are shown in Table 6. These predictions are based on the values for the specific individual using the estimate computed by noncompartmental methods, rather than the typical (population) values of these parameters, which are based on covariate information. The results are presented by combining data from all the adult studies into one group and separating each pediatric study by its corresponding age group (adults, children 6–12 years, 2–5 years, and 6 months–<2 years).

Simulation of potential dosing regimens for children 6 months to 2 years

Pharmacokinetic simulations were performed in order to determine dosing regimen(s) in children

Table 4. Stepwise addition of covariates for C_{max}

Model no. (*.ctl) (*.out)	Covariate added	Model reference 1: $C_{max_i} = \theta_{tv}\left(\frac{WGT_i}{70}\right)^{PWR_1}$	Delta OBJ	% decrease in IIV	Comment
203	Age	$C_{max_i} = \theta_{tv}\left(\frac{WGT_i}{70}\right)^{PWR_1}\left(\frac{Age_i}{26}\right)^{PWR_2}$	0.433	0%	Not significant
2031	Height	$C_{max_i} = \theta_{tv}\left(\frac{WGT_i}{70}\right)^{PWR_1}\left(\frac{HGT_i}{180}\right)^{PWR_2}$	1.583	2%	Not significant
2032	Dose	$C_{max_i} = \theta_{tv}\left(\frac{WGT_i}{70}\right)^{PWR_1}\left(\frac{Dose_{ij}}{80}\right)^{PWR_2}$	1.258	1%	Not significant
2033	Gender	$C_{max_i} = \theta_{tv}\left(\frac{WGT_i}{70}\right)^{PWR_1}(1 + Sex\,\theta)$	0.96	1%	Not significant
		Sex=0 for male; =1 for female			
2034	Race	$C_{max_i} = \theta_{tv}\left(\frac{WGT_i}{70}\right)^{PWR_1}(1 + Rac^*\theta)$	0.021	0%	Not significant
		Rac=0 for Caucasian; = 1 for non-Caucasian			

Table 5. Summary of final models describing variability in fexofenadine clearance and peak concentrations

Parameter	CL_{po}	C_{max}
Model	$P_i = \theta_{tv}\left(\frac{WGT_i}{70}\right)^{0.75} e^{[(Age_i - 26)PWR_2]}$	$P_i = \theta_{tv}\left(\frac{WGT_i}{70}\right)^{PWR}$
Parameter estimate (SEE)	$\theta_{tv} = 46.8$ (3%)	$\theta_{tv} = 211$ (3%)
	$PWR_2 = -0.0212$ (11%)	$PWR = -0.611$ (7%)
Inter-individual variability, %CV (SEE of variance)	37% (11%)	39% (13%)
Residual variability, %CV (SEE of variance)	19% (13%)	26% (16%)
Control file (*.ctl)	105	204
Output listing (*.out)		

SEE, standard error of the estimate.

6 months to <2 years that would produce similar exposures as in adults receiving the approved dose of fexofenadine HCl 60 mg BID. The estimated parameter estimates (C_{max} and $AUC = Dose/CL_{po}$) and their coefficients of variation were used to predict peak and overall exposures using the final population models. Pharmacokinetic parameter variability was assumed to have a log normal distribution. Individual weights and ages were simulated using mean (SD) estimates derived from the studies used in this analysis: 11.1 ($\pm$ 1.7) kg and 1.3 ($\pm$ 0.4) years for children 6 months to <2 years and 77.9 ($\pm$ 8.4) kg and 22.8 ($\pm$ 5.4) years for adults (data on file). Proportional measurement/model misspecification errors (%CV) of 26% and 19% derived from the present analysis for peak and overall exposures, respectively, were incorporated into the simulation. The trial was designed as a 3×3 crossover study in 18 subjects comprising three potential dosing regimens: (a) 15 mg for all subjects, (b) 15 mg for age <1 year and body weight $\leqslant$10.5 kg and 30 mg for age $\geqslant$1 year and body weight >10.5 kg and (c) 30 mg for all subjects. One hundred such trials were simulated using the $SIMULATION step in NONMEM. The 10th, 50th and 90th percentiles of the predicted values were calculated by treatment for each trial. Figure 4 contains box plots that show the distribution of the percentiles for *AUC* for the three potential regimens in reference to simulated data for adults after 60 mg fexofenadine

Table 6. Summary of fexofenadine population and individual parameter estimates from final model

Parameter	Population model (expression)	Population	Non-compartmental analysis Mean (%CV)	Individual predicted[b] Mean (%CV)
CL_{po} (l/h)	$P_i = 46.8\left(\frac{WGT_i}{70}\right)^{0.75} e^{[-0.0212(Age_i-26)]}$	Adults ($n = 136$)	55.0 (42%)	53.6 (34%)
		6–12 years ($n = 14$)	29.0 (36%)	30.1 (27%)
		2–5 years ($n = 21$)	37.9 (29%)[a]	34.3 (25%)
		6 months–<2 years ($n = 42$)	22.0 (54%)	20.9 (45%)
		6 months–<2 years ⩽10.5 kg ($n = 13$)	14.9 (34%)	14.9 (26%)
		6 months–<2 years >10.5 kg ($n = 29$)	25.3 (50%)	23.6 (42%)
C_{max} (ng/ml)	$P_i = 211\left(\frac{WGT_i}{70}\right)^{-0.611}$	Adults ($n = 136$)	221.3 (39%)	208.0 (32%)
		6–12 years ($n = 14$)	489.4 (48%)	408.9 (36%)
		2–5 years ($n = 21$)	391.6 (36%)	411.0 (25%)
		6 months–<2 years ($n = 42$)	893.7 (57%)	783.9 (43%)
		6 months–<2 years ⩽10.5 kg ($n = 13$)	1146.6 (40%)	971.8 (30%)
		6 months–<2 years >10.5 kg ($n = 29$)	780.4 (63%)	699.6 (47%)

Data for C_{max} have been dose normalized to 80 mg fexofenadine HCl.
Body weight (WGT_i) in kg; Age (Age_i) in years.
[a] Based on compartmental NONMEM analysis of single dose and steady state data.
[b] Bayesian individual estimates from NONMEM analysis using first order conditional estimation (FOCE) method.

HCl (18 subjects per trial × 100 trials). Of the three regimens simulated, regimen (b), the split-dosing regimen based on age and body weight, produces a similar range of *AUC* in children 6 months to <2 years as the 60 mg regimen in adults, whereas regimens (a) and (c) provide lower exposures at the lower extremes and higher exposures at the upper extremes, respectively, in majority of the subjects. With respect to C_{max}, although the central tendency of the split-dosing regimens are slightly higher than those observed with 60 mg in adults, there is a considerable overlap at the 10th, 50th and 90th percentiles across the 100 simulated trials (data not shown). Overall, given the inherent uncertainty around the peak metric and the almost complete overlap of *AUC* with adults, the simulation results significantly favor regimen (b) for children 6 months to <2 years.

Simulation of potential dosing regimens for children 2–5 years

Pharmacokinetic simulations were performed in order to determine dosing regimen(s) in children 2–5 years that would produce similar exposures as in adults receiving the approved dose of fexofenadine HCl 60 mg BID. The estimated parameter estimates (C_{max} and $AUC = Dose/CL_{po}$) and their coefficients of variation were used to predict peak and overall exposures using the final population models. Pharmacokinetic parameter variability was assumed to have a log normal distribution. Individual weights and ages were simulated using mean (SD) estimates derived from the studies used in this analysis: 16.3 (± 3.4) kg and 3.5 (± 1.2) years for children 2–5 years and 77.9 (± 8.4) kg and 22.8 (± 5.4) years for adults (data on file). Proportional measurement/model mis-specification errors (%CV) of 26% and 19% derived from the present analysis for peak and overall exposures, respectively, were incorporated into the simulation. The trial was designed as a 3 × 3 crossover study in 18 subjects comprising three potential doses: 30, 45 and 60 mg. One hundred such trials were simulated using the $SIMULATION step in NONMEM. The 10th, 50th and 90th percentiles of the predicted values were calculated by treatment for each trial. Figure 5 contains box plots that show the distribution of the percentiles for *AUC*, for the three potential regimens in reference to simulated data for adults after 60 mg fexofenadine HCl (18 subjects per trial × 100 trials). Of the three doses simulated, the 30 mg dose produces a similar range of

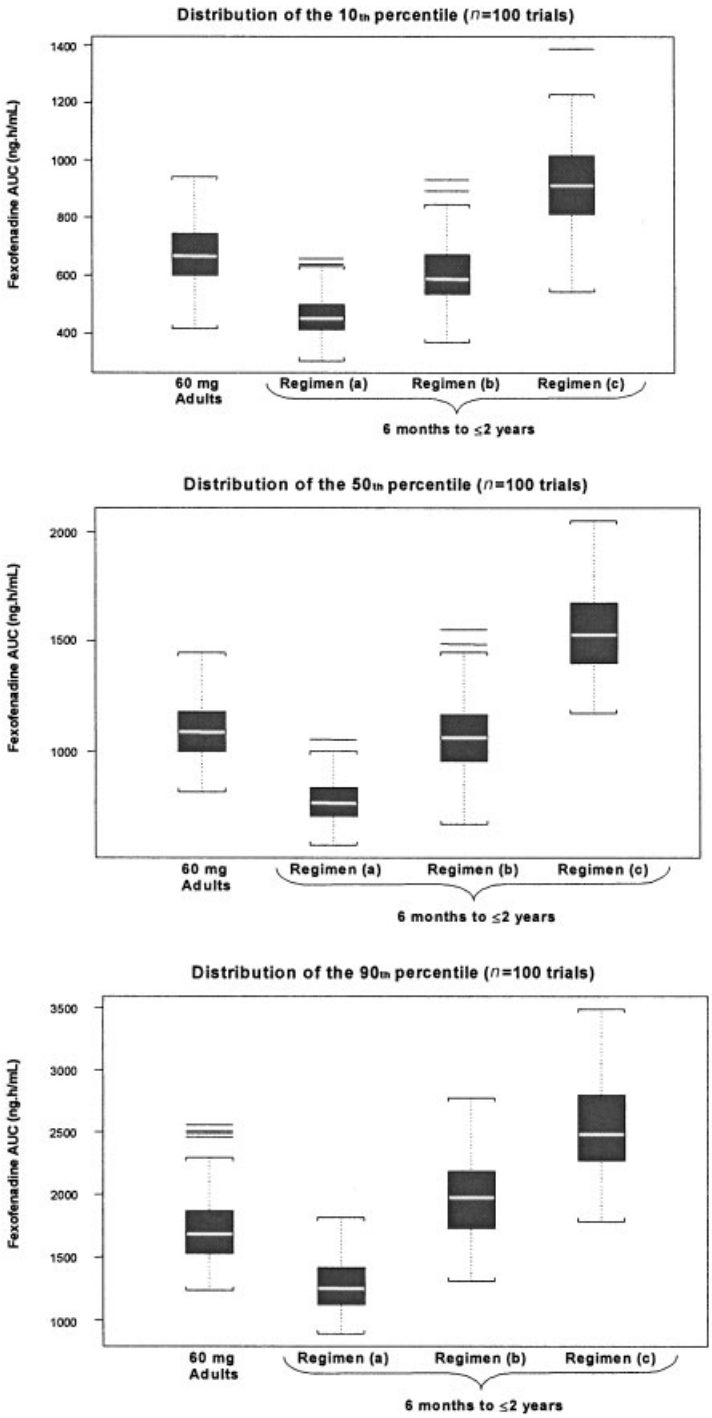

Figure 4. Distribution of 10th, 50th and 90th percentiles of *AUC* for children 6 months to <2 years

AUC in children 2–5 years as the 60 mg dose in adults, whereas 45 and 60 mg produces higher than adequate exposures at the median as well at the upper extremes. With respect to C_{max}, although the central tendency of the 30 mg dose is slightly higher than that observed with 60 mg

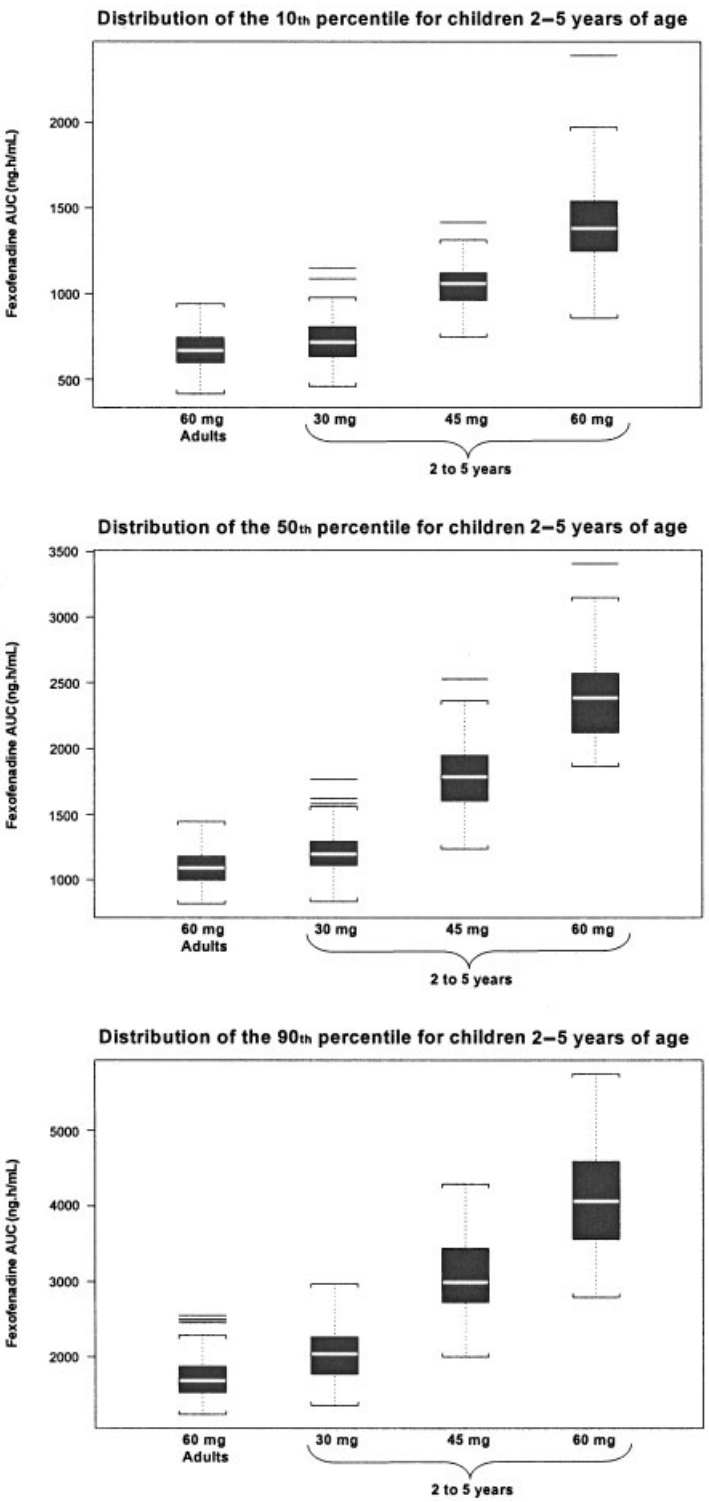

Figure 5. Distribution of 10th, 50th and 90th percentiles of *AUC* for children 2–5 years

in adults, there is a considerable overlap at the 10th, 50th and 90th percentiles across the 100 simulated trials (data not shown). Overall, given the inherent uncertainty around the peak metric and the almost complete overlap of *AUC* with adults, the simulation results significantly favor the 30 mg dose for children 2–5 years.

Dosing rationale for children 6 months–5 years of age

To examine the impact of weight and age on fexofenadine exposure, clearance estimates were derived using the final population model by fixing the value of one covariate (age or weight) to its average value (weight of 15 kg; age of 6 years) while estimating the impact of the other covariate at the extremes of the observed range. The resulting extreme clearance estimates were divided by the value calculated using a mean age of 6 years and weight of 15 kg in order to obtain the corresponding ratios. As shown in Table 7, the clearance ratios derived over the observed pediatric weight range (7.8–51.5 kg) by fixing age to 6 years are significantly greater than those derived over the observed pediatric age range (6 months–12 years) by fixing weight to 15 kg. Hence, body weight is more clinically relevant than age in children. The magnitude of influence of both covariates is reduced as children reach adulthood such that the exposure is mainly governed by the inherent variability in drug absorption, disposition and other residual factors (e.g. assay) rather than by age or body weight.

Dosing rationale for children 6 months–2 years

Comparison of the individual predicted CL_{po} values based on the final population model revealed a 61% lower apparent oral clearance in children 6 months to <2 years compared with adults. As shown in the simulations, due to the higher degree of variability within this age group, recommending either the 15 mg or the 30 mg dose for this age group will result in exposures that are either below or above those observed with 60 mg in adults for a majority of the patients. Upon stratification by body weight of 10.5 kg (90th percentile weight of a 1-year-old child) within this age group [12], clearance estimates of 14.9 l/h (25% CV, $n = 13$) for children weighing $\leqslant 10.5$ kg and 23.6 l/h (42%, $n = 29$) for children weighing >10.5 kg were derived. These estimates were 72% and 56% lower than in adults for the $\leqslant 10.5$ and >10.5 kg groups, respectively. Hence, based on the adult approved dose of 60 mg fexofenadine HCl, the 15 mg dose was considered appropriate for children aged $\geqslant 6$ months to <1 years and weighing $\leqslant 10.5$ kg and the 30 mg dose was considered appropriate for children aged $\geqslant 1$ to <2 years and weighing >10.5 kg. The results from trial simulations strongly support the recommendations based on individual predicted and observed data. The similarity in distribution of the central tendency (50th percentile) as well at the extremes (10th and 90th percentiles) between regimen (b) and the 60 mg adult regimen confirm the need for stratifying by age and weight within this age group. For subjects who may weigh $\leqslant 10.5$ kg but are aged $\geqslant 1$ year, the 15 mg

Table 7. Magnitude of age and weight covariate effects on fexofenadine clearance

Covariate tested	Covariate range	Age (years)	Weight (kg)	CL_{po}* (l/h)	Ratio (relative to mean value)
Age					
	Low	0.5	15	25.3	1.12
	Mean	6	15	22.5	NA
	High	12	15	19.8	0.88
Weight					
	Low	6	7.8	13.8	0.61
	Mean	6	15	22.5	NA
	High	6	51.5	56.8	2.52

*CL_{po} estimates are derived from the final population model and parameter estimates.

regimen may be more appropriate and for those who weigh >10.5 kg but are aged <1 year, the 30 mg regimen may be more appropriate.

Dosing rationale for children 2–5 years

In children 2–5 years, the individual predicted CL_{po} values are on an average 36% lower than in adults and 14% higher than in children 6–12 years of age. In addition, the individual predicted C_{max} values in children 2–5 years are on an average 98% higher than in adults when normalized to the 80 mg dose and almost identical to children 6–12 years (411 vs 409 ng/ml) for the same dose.

There is considerable overlap in peak and overall exposures with similar degree of variability between 2- to 5-year-olds and 6- to 12-year-olds. Hence, based on the approved doses of 60 mg for adults and 30 mg for children 6 to 12 years, the 30 mg dose was determined to be appropriate for children 2–5 years. The results from trial simulations strongly support this recommendation based on individual predicted data. The similarity in distribution of the central tendency (50th percentile) and at the extremes (10th and 90th percentiles) of clearance between the 30 mg dose in children 2–5 years and the 60 mg dose in adults confirm that the 30 mg dose is appropriate for the 2–5 year age group.

Discussion

The overall aim of this analysis was to assess the exposure of fexofenadine in children 6 months to 12 years and adults and to examine the influence of covariates such as weight, age, gender, race, height and body surface area on pharmacokinetics in order to determine the dose(s) in children 6 months–5 years of age that would result in similar exposures to adults receiving the approved dose of 60 mg BID fexofenadine HCl. The pooled population pharmacokinetic analysis shows that body weight and age are the most influential covariates of fexofenadine exposure in children. The individual apparent oral clearance estimates of fexofenadine were on an average 44% and 36% lower in children 6–12 years ($n = 14$) and 2–5 years ($n = 21$), respectively, compared with adults. In the 6 months to <2 year age group, when stratified by a body weight of 10.5 kg (90th percentile value of a 1-year-old child), the individual clearance estimates were on average 72% and 56% lower than in adults for the $\leqslant$10.5 kg ($n = 13$) and >10.5 kg ($n = 29$) groups, respectively. This indicates that a 30 mg dose of fexofenadine HCl for children 1–12 years of age and weighing >10.5 kg and a 15 mg dose for children 6 months and older and weighing $\leqslant$10.5 kg produce exposures comparable to those seen with the approved dose of 60 mg in adults. As fexofenadine exhibits linear pharmacokinetics in this dose range [7], single dose comparisons can be extrapolated to multiple dose steady state conditions during a twice-daily regimen. Hence, a common dose of 30 mg BID fexofenadine HCl can be administered for children 1–12 years of age with only a small group ($\leqslant$10.5 kg body weight) of children needing a reduced dose of 15 mg BID to achieve the target adult exposure.

In conclusion, equivalent doses of fexofenadine HCl administered to children result in higher exposures compared with those observed in adults. Age and body weight are significant predictors of variability in fexofenadine pharmacokinetics. A 30 mg BID regimen of fexofenadine HCl for children aged 6 months–5 years and weighing >10.5 kg and a 15 mg BID regimen for children weighing $\leqslant$10.5 kg will provide a similar range of exposures to those observed with the 60 mg BID regimen in adults.

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