

Montelukast adult (10-mg film-coated tablet) and pediatric (5-mg chewable tablet) dose selections

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Montelukast is a selective leukotriene receptor antagonist that has been shown to be effective in the treatment of chronic asthma. It is approved in more than 70 countries for patients 6 years of age and older. For adults (≥ 15 years of age), a 10-mg film-coated tablet (FCT) is available, and for children (aged 6 to 14 years), a 5-mg chewable tablet (CT) is available. The adult montelukast dose (10-mg FCT) was selected on the basis of classic dose-ranging studies as the lowest dose that produces maximal improvement in both measures of airway function and patient-reported outcomes in chronic asthma and in the attenuation of exercise-induced bronchoconstriction. The strategy used for the pediatric dose selection for montelukast was based on the determination of a CT dose that would provide an overall systemic exposure to montelukast in children similar to that in adults who receive a 10-mg FCT dose. Because montelukast was to be given chronically for the treatment of asthma, the area under the plasma concentration-time curve was considered to be the pharmacokinetic measurement that best represented systemic exposure to the drug. A 5-mg CT yielded a comparable single-dose area under the plasma concentration-time curve profile to that of the adult 10-mg FCT dose and, therefore, was selected as the pediatric dose for children aged 6 to 14 years with asthma. Subsequently, 2 studies of efficacy and tolerability validated the choice of the 5-mg CT dose. (*J Allergy Clin Immunol* 2000;106:S171-8.)

Key words: *Leukotrienes, pharmacokinetics, dose selection, montelukast*

It is currently understood that cysteinyl leukotrienes (CysLTs) play a role in the pathogenesis of asthma.¹⁻³ The CysLTs (LTC₄, LTD₄, and LTE₄) are formed from the breakdown of membrane arachidonic acid and interact with the CysLT₁ (leukotriene D₄) receptor.^{4,5} Data suggest that activation of this receptor mediates mucus secretion,⁶ smooth muscle contraction,⁷ microvascular leakage,⁸ and receptor-enhanced eosinophilic migration into the airways.^{9,10} The biologic effects of the CysLTs can be pharmacologically inhibited by leukotriene-blocking agents (synthesis inhibitors or receptor antagonists).¹¹⁻¹⁴ Clinical studies that demonstrate the benefit of leukotriene-blocking agents in the treatment of chron-

Abbreviations used

AUC:	Area under the plasma concentration-time curve
C _{max} :	Maximum plasma concentration of drug
CT:	Chewable tablet
CysLT:	Cysteinyl leukotriene
EIB:	Exercise-induced bronchoconstriction
FCT:	Film-coated tablet
T _{max} :	Time to maximum concentration

ic asthma and the attenuation of exercise-induced bronchoconstriction (EIB) in asthmatic patients 6 years of age and older have shown that CysLTs are important mediators of asthma.¹⁵⁻²⁰

MONTELUKAST

Montelukast is an oral, selective leukotriene receptor antagonist that has been shown to be effective in the treatment of chronic asthma.^{17,18,21-24} Additionally, montelukast has been shown to attenuate EIB.¹⁵ Currently, montelukast is approved for the treatment of asthma in patients 6 years of age and older in over 70 countries, including the United States. For adults (aged ≥ 15 years), a 10-mg film-coated tablet (FCT) dose is available, and for children (aged 6 to 14 years), a 5-mg chewable tablet (CT) dose is available. Although the dose selection process in adults was based on classic dose-ranging studies, the pediatric dose selection for children aged 6 to 14 years was based on a comparison of the pharmacokinetic profiles of montelukast between children and adults. The purpose of this article is to summarize the data that support the 10-mg FCT adult and 5-mg CT pediatric dose selections of montelukast.

PHARMACOKINETICS OF MONTELUKAST IN ADULTS

In adults, the plasma half-life of montelukast ranged from 2.7 to 5.5 hours.²⁵ At the therapeutic 10-mg FCT dose, montelukast is primarily eliminated by hepatic metabolism, followed by biliary excretion with minimal urinary excretion of the parent drug or its metabolites.²⁵ The single-dose pharmacokinetic profile of montelukast FCTs (range, 1 to 50 mg) in adults was nearly dose proportionate, with only a slight deviation from linearity for the 50-mg dose (Fig 1).²⁶ There was no difference in pharmacokinetic profiles for morning versus evening

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FIG 1. The AUC (d) and $C_{\max}$ (h) of montelukast as a function of dose in adults. Both relationships are linear.

dosing. After multiple dose administration, there was little plasma accumulation of montelukast and no detectable circulating metabolites in the plasma of young adult subjects on days 1 and 7 of dosing.²⁶ In adults, neither age, gender, nor food had clinically important effects on the pharmacokinetics of the 10-mg FCT.²⁵ Additionally, at the 10-mg FCT therapeutic dose, no clinically important drug interactions occurred with therapies that are commonly used in patients with asthma such as terfenadine, corticosteroids, oral contraceptives, and theophylline, in addition to digoxin and warfarin.²⁵

Fig 2 shows the course of plasma concentration of montelukast versus time for 24 hours after intravenous (9-mg) or oral (10-mg) doses.²⁷ The area under the plasma concentration-time curve (AUC) is measured from data such as these. Administering a drug intravenously ensures that the dose is maximally bioavailable. For an oral dosage form, the dissolution and subsequent absorption of a drug across the gastrointestinal tract both delay and decrease the peak plasma concentration compared with an equivalent intravenous dose. This results in an increase in the time to maximum concentration ($T_{\max}$) and a decrease in the maximum plasma concentration of drug ($C_{\max}$). The $T_{\max}$ of the oral 10-mg FCT dose of montelukast occurred at approximately 4 hours, with a $C_{\max}$ of approximately 385 ng/mL. To provide an indication of bioavailability of the oral FCT dose relative to the intravenous dose of montelukast, the AUC was calculated from time = 0 to time = infinity for both dosage forms, and these AUCs were then compared. The bioavailability of the oral FCT of montelukast was approximately 60% to 70% of that of the intravenous dose.²⁷

ADULT DOSE SELECTION

Multiple doses and dosage schedules were evaluated in dose-ranging studies in adults to determine the optimal dosing regimen for montelukast. Two dose-ranging studies in patients with chronic asthma and 1 study in mild asthmatic patients with significant EIB were conducted. Because airway patency is circadian, montelukast was administered in these studies in the evening to provide peak plasma concentrations at the time of maximal airway narrowing during the early morning hours.²¹⁻²⁴ Montelukast was well tolerated at all doses tested (0.4 to 200 mg); there were no dose-limiting toxicities.

In the first dose-ranging study,²³ montelukast was evaluated over several doses and dosing intervals (10, 100, and 200 mg once daily in the evening and 10 and 50 mg twice daily). Montelukast demonstrated significant improvements in measures of airway obstruction and patient-reported endpoints. All dosing regimens were equally effective. Based on this study, once-daily dosing was deemed appropriate for future studies, but a dose-response relationship for montelukast was not established. Therefore, 2 additional studies were conducted to evaluate the effect of lower once-daily bedtime doses of montelukast. These simultaneous dose-ranging studies were conducted to verify that improvement in both chronic asthma and EIB occurred throughout and persisted to the end of the once-daily dosing interval.

In the low-dose-ranging chronic asthma study,²⁴ montelukast substantially and similarly improved measures of airway obstruction at all doses tested (2, 10, and 50 mg). For most patient-related measurements (daytime

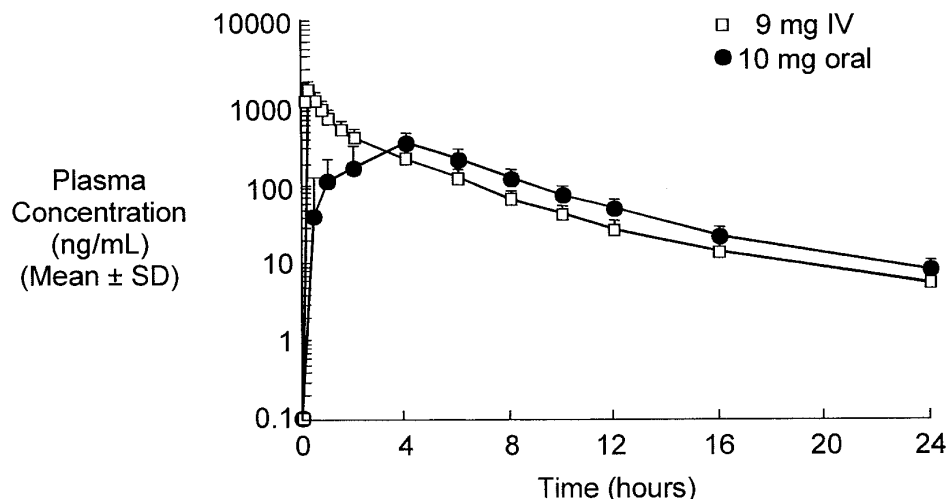


FIG 2. The plasma concentration of montelukast for 24 hours after 1 dose of 9-mg intravenous montelukast (h) or 10-mg FCT of montelukast (d) in adults. (Adapted courtesy of Kluwer Academic/Plenum Publishers, from Cheng H, Leff JA, Amin R, Gertz BJ, De Smet M, Noonan N, et al. Pharmacokinetics, bioavailability, and safety of montelukast sodium (MK-0476) in healthy males and females. *Pharmacol Res* 1996;13:445-8.)

symptom score, β -agonist use, and asthma-specific quality of life), however, the 2-mg dose was not different from placebo, while the 10- and 50-mg doses were significantly different ($P < .05$) from placebo and numerically similar to each other (Table I).²⁴

In the dose-ranging exercise study, both the 10- and 50-mg doses of montelukast showed similar attenuation of EIB at the end of the once-daily dosing interval after 2 doses, while the 0.4- and 2-mg doses showed less attenuation.²¹

On the basis of the results of these 3 adult dose-ranging studies, a 10-mg FCT taken once daily in the evening was identified as the lowest dose that produced significant clinical improvements in both measures of airway obstruction and patient-reported outcomes in chronic asthma and that attenuated EIB at the end of the dosing interval, and was selected for use in adults.

PEDIATRIC DOSE FORMULATION

To initiate clinical studies in children, an age-appropriate CT formulation of montelukast was developed. Before this formulation was evaluated in children, it was evaluated in adults. Healthy adults received 2-, 5-, and 10-mg CT doses and a 10-mg FCT dose to determine whether the CT formulation was dose proportional and whether the CT and FCT formulations were bioequivalent. Montelukast plasma levels were obtained before and at specified time points for 24 hours after study drug administration.²⁶ The plasma concentration profiles for the CT and FCT formulations are in Fig 3. Plasma concentrations increased in a dose-proportionate fashion over the range of 2- to 10-mg CT. For the CT formulation, T_{max} occurred at approximately 2 hours after the dose compared with approximately 4 hours for the FCT, consistent with slow-

er absorption and slightly reduced bioavailability with the FCT formulation compared with the CT. The CT formulation had an AUC approximately 20% greater and a C_{max} approximately 50% greater than the FCT formulation.²⁶ These data show that, at a given dose of montelukast, the FCT and CT formulations are not bioequivalent, but the magnitude of the plasma concentration of both are linearly dependent on dose (Figs 1 and 3).

STRATEGY FOR PEDIATRIC DOSE SELECTION

In conducting dose-ranging studies in pediatric populations, there are certain technical and ethical limitations, including the necessity of defining age-appropriate endpoints and minimizing patient risk by limiting unnecessary exposure. In 1994, the United States Food and Drug Administration issued a rule that made it possible, under certain circumstances, to select a pediatric dose that was based on pharmacokinetic data:

...A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted...²⁸

Because the clinical expression, pathophysiologic features, and pharmacologic treatment of asthma have been

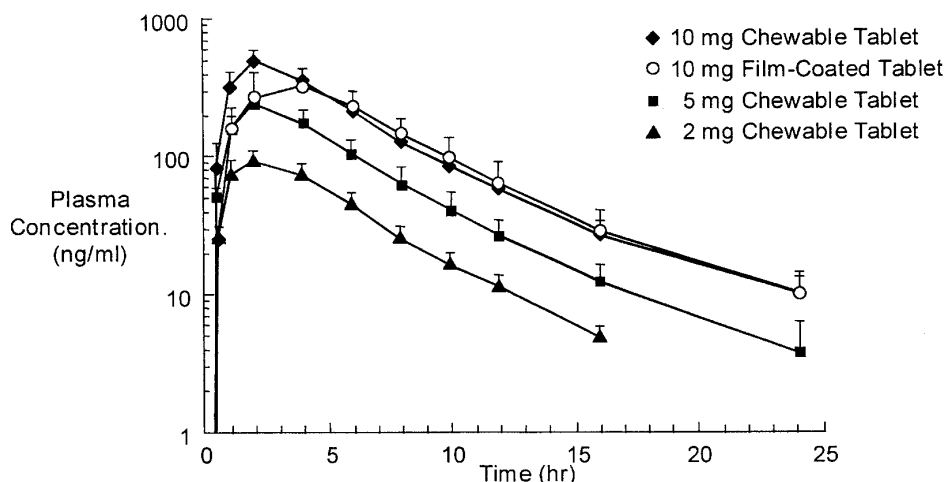


FIG 3. The plasma concentration of montelukast for 24 hours after 1 oral CT dose of 2-, 5-, and 10-mg or a 10-mg FCT dose in adults. The T_{max} is shorter with the CT. C_{max} is proportional to the CT dose. (Note, at the 24-hour timepoint for the 2-mg CT dose, the mean plasma concentration was 0.6 ng/mL and is not represented in the figure.)

TABLE I. Low-dose-ranging study: changes in patient-reported endpoints

	Daytime symptom score*	β -agonist use†	Asthma-specific quality of life‡	Patients with exacerbations§ (%)
Placebo	-0.1	-0.2	0.4	69.6
2 mg	-0.3	-0.7	0.5	54.2
10 mg	-0.4(	-1.1(	0.7(	44.1¶
50 mg	-0.4(	-0.9(	0.8(	50.0¶

From Noonan MJ, Chervinsky P, Brandon M, Zhang J, Kundu S, McBurney J, et al. Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma: Montelukast Asthma Study Group. *Eur Respir J* 1998;11:1232-9. With permission.

*Baseline score 3.0; diary card questions were answered on a 7-point scale that ranged from 0 (best) to 6 (worst).

†Baseline 5.5 puffs/d.

‡Combined average of 4 domains (activity, symptoms, emotions, environment); questions in each domain were answered on a 7-point scale that ranged from 0 (worst) to 6 (best).

§According to a predefined definition over the 3-week treatment period (the days with an asthma exacerbation were determined by the occurrence of any 1 of the following events: a decrease in morning peak expiratory flow rate of more than 20% from baseline, a morning peak expiratory flow rate of less than 180 L/min, an increase from baseline in β -agonist use of more than 70% [and a minimum increase of 2 puffs or more], an increase of more than 50% from baseline in daytime symptom score, awake "all night" because of asthma, or an unscheduled visit to a doctor or hospital).

¶ $P < .050$, compared with placebo based on stepwise linear trend test.

¶¶ $P < .050$, compared with placebo based on pairwise comparison with placebo using Cochran-Mantel-Haenszel test.

demonstrated to be similar in children and adults, the strategy for the pediatric montelukast dose selection was to identify a CT dose in children that provided overall drug exposure similar to that of a 10-mg FCT dose in adults, the optimal dose determined by dose-ranging studies. Because montelukast would be administered chronically for the treatment of asthma, the AUC was considered to be the pharmacokinetic parameter that best represented systemic exposure to the drug; therefore, AUC was selected as the primary pharmacokinetic parameter for comparison between children and adults. With this approach, an AUC in children similar to that measured in adults would be expected to result in an efficacious and well-tolerated dose.²⁶ The absence of C_{max} -related safety issues further supported the utility of this approach.

Several characteristics of montelukast strengthened the use of pharmacokinetic comparisons to determine the

pediatric dose in children aged 6 to 14 years. First, no clinically important preclinical safety issues were identified across species or age of animals. Second, dose-ranging studies in adults provided substantial safety information, with data accumulated for doses as high as 20 times the therapeutic 10-mg FCT dose. Third, dose-ranging studies in adults demonstrated that montelukast had a relatively flat dose-response relationship above the 10-mg dose.²¹⁻²⁴

Before pharmacokinetic studies in children aged 6 to 14 years were conducted, doses were estimated for the evaluation in these studies based on linear regression analyses of AUC-versus-weight data from previously completed pharmacokinetic studies in adults and adolescents. The selected doses were predicted to provide AUCs in a particular age range similar to that provided by a 10-mg FCT dose in adults, if no important changes

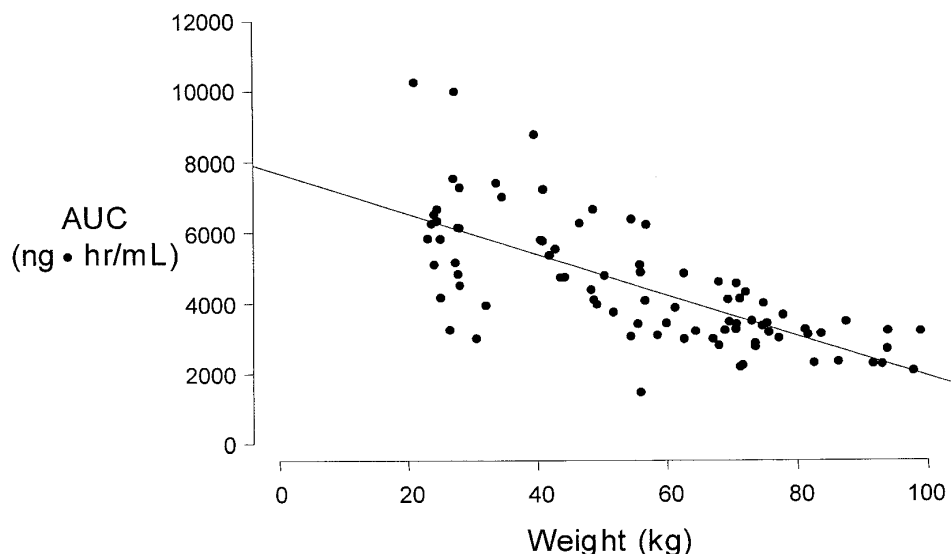


FIG 4. AUC as a function of patient weight in adults and pediatric patients. Each *point* represents the AUC of a single subject resulting from a single oral dose normalized to a 10-mg CT dose. The *solid line* is the resulting line of regression.

TABLE II. Pharmacokinetics of montelukast administration as FCTs and CTs in adults and children

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in the disposition of montelukast occurred between children and adults.^{27,29,30}

To estimate doses for evaluation in pharmacokinetic studies in children, AUCs from available historic adult and pediatric measurements were dose-normalized to a 10-mg CT dose and then plotted as a function of patient weight (Fig 4). For this dose-normalization, 2 assumptions were made: (1) the pharmacokinetics of the FCT and CT formulations are dose proportional and (2) a 10-mg CT produces an AUC approximately 20% greater than that of a 10-mg FCT (Table II).²⁶ The linear regression analysis of AUC versus weight was subsequently extrapolated to younger, lower-weight groups. The proportion by which the extrapolated AUC would need to be reduced in a particular age range and a particular weight range, to obtain the target adult 10-mg FCT AUC, would be the same proportion by which the dose would need to be reduced.

The mean AUC of the 10-mg FCT dose in the adult studies was approximately 2448 ng·h/mL. With the use of the linear regression analysis shown in Fig 4, an AUC that approximates 2448 ng·h/mL would be obtained in children aged 6 to 14 years from a 5-mg CT dose (equivalent to a 6-mg FCT when bioavailability is taken into account). Subsequently, studies were designed to evaluate the pharmacokinetics of several of these estimated doses in children to determine the actual dose that would produce the desired AUC.²⁶

Pediatric pharmacokinetic studies were conducted in a systematic fashion that proceeded from older to younger children and from children at Tanner stage V to children at Tanner stage I. The first study evaluated the pharmacokinetics of single oral FCT doses of montelukast in children with asthma aged 9 to 14 years. Patients were divided into those who were more mature and weighed more than 45 kg and those who weighed 45 kg or less.

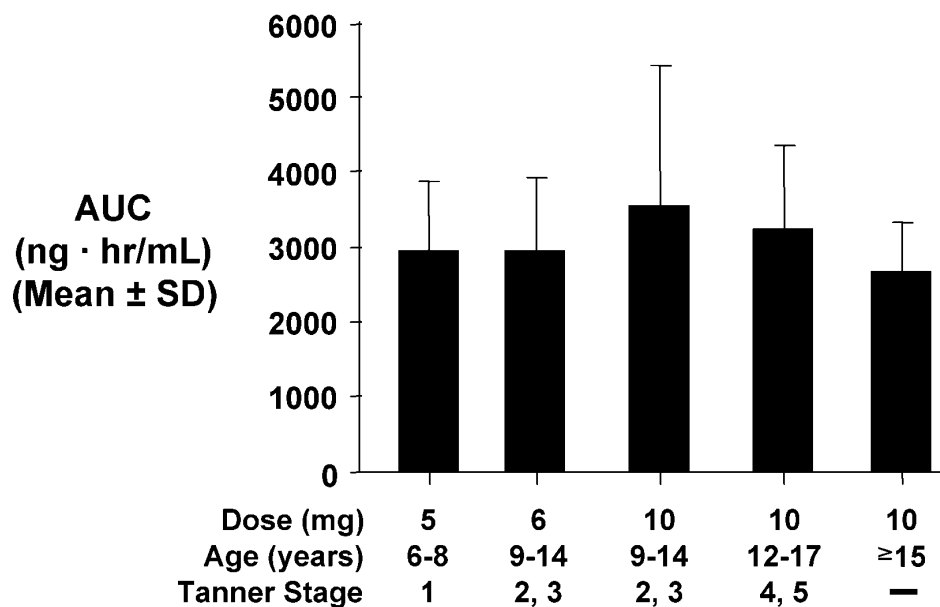


FIG 5. The effect of age and pubertal stage (Tanner stage) on AUC at each respective dose in children or adolescents. The 5-mg dose was administered as a CT; all other doses were administered as FCTs.

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FIG 6. Actual $AUC_{0-\infty}$ values (6- to 8-year-olds) or $AUC_{0-\infty}$ values normalized to the 5-mg CT dose (9- to 14-year-olds) were compared with actual adult $AUC_{0-\infty}$ (10-mg FCTs). The gray horizontal lines represent the geometric mean $AUC \pm 2$ SDs for the 10-mg FCT dose in adults. The bottom and the top of each box represent the 25th and 75th percentile of the AUC data, respectively. The white line within each box represents the median. The bars represent the furthest data points within a predefined nonoutlier range. Asterisks represent potential outliers. The outlier range is defined as the interval (25th percentile value -1.5[75th-25th percentile values], 75th percentile value + 1.5[75th-25th percentile values]). (From Knorr B, Larson P, Nguyen HH, Holland S, Reiss TF, Chervinsky P, et al. Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol* 1999;39:786-93. Copyright © 1999 by Sage Publications, Inc. Reprinted by permission of Sage Publications, Inc.)

The smaller children received a 6-mg dose (three 2-mg FCTs), and the larger children received a 10-mg FCT. In a subsequent study, the pharmacokinetics of single oral doses of montelukast (5-mg CT) once daily for 15 days were evaluated in children with asthma aged 6 to 8 years. The first study day included a full pharmacokinetic profile, with safety data obtained over the next 14 days. In

addition, peak and trough levels of montelukast were assessed on days 8 and 15 of the study.²⁶

PHARMACOKINETIC RESULTS

The results from these pharmacokinetic studies, categorized by patient age, are shown in Table II.²⁶ The mean

AUC and $C_{\max}$ generated by the 6-mg FCT dose (equivalent to a 5-mg CT when bioavailability is taken into account) in adolescents who weighed 45 kg or less were similar to the mean AUC and $C_{\max}$ observed in adults after a 10-mg FCT dose. The mean AUC and $C_{\max}$ generated by the 10-mg dose in adolescents who weighed more than 45 kg were approximately 25% higher than the respective parameters measured after the 10-mg FCT dose in adults. The $t_{1/2}$ and $T_{\max}$ of montelukast were similar to those observed in adults. Compared with historic adult data at steady state (10-mg FCT), mean AUC and $t_{1/2}$ of the 5-mg CT dose in children aged 6 to 8 years were generally similar to those observed in adults (Table II). At the 5-mg CT dose, there was no drug accumulation from day 1 to day 15. As in adults, metabolites were not detectable in plasma at steady state. No effect of age or pubertal stage was observed on the pharmacokinetic profile of montelukast (Fig 5). Based on the previously mentioned data, a 5-mg CT dose should achieve plasma concentrations of montelukast in children aged 6 to 14 years similar to those achieved with a 10-mg FCT in adults.

Fig 6 shows a box plot of the AUC data used to select the pediatric dose of montelukast.²⁶ This plot illustrates the approximately equal exposure among all patients to the respective doses. Actual 5-mg CT AUC data in children aged 6 to 8 years, dose-normalized (to a 5-mg CT) AUC data from children aged 9 to 14 years, and actual adult data from 10-mg FCTs are in this figure. Both the actual and normalized AUC data for a 5-mg CT dose of montelukast in children demonstrate pharmacokinetic profiles comparable across the pediatric age range to that observed with the 10-mg FCT adult dose. Based on these results, a 5-mg CT dose of montelukast, taken once daily in the evening, was selected as the dose of montelukast for children aged 6 to 14 years with asthma. Subsequently, 2 clinical studies were conducted to confirm that the 5-mg CT dose would yield the desired efficacy and tolerability profiles.

A study of chronic asthma¹⁸ and a study of EIB (with exercise challenges performed at the end of the dosing interval)¹⁶ were conducted, and the results confirmed the efficacy and tolerability of the 5-mg CT dose (taken once daily in the evening) in children aged 6 to 14 years with asthma. The results from both studies were consistent with the results obtained in adult efficacy studies and were consistent across the 6- to 14-year age range. In these studies, the adverse experience profile of montelukast was generally similar to that of placebo and to that observed in adult studies.^{16-18,31} The selection of the 5-mg CT dose of montelukast for children aged 6 to 14 years, based on a comparison of pharmacokinetic profiles, was therefore validated in these efficacy studies.

CONCLUSIONS

The 10-mg FCT once-daily evening dose of montelukast for adults was selected on the basis of the results of 3 classic dose-ranging studies. This dose of montelukast was identified as the lowest dose that produced the maximal response in measures of airway obstruction and

patient-reported outcomes in chronic asthma and attenuation of EIB at the end of the once-daily dosing interval.

The 5-mg CT dose of montelukast for children aged 6 to 14 years was selected on the basis of the similarity of the pharmacokinetic profile (AUC) of this dose (actual or dose-normalized) in children to that of the 10-mg FCT dose in adults (the optimal dose selected by dose-ranging studies). The efficacy and tolerability of the 5-mg CT dose were subsequently confirmed in 2 clinical studies in asthmatic children, the findings of which were similar to those in adults. Studies have subsequently been conducted with a 4-mg CT dose of montelukast in children aged 2 to 5 years. A similar strategy was used to select the 4-mg dose of montelukast for children aged 2 to 5 years.^{32,33}

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