

Population pharmacokinetics of levocetirizine in very young children: the pediatricians' perspective

Simons FER, on behalf of the ETAC Study Group. Population pharmacokinetics of levocetirizine in very young children: the pediatricians' perspective.

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Developmental changes during infancy and childhood can affect drug pharmacokinetics (PK), i.e., absorption, distribution, metabolism, and renal excretion. This, in turn, influences optimal dosing, efficacy, and safety. To date, of the 40 H₁-antihistamines available worldwide, only 11 have been studied in children using a PK approach. Here, we provide the pediatricians' perspective on the population PK of levocetirizine, the pharmacologically active enantiomer of cetirizine, in very young children who received oral cetirizine, and describe the factors that influence levocetirizine PK in this population. In a prospective, randomized, double-blind, parallel-group, placebo-controlled study, very young children received oral cetirizine 0.25 mg/kg twice daily for 18 months. Plasma levocetirizine concentrations were measured in timed, sparse blood samples collected at steady-state (3, 12 and 18 months after commencement of treatment) for the purpose of monitoring safety, and levocetirizine population, PK parameters were derived by using non-linear mixed effects modeling. In 343 children (age 14–46 months, body weight 8.2–20.5 kg), a total of 943 blood samples were obtained. Compliance with cetirizine dosing was documented. The population PK model used predicted that with increasing body weight, levocetirizine oral clearance would increase by 0.044 l/h/kg, and levocetirizine volume of distribution would increase by 0.639 l/kg. Levocetirizine PK were not influenced by eosinophilia, sensitization to allergens, allergic disease, gastroenteritis/diarrhea, or concomitant ingestion of other medications. This population PK model predicts that in very young children, the oral clearance of levocetirizine will be rapid and will increase as body weight and age increase, therefore, levocetirizine dosing should be based on body weight and age in this population. Compared with older patients, on a mg/kg basis, relatively higher doses may be needed, and twice-daily dosing may be necessary, as previously reported for the related racemic H₁-antihistamine cetirizine.

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Despite the widespread administration of H₁-antihistamines to very young children with allergic rhinitis, urticaria, and other disorders, information is lacking about the pharmacokinetics (PK) of most of these medications in this population (1). Such data are important for optimizing H₁-antihistamine dosing, efficacy and safety, because in this age group, incomplete maturation of organ function may affect drug

absorption, distribution, metabolism, and renal excretion (2–4) and potentially influence optimal dosing, efficacy, and safety.

There are inherent limitations to the number and extent of pharmacokinetic studies that can be performed in an individual child, due to ethical considerations about blood sampling at frequent intervals and the total volume of blood removed during repeated sampling for drug

measurements (2). Therefore, there are few pharmacokinetic studies of H₁-antihistamines in infants and children under the age of 6 yr (5–11), and even in school-age children, there are not many pharmacokinetic studies of drugs in this class (11–21).

The term ‘population pharmacokinetics’ is sometimes used to describe a two-stage approach involving retrospective analyses of traditional data-rich pharmacokinetic studies with multiple measurements of drug concentrations in each participant in specific populations (20–22). The term ‘population pharmacokinetics’ is also used to describe non-linear mixed effects modeling analyses of drug plasma concentrations measured in timed, sparse blood samples (21, 22), for example, those obtained in clinical trials for the purpose of monitoring drug safety. Using the second approach, the data are pooled and can be used not only to estimate pharmacokinetic parameters but also the influence of covariate factors on these parameters (Table 1). Seldom are either of these population pharmacokinetic approaches utilized to obtain clinically relevant pharmacokinetic information about H₁-antihistamines in children.

Levocetirizine is the pharmacologically active enantiomer of the racemate cetirizine, and can be measured in the blood after cetirizine administration. It is also a newly synthesized chemical entity (19) which is indicated in the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in adults and children. We hypothesized that levocetirizine population PK could be investigated in the young children who received cetirizine in the prospective, randomized, double-blind, placebo-controlled Early Treatment of the Atopic Child (ETAC) Study (23–28). Our objective was to demonstrate for pediatricians that the levocetirizine concentrations measured in timed, sparse blood samples obtained at steady-state for safety monitoring in children in the ETAC study could

be utilized to derive clinically relevant pharmacokinetic information. A companion paper for pharmacologists, containing the technical description of the analytical methods, database construction, population pharmacokinetic modeling equations, and pharmacostatistical modeling, has recently been published (29).

Methods

The ETAC study protocol was approved by the institutional review board in each of the participating centers. The children, who had atopic dermatitis and a family history of allergy, and were at high risk for developing asthma and other allergic disorders, were enrolled after informed consent was obtained from their parents or guardians. The inclusion and exclusion criteria for the study, and the methods of monitoring for efficacy and safety have been described in detail in previous ETAC study publications (23–28). Cetirizine 0.25 mg/kg or placebo solution were administered as drops with breakfast and with the evening meal every day for 18 months.

Throughout the study, the child’s primary caregiver used a diary card to record all symptoms, events, and non-study medications administered. This information was recorded on a weekly basis when the child was well, and on a daily basis if the child was having symptoms of any kind. Children were examined at eight regularly scheduled visits: before treatment with cetirizine or placebo, and at 1, 3, 6, 9, 12, 15, and 18 months after beginning treatment. Blood samples were obtained before, and after 3, 12, and 18 months of cetirizine treatment, when cetirizine and levocetirizine PK were presumed to be at steady-state. The time interval between blood sample collection and the previous cetirizine dose was recorded for each child. Population pharmacokinetic parameters were derived by using non-linear mixed effects modeling with first-order estimation (NONMEM-FO) (29–31).

Table 1. Classification of population pharmacokinetic studies (22)

	Retrospective analyses of traditional data-rich pharmacokinetic studies	Non-linear mixed effects modeling analyses
Timed blood samples for drug quantitation	Multiple, repeated at frequent intervals (eg, hourly), generally 10–12 samples over 24 h	Sparse (generally 1–4 samples); sometimes obtained over weeks, months or years during safety monitoring in clinical trials or during therapeutic drug monitoring
Number of participants	Small (eg, n = 10–20 in individual studies) data from all studies are then pooled	May be large (n > 100)
Invasiveness	++++	+
Control of covariates (diet, illness, medications)	Rigorous inclusion and exclusion criteria at study entry, and rigorous control during the study	Rigorous inclusion and exclusion criteria at study entry; in long-term studies, control is modified by real-life circumstances, e.g. ingestion of foods and xenobiotics, intermittent acute illness, concomitant medication use

Information entered into the NONMEM database included H₁-antihistamine concentrations, demographics (age, sex, weight, height, and body surface area), creatinine clearance, severity of allergic disease (blood eosinophil count), allergic sensitization (specific IgE to grass pollen or house dust mite), intercurrent illness (gastroenteritis/diarrhea), and concomitant use of penicillins, macrolide antibiotics, oral corticosteroids, and hydroxyzine. Creatinine clearance (Cl_{cr}) was calculated using the formula (32):

$$Cl_{cr} = \frac{0.28 \times ht \text{ (cm)} \times BSA}{\text{Plasma creatinine (mg/dl)}}$$

where ht is height and BSA is body surface area. BSA was calculated using the formula (33):

$$BSA = \frac{\sqrt{ht \times wt}}{3600}.$$

Levocetirizine and dextrocetirizine concentrations were determined in plasma samples by using chiral high performance liquid chromatography with tandem mass spectrometric detection. The quantification range was 12–1000 ng/ml for both validated assays. Quality control samples at 7.5, 150, and 750 ng/ml were assayed in duplicate with each batch of clinical samples (29, 30).

The software NONMEM (Version V, level 1.1) (31) with first-order estimation (NONMEMFO) was used throughout the population analysis and simulations. Time zero in NONMEM was the time of the last cetirizine dose administered before the sample was taken. Levocetirizine and dextrocetirizine concentrations were correlated with the demographic and clinical information entered into the NONMEM database. Specifically, the effect of the demographic and clinical covariates on oral clearance (Cl/F , in L/h), and on apparent volume of distribution (V/F , in L) were evaluated (29).

A one-compartment open model with first-order absorption and elimination was fitted to the plasma profile of levocetirizine (29, 30, 34). This model was selected based on visual inspection of the data and experience with previous analyses of total cetirizine concentrations in children (5–7, 15, 20). The pharmacokinetic parameters used to characterize the model were: Cl/F , V/F , and absorption rate constant (K_a , in h⁻¹). The analysis strategy involved selection of the basic pharmacokinetic model followed by univariate analysis, forward selection analysis, and backward elimination analysis, resulting in the final pharmacokinetic model (29).

Results

At the time of blood sampling during the 18 month study, children ranged in age from 14 to 46 months and ranged in weight from 8.2 to 20.5 kg (Table 2). More boys than girls were included, as was representative of the entire ETAC Study population. As expected, body weight, body surface area, and creatinine clearance increased with age in a linear manner (Table 2), and body weight and body surface area were highly correlated ($r = 0.964$). There were no significant differences in body weight, body surface area, or creatinine clearance between boys and girls.

Of the 399 children receiving cetirizine, 343 (86%) had one or more blood samples accompanied by an accurate history of the time interval between the preceding cetirizine dose and the sample. The frequency distribution of the number of samples per sampling interval taken within the dose interval of 12 h at each of the visits (months 3, 12, and 18) is shown in Fig. 1, with 75% of the total number of samples being obtained between 1 and 5 h of dosing.

Cetirizine (levocetirizine) was rapidly absorbed (Fig. 2). Three, 12, and 18 months after cetirizine

Table 2. Demographics and clinical information

Month*	n	M/F	Age† (months)	Weight† (kg)	BSA†(m ²)	CREAT (ml/min)	EOS (>500/μl)	SENS (n)	DIAR (n)	PEN (n)	MAC (n)	CORT (n)	HYD (n)
Baseline	395	244/151	16.7 ± 4.1	10.8 ± 1.4	0.49 ± 0.05	26.6 ± 4.61	140	74	n/a	n/a	n/a	n/a	n/a
3	248	156/92	19.8 ± 4.1	11.9 ± 1.6	0.52 ± 0.05	28.18 ± 5.78	53	57	9	18	2	4	3
12	279	170/109	29.0 ± 4.3	13.9 ± 1.6	0.59 ± 0.05	30.21 ± 4.33	95	62	17	17	4	1	9
18	226	137/89	35.3 ± 4.3	15.0 ± 1.9	0.63 ± 0.05	32.75 ± 4.87	75	47	10	6	2	2	5
Total (excludes baseline)	753	463/290	n/a	n/a	n/a	n/a	223	166	36	41	8	7	17

n, number of records; M/F, male/female; BSA, body surface area; CREAT, creatinine clearance; EOS, eosinophilia; SENS, sensitization to grass pollen or to house dust mite, defined as specific IgE > 0.35 kUA/ml; DIAR, diarrhea; concurrent medications: PEN, penicillin; CORT, oral corticosteroids; MAC, macrolide; HYD, hydroxyzine; n/a, not applicable.

*Number of months after cetirizine treatment was started.

†Mean ± SD.

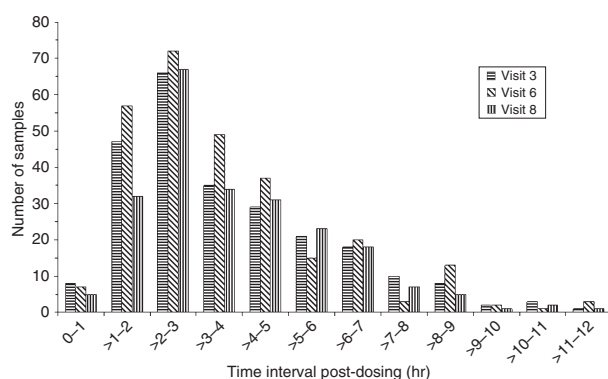


Fig. 1. Frequency of distribution of samples per sampling interval from the latest morning dose following twice-daily oral doses of levocetirizine 0.25 mg/kg.

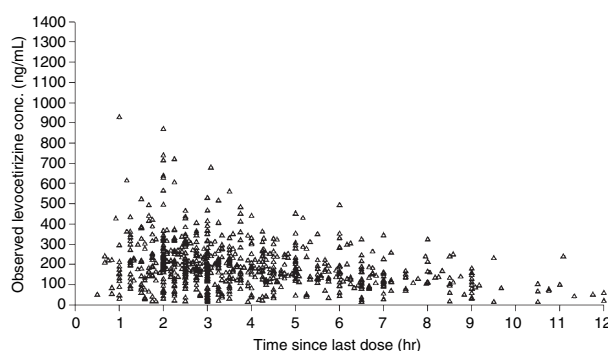


Fig. 2. Scatter plot of levocetirizine concentrations measured at steady-state vs. time.

was started, the children had mean ages of 19.8, 29.0, and 35.3 months, and mean body weights of 11.9, 13.9, and 15.0 kg, and the population estimates of Cl/F were 0.77, 0.86, and 0.91 l/h, respectively. Inter-patient variability in Cl/F in the basic model was 26.1%, explained in part by the significant association between Cl/F and weight, which decreased the inter-patient variability slightly (to 24.4%) in the final model. Clearance increased linearly with weight as follows: $Cl/F = 0.044 \text{ l/h/kg}$ from 0.22 l/h, the extrapolated intercept of the Cl/F vs. body weight plot.

The apparent distribution volume of levocetirizine was strongly associated with body weight according to the simple relationship $V/F \text{ (l)} = 0.693 \text{ l/kg} \times \text{BW (kg)}$. The inter-patient variability in levocetirizine V/F seen in the basic model (37.3%) was almost completely explained by the significant association between V/F and weight, which reduced the inter-patient variability to 14.7% in the final model. As V/F increased faster than Cl/F increased with increasing weight (or age), the terminal elimination half-life of levocetirizine also increased with weight (or age),

based on the fundamental pharmacokinetic relationship: $t_{1/2} = \ln 2 \times (V/F)/(Cl/F)$.

Except for body weight and age, none of the covariates assessed were found to affect levocetirizine PK, although the number of children was too small in some subgroups to permit a statistically valid conclusion (Table 2). These covariates included: sex, allergy (eosinophil count $> 500/\mu\text{l}$, $n = 223$), gastroenteritis/diarrhea ($n = 36$), or concomitant medications: penicillins, $n = 41$; macrolides, $n = 8$; oral corticosteroids, $n = 7$ and hydroxyzine ($n = 17$), the latter being of interest because it is biotransformed to levocetirizine, dextrocetirizine, and another metabolite, PO26.

Discussion

H_1 -antihistamines are widely used in the treatment of allergic disorders in very young children, especially for allergic rhinitis and urticaria. In order to recommend optimal doses and dose intervals for this age group, it is important that the PK (absorption, distribution, metabolism, and renal excretion) of the medications in this class be investigated in this population (5–21), as in the absence of such studies, dose and dose interval are extrapolated from those recommended for adults and the dose selected may not be optimal for efficacy or safety.

Development of organ function is ongoing throughout infancy and childhood. Although many of the maturational changes affecting pharmacokinetic disposition of drugs are complete by age 14 months, some maturational issues remain clinically relevant in children aged 14–46 months, the age group we studied (3, 4). Gastric pH, which can affect the rate and extent of absorption of orally administered drugs, does not reach adult levels of acidity (pH 2–3) until approximately age 20–30 months. Gastric emptying time and intestinal motility are slightly increased in young children; during episodes of diarrhea, motility is further increased and this may affect drug absorption. With regard to drug disposition, infants and very young children may have a higher percentage of extracellular water than adults and as a result may require higher doses of hydrophilic medications such as cetirizine and levocetirizine in order to achieve similar plasma concentrations. Different drug-metabolizing enzymes reach adult levels of activity at different ages: for example, CYP3A4 reaches adult activity by age 6 months and may exceed adult activity between 1 and 4 yr. Although glomerular filtration and renal tubular function mature during the first year of life, acquisition of

renal function continues during early childhood, which may be important for drugs such as levocetirizine which are eliminated largely (85%) unchanged in the urine.

Although most of the 40 H₁-antihistamines currently available are widely used in infants and young children, and many are available in palatable liquid formulations including infant drops, to date, only 11 of these medications have been studied pharmacokinetically in children. The first-generation H₁-antihistamines hydroxyzine, diphenhydramine, chlorpheniramine, brompheniramine and ketotifen, and the second-generation H₁-antihistamines cetirizine, ebastine, fexofenadine, levocetirizine, loratadine and mizolastine have been studied in children aged 6–11 yr (11–21). Cetirizine, levocetirizine, loratadine, ketotifen, and hydroxyzine have been studied in children younger than age 6 yr (5–11, 20); and cetirizine and levocetirizine have been studied in infants (5, 8). All other H₁-antihistamine doses for the pediatric population have either been extrapolated from adult doses using age de-escalation paradigms, or are based on anecdotal experience and educated guesses (2).

In pharmacokinetic studies in infants and children to date, H₁-antihistamines have generally been found to be well absorbed after oral administration, with peak plasma concentrations usually being reached within 2 h (5–21). Clearance rates are similar to or faster than those reported in adults, and terminal elimination half-life values are similar to, or shorter than, those in adults. In the pediatric population, there are no prospective studies of concomitant administration of any H₁-antihistamines with cytochrome P450 inhibitors; for example, erythromycin and other potential pharmacokinetic drug–drug or drug–food interactions, with the exception of a novel study of the effects of chlorpheniramine on the PK of chloroquine (35). Many of the H₁-antihistamine pharmacokinetic studies in children have included a pharmacodynamic component, suppression of the histamine-induced wheals and flares, thus providing information about onset, amount, and duration of H₁-antihistaminic activity (5, 8, 11–15, 17–19).

In traditional pediatric pharmacokinetic studies of medications, including H₁-antihistamines, inclusion and exclusion criteria are extremely rigorous, and children with intercurrent disease or those using concomitant medications are not involved. In the ETAC Study, the inclusion and exclusion criteria for entry were strict; however, during the course of the 18-month investigation, the children ingested a wide variety of foods, and were inadvertently exposed to various

xenobiotics; moreover, most of them inevitably developed intercurrent illness and received concomitant medications in addition to cetirizine (26). This provided the opportunity of studying the effect of intercurrent diseases such as gastroenteritis/diarrhea and of concomitantly used oral medications such as antibiotics and corticosteroids on levocetirizine elimination.

In this population pharmacokinetic study of an H₁-antihistamine in very young children, we used the non-linear mixed effect modeling approach, which involved timed, sparse blood samples during 18 months of regular cetirizine treatment. At steady-state, we found that the rate of increase in levocetirizine clearance with body weight or age was slower than the rate of increase of volume of distribution with body weight or age. In the age range studied (14–46 months), based on these pharmacokinetic relationships, we predict that the oral clearance rate of levocetirizine will increase as body weight and age increase. Levocetirizine dose and dose frequency should therefore be based on weight and age in this population. An algorithm could be developed for an optimal pediatric levocetirizine dosage regimen: dose in mg twice daily = $0.20 \text{ mg/L} [0.244 \text{ L/h} + (0.044 \text{ L/h/kg} \cdot \text{BW})] \times 12 \text{ h}$, where 0.20 mg/l is mean maximum steady-state levocetirizine plasma concentration at steady-state, 0.244 l/h is the extrapolated intercept of the *Cl/F* vs. body weight plot, and BW is body weight in kg. In daily clinical practice, due to the favorable therapeutic index (benefit-to-risk ratio) of levocetirizine arising from cetirizine (23–28), it may not be necessary to apply this formula.

In summary, as elimination of levocetirizine is rapid in very young children, relatively high doses may be needed, similar to those used in adults, and twice-daily dosing may be necessary. This is also true for the recommended dosing strategy for cetirizine in very young children, which is based on increasing cetirizine clearance with weight and age (5–7, 20). Population pharmacokinetic studies of additional H₁-antihistamines are needed in infants and children in order to facilitate optimal dosing recommendations for these medications in this age group.

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References

1. SIMONS FER. H₁-antihistamines in children. In: SIMONS FER, ed. Histamine and H₁-Antihistamines in Allergic Disease, 2nd edn. New York: Marcel Dekker, Inc., 2002: 437–64.
2. STEINBROOK R. Testing medications in children. *N Engl J Med* 2002; 347: 1462–70.
3. KEARNS GL. Impact of developmental pharmacology on pediatric study design: overcoming the challenges. *J Allergy Clin Immunol* 2000; 106(Suppl. 3): S128–38.
4. KEARNS GL, ABDEL-RAHMAN SM, ALANDER SW, BLOWEY DL, LEEDER JS, KAUFFMAN RE. Developmental pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; 349: 1157–67.
5. SPICAK V, DAB I, HULHOVEN R, et al. Pharmacokinetics and pharmacodynamics of cetirizine in infants and toddlers. *Clin Pharmacol Ther* 1997; 61: 325–30.
6. DESAGER JP, DAB I, HORSMANS Y, HARVENGT C. A pharmacokinetic evaluation of the second-generation H₁-receptor antagonist cetirizine in very young children. *Clin Pharmacol Ther* 1993; 53: 431–5.

7. PARIENTE-KHAYAT A, REY E, DUBOIS MC, et al. Pharmacokinetics of cetirizine in 2- to 6-year-old children. *Int J Clin Pharmacol Ther* 1995; 33: 340–4.
8. CRANSWICK NE, FUCHS M, TURZIKOVA J. Efficacy, safety and pharmacokinetics of levocetirizine in allergic children age 1–2 years. *Clin Pharmacol* 2004; 75: P46.
9. SALMUN LM, HERRON JM, BANFIELD C, PADHI D, LORBER R, AFFRIME MB. The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years. *Clin Ther* 2000; 22: 613–21.
10. SCHMIDT-REDEMANN B, BRENNEISEN P, SCHMIDT-REDEMANN W, GONDA S. The determination of pharmacokinetic parameters of ketotifen in steady state in young children. *Int J Clin Pharmacol Ther Toxicol* 1986; 24: 496–8.
11. SIMONS FER, SIMONS KJ, BECKER AB, HAYDEY RP. Pharmacokinetics and antipruritic effects of hydroxyzine in children with atopic dermatitis. *J Pediatr* 1984; 104: 123–7.
12. SIMONS KJ, WATSON WTA, MARTIN TJ, CHEN XY, SIMONS FER. Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. *J Clin Pharmacol* 1990; 30: 665–71.
13. SIMONS FER, LUCIUK GH, SIMONS KJ. Pharmacokinetics and efficacy of chlorpheniramine in children. *J Allergy Clin Immunol* 1982; 69: 376–81.
14. SIMONS FER, ROBERTS JR, GU X, KAPUR S, SIMONS KJ. The clinical pharmacology of brompheniramine in children. *J Allergy Clin Immunol* 1999; 103: 223–6.
15. WATSON WTA, SIMONS KJ, CHEN XY, SIMONS FER. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1989; 84: 457–64.
16. LIN CC, RADWANSKI E, AFFRIME MB, CAYEN MN. Pharmacokinetics of loratadine in pediatric subjects. *Am J Ther* 1995; 2: 504–8.
17. SIMONS FER, BERGMAN JN, WATSON WTA, SIMONS KJ. The clinical pharmacology of fexofenadine in children. *J Allergy Clin Immunol* 1996; 98: 1062–4.
18. SIMONS FER, WATSON WTA, SIMONS KJ. Pharmacokinetics and pharmacodynamics of ebastine in children. *J Pediatr* 1993; 122: 641–6.
19. SIMONS ER, GORITZ SS, SIMONS KJ. Clinical pharmacology of levocetirizine, the active enantiomer of cetirizine, in children age 6–11 years. *J Allergy Clin Immunol* 2005; 115: S105.
20. PITSIU M, HUSSEIN Z, MAJID O, AARONS L, DE LONGUEVILLE M, STOCKIS A. Retrospective population pharmacokinetic analysis of cetirizine in children aged 6 months to 12 years. *Br J Clin Pharmacol* 2004; 57: 402–11.
21. MENTRÉ F, DUBRUC C, THÉNOT J-P. Population pharmacokinetic analysis and optimization of the experimental design for mizolastine solution in children. *J Pharmacokinet Pharmacodyn* 2001; 28: 299–319.
22. FDA Guidance for Industry: Population Pharmacokinetics. February 1999.
23. WARNER JO, on behalf of the ETAC study group. A double-blind, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' post-treatment follow-up. *J Allergy Clin Immunol* 2001; 108: 929–37.

24. DIEPGEN TL, on behalf of the ETAC Study Group. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatr Allergy Immunol* 2002; 13: 278–86.
25. SIMONS FER, on behalf of the ETAC Study Group. Prevention of acute urticaria in young children with atopic dermatitis. *J Allergy Clin Immunol* 2001; 107: 703–6.
26. SIMONS FER, on behalf of the ETAC Study Group. Prospective, long-term safety evaluation of the H₁-receptor antagonist cetirizine in very young children with atopic dermatitis. *J Allergy Clin Immunol* 1999; 104: 433–40.
27. STEVENSON J, CORNAH D, EVRARD P, et al. Long-term evaluation of the impact of the H₁-receptor antagonist cetirizine on the behavioral, cognitive and psychomotor development of very young children with atopic dermatitis. *Pediatr Res* 2002; 52: 251–7.
28. de LONGUEVILLE M, DERUYTER B. RR, QT, and QTc in 799 infants aged 1–2 years. *J Allergy Clin Immunol* 1998; 101: S198.
29. HUSSEIN Z, PITSIU M, MAJID O, AARONS L, DE LONGUEVILLE M, STOCKIS A. Retrospective population pharmacokinetics of levocetirizine in atopic children receiving cetirizine: the ETAC study. *Br J Clin Pharmacol* 2005; 59: 28–37.
30. CHOI SO, LEE SH, KONG HS, KIM EJ, CHOO HY. Stereoselective determination of cetirizine and studies on pharmacokinetics in rat plasma. *J Chromatogr B Biomed Sci Appl* 2000; 744: 201–6.
31. SHEINER L, BEAL S. NONMEM, Version 5.1, NONMEM Project Group. San Francisco: University of California, 1998.
32. TRAUB SL, JOHNSON CE. Comparison of methods of estimating creatinine clearance in children. *Am J Hosp Pharm* 1980; 37: 195–201.
33. REED MD, GAL P. Principles of drug therapy. In: BEHRMAN RE, KLIEGMAN RM, JENSON HB, eds. *Nelson Textbook of Pediatrics*, 17th edn. Philadelphia: Elsevier Science, 2004: 2427–32.
34. GIBALDI M, PERRIER D. *Pharmacokinetics*, 2nd edn. New York: Marcel Dekker, Inc., 1982: 16.
35. OKONKWO CA, COKER HAB, AGOMO PU, et al. Effect of chlorpheniramine on the pharmacokinetics of and response to chloroquine of Nigerian children with falciparum malaria. *Trans R Soc Trop Med Hyg* 1999; 93: 306–11.