





Population pharmacokinetic modelling of cetirizine concentrations in human breast milk—A contribution from the ConcePTION project

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Abstract

Cetirizine is an antihistamine commonly used to treat allergic rhinitis and other allergic conditions. Cetirizine is often prescribed to breastfeeding mothers although there is limited information on infant exposure via breast milk. The aim of this study was to develop a popPK model based on data from a lactation study to predict cetirizine breast milk concentrations and estimate the relative infant dose (RID) in a breastfed infant. A popPK model was developed in NONMEM on data from a human lactation study including 35 women using cetirizine or levocetirizine while breastfeeding. Serial samples of breast milk were collected ($n = 205$) and the cetirizine concentrations quantified using a validated LC–MS/MS method. A one-compartment model of cetirizine in breast milk was developed and employed to calculate the relative infant dose (RID). Covariates related to the maternal characteristics and breastfeeding patterns were evaluated in the model; only milk sampling pumping duration was found to be a significant covariate, with an increasing pumping duration leading to an increased apparent milk volume of distribution (V_m). The mean RID was 1.99% with the highest RID being 3.36% at C_{max} . PopPK modelling could be used to estimate infant exposure to cetirizine via breast milk. The low predicted exposure in infants supports that cetirizine is compatible with breastfeeding.

KEYWORDS

antiallergic drugs, drugs during pregnancy and nursing, histamine, pharmacokinetics, pharmacokinetic modelling

For affiliations refer to page 8

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Plain English Summary

Breastfeeding mothers often use the anti-allergy drug cetirizine. Despite this, little is known about its transfer to breastmilk and how much of the drug the infant ingests after feeding. In this paper, a mathematical population pharmacokinetic model was applied to data from a human lactation study on cetirizine to evaluate the relative infant dose and factors affecting the transfer of cetirizine to breast milk. We show that the relative infant dose was low, indicating that cetirizine use is compatible with breastfeeding.

1 | INTRODUCTION

Allergic diseases such as allergic rhinitis occur in about 20–30% of women of reproductive age.¹ Thus, many breastfeeding mothers are prescribed antihistamines.^{2,3} Despite their widespread use, there is sparse knowledge on the transfer of these drugs into breast milk and the amounts ingested by breastfeeding infants.^{4,5}

Cetirizine is an antihistamine with a recommended dose of 10 mg once daily.⁶ Currently, few studies have quantified the transfer of cetirizine to human breast milk^{4,5}. The limited data on infant cetirizine exposure via breast milk results in conflicting recommendations concerning its use during breastfeeding. Market authorisation holders, who are required to follow regulatory guidelines on product labelling, recommend caution due to the lack of clinical studies in breastfeeding women. In contrast, clinical guidelines, that take the broader clinical experience into account, consider that cetirizine can be used during breastfeeding. The internationally recognised LactMed database states that cetirizine is a recommended choice if an antihistamine is needed during breastfeeding.⁷ These inconsistent recommendations can be confusing for patients and challenging for caregivers, and can lead to sub-optimal treatment of allergic conditions in breastfeeding mothers, or that mothers opt not to breastfeed their infant whilst on cetirizine. The solid evidence of the benefits of breastfeeding for the infant, not only with regards to nutritional and immunological reasons but also for mother–child bonding and maternal health, underscores the importance of clear evidence on the transfer of cetirizine to breast milk. This is crucial for developing consistent guidelines and recommendations.^{8–10}

This study is an extension of our human lactation study of cetirizine breast milk transfer where we used

traditional pharmacokinetic calculations to estimate the absolute and relative infant doses.^{11,12} The added benefit of the popPK approach is that all the data collected could be used to evaluate the pharmacokinetics of cetirizine in human breast milk, whilst simultaneously assessing any co-variate effects on cetirizine PK. The popPK approach enables the integration of both sparse and dense data from multiple individuals, offering distinct advantages in addressing inter-individual variability.¹³ Specifically, the popPK model can account for patient-specific factors, such as maternal weight and breastfeeding practices, that may influence drug transfer into breast milk.¹⁴ This approach provides a more comprehensive understanding of pharmacokinetics in real-world settings, where patient characteristics can vary significantly.

The objective of the presented study was to develop a population pharmacokinetic (popPK) model of cetirizine concentrations in human breast milk and calculate the relative infant dose (RID) based on the predicted milk concentrations. The influence of covariates such as maternal age, body weight and body mass index (BMI), factors related to the feeding and the age of the infant was assessed.

2 | METHODS

2.1 | Patient data

Thirty-five mothers living in Norway were included, each providing 4–6 milk samples.^{11,12} To ensure steady-state conditions, all mothers had been using cetirizine or levo-cetirizine, the pure (R)-enantiomer for cetirizine, for at least two days before the sampling day. The included mothers had an average age of 30 years (range: 22–40 years) and an average body weight of 78 kg (range: 53–110 kg). The infants had a mean age of 8.2 months (range: 8.3 weeks to 21 months) and a mean body weight of 8.3 kg (range: 3.7–11.9 kg). The mothers used on average 14.9 minutes (range 2–50 minutes) to pump the milk samples. Further details about the included mothers and infants are presented elsewhere.¹² One of the included mothers used the pure enantiomer levocetirizine at a dose of 5 mg per day, and two of the included individuals used cetirizine at a dose of 20 mg per day instead of the standard dose of 10 mg per day used by the 32 other mothers included in the study.

The included mothers collected the milk samples themselves in their home and used their home freezer for storage, with the samples subsequently shipped to the Uppsala Biobank before being transferred to Uppsala University for analysis.¹² To ease the sampling procedure and allow for all sampling to be performed at home by

the mothers, no maternal plasma samples were obtained. The mothers were given the necessary equipment for milk sampling including an electric milk pump, as well as instructions on taking a 20 ml milk sample before the dose (time 0) and at five time points following dose intake (2, 4, 8, 12 and 24 hours after dose intake). Exact time and date of levocetirizine dose intake and milk sampling were recorded. Dose intake occurred in the morning to allow for milk sampling during daytime. This sampling schedule was chosen to determine the pharmacokinetics of cetirizine using a traditional approach described in Nordeng et al.¹² The women were instructed to pump until the breast felt empty and to take 20 ml of the full volume of pumped milk at each sampling. The remaining milk could be given to the infant. A full breast milk sample was taken to ensure average cetirizine concentration samples at each time point. This also led to the averaging of milk composition from each sample. In total, 40 µl was used for the bioanalytical assay¹¹ and the remaining milk volume was stored in 1 ml aliquots in the Uppsala biobank for future research.

The study was approved by the Regional Committee for Medical and Health Research Ethics in South-East Norway (REK no. 232351, date: 01 June 2021) and the Data Protection Officer at the University of Oslo (date: 03 June 2021). Written informed consent was given by all women prior to their inclusion in the study. Both parents gave their consent for the collection of health information about the infant.¹²

2.2 | Sample analysis

Upon arrival at the Uppsala Biobank, the samples were examined and aliquoted into maximum 16 x 1 ml aliquots. They were subsequently stored at -80°C until the day of analysis at Uppsala University. The bioanalysis was performed according to a LC-MS/MS method specifically developed for the study by Wegler et al.¹¹ The method had a lower limit of quantification (LLOQ) of 0.39 µg/l, however, concentrations lower than the LLOQ were recorded when a concentration was detected (i.e. was above the lower limit of detection).¹¹ Whilst concentrations between the LLOQ and the limit of detection are less certain and are generally not utilised in traditional analysis, they can be utilised in a model-based approach with the uncertainty being estimated by the model.

2.3 | Pharmacokinetic modelling

Modelling was performed using NONMEM version 7.5 (ICON Development Solutions, TX, USA) and the

programs Perl-speaks-NONMEM, version 5.3.1 (PsN, Uppsala University, Uppsala, Sweden) and the modelling workbench Pirana, version 21.11.1 (Certara, UK).¹⁵ Population PK modelling guidelines were adhered to as appropriate.¹⁶ The tested base models to describe the milk concentrations of cetirizine included one- and two-compartment models with first-order absorption, with additive, proportional or combined additive and proportional residual error models. Detectable concentrations below the LLOQ ($n = 17$ samples from three women) were included in the model building to utilise all available data ($n = 205$ samples), no samples were below the lower limit of detection ($0.04\ \mu\text{g/l}$). The data was fitted with the First Order Conditional Estimation method with interaction (FOCE-I) in NONMEM. Model selection was done based on minimum objective function values (OFV) through the comparison of the ΔOFV , goodness-of-fit (GOF) plots and the pharmacokinetic parameter estimates with associated parameter uncertainty. Inter-individual variability (IIV) was evaluated assuming log-normally distributed individual parameters and included on parameters if resulting in a statistically significant drop in OFV. Covariates were investigated using the stepwise covariate modelling (SCM) function in PsN.¹⁷ The following covariates were evaluated: maternal age (years, continuous variable), maternal body weight (kg, continuous variable), BMI (kg/m^2 , continuous variable), pumping duration (minutes, continuous variable), breastfeeding exclusivity (yes/no, categorical variable) and age of the infant (months, continuous variable). Age of the child gave an indication of the maturity of the milk, which potentially could impact milk composition and thus milk cetirizine concentration.¹⁸

2.4 | Calculations of infant dose

The relative infant dose (RID) was calculated using the average estimated milk concentration $C_{\text{ss,av}}$ over a 24-hour period. First, the absolute weight-adjusted infant dose was calculated by multiplying the $C_{\text{ss,av}}$ with a daily milk intake of 150 ml/kg body weight, according to the US Food And Drug Administration (FDA) guidelines on clinical lactation studies.¹⁹ The relative infant dose in percent was then calculated by comparing the calculated absolute infant dose per kg body weight to the reported maternal dose per kg body weight.

$$\text{Absolute infant dose per kg body weight} = C_{\text{ss,av,milk}} * 150 \frac{\text{mL}}{\text{kg}}$$

$$\text{Relative infant dose} = \frac{\text{Infant dose per kg body weight}}{\text{Maternal dose per kg body weight}} * 100$$

The RID was calculated for every mother-infant pair, to accurately represent the sampled population. The $AUC_{0-24, \text{milk}}$ from the model was calculated as dose/apparent clearance in milk.

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.²⁰

3 | RESULTS

For the development of the structural model, one- and two-compartment models with a first-order absorption were tested. The one-compartment model was selected as the two-compartment model was not able to estimate all parameters with adequate precision and failed to converge successfully. The differential equation for the model was as follows:

$$\frac{dA(\text{cet})}{dt} = k_a * \text{Dose} - k_e * A(\text{cet})$$

Where A (cet) is the amount of cetirizine in the milk compartment, dose is the given dose of cetirizine at each dosing event, k_a is the absorption rate constant and k_e is the elimination rate constant. IIV was included in CL and a combined additive and proportional residual error model was used, with the additive part only included for BLQ data. Final parameter estimates and associated parameter uncertainty can be found in Table 1. Goodness of fit plots and a prediction corrected visual predictive check plot can be found in Figures 1 and 2, respectively. The time the mother spent pumping the breast milk sample using the supplied electric breast milk pump being a significant covariate on the apparent milk volume of

distribution in the model, where an increasing pumping duration led to an increasing apparent milk volume of distribution. The covariate-parameter relationship was described according to the following equations:

$$VT_{\text{pump}} = (1 + VT_{\text{pump}1}) * (TPUMP - 0.22)$$

$$V_m = VT_{\text{pump}} * TVV$$

Where VT_{pump} is the covariate effect of the pump time on the individual apparent milk volume of distribution, V_m , $VT_{\text{pump}1}$ is the estimated effect of pumping duration on the apparent milk volume of distribution and $TPUMP$ is the recorded pumping duration in the individual in hours.

No significant effects were found from maternal characteristics such as body weight or BMI, nor was the age of the infant found to be a significant covariate (Table 2).

3.1 | Model evaluation

The visual predictive check showed an adequate model performance (Figure 2). The observed median, 5th and 95th percentiles of the observed data fall within the confidence intervals of the median, 5th and 95th percentiles of the model predictions. The relative standard errors of the model estimated parameters were generally low, with the exception of the additive residual error for data below the limit of quantification (Table 1). The GOF plots show a good correlation between the predicted and observed correlations (Figure 1 and Figure 2). The conditional weighted residuals were scattered evenly around 0, both when compared with the population-predicted

TABLE 1 Final parameter estimates of cetirizine breast milk popPK model, n = 205 samples.

Description	Estimate	RSE (%) [SHR %]	95%CI
k_a (h^{-1})	0.095	4.5	0.088–0.110
Apparent Clearance _{milk} (L/h)	25.2	6.7	22.8–29.7
Apparent V_M (L)	19.9	11.6	15.6–24.8
Covariate effect of pumping duration on V_M (L)	3.47	24.1	1.86–5.20
Proportional error (–)	0.35	9.1 [4.3]	0.30–0.44
Additive error for BLQ samples ($\mu\text{g/L}$)	4.28	115.5 [4.3]	–0.64–1.64
Inter-individual variability in Clearance (%CV)	12.2	21.1 [5.3]	
Calculated parameters from model estimates			
T_{max}	2.53 ± 1.09		
C_{max}	30.6 ± 7.02		

Abbreviations: RSE is relative standard error, SHR is shrinkage, 95%CI is 95% confidence interval, k_a is the absorption rate coefficient. V_M is the apparent volume of distribution of the milk compartment. CV:

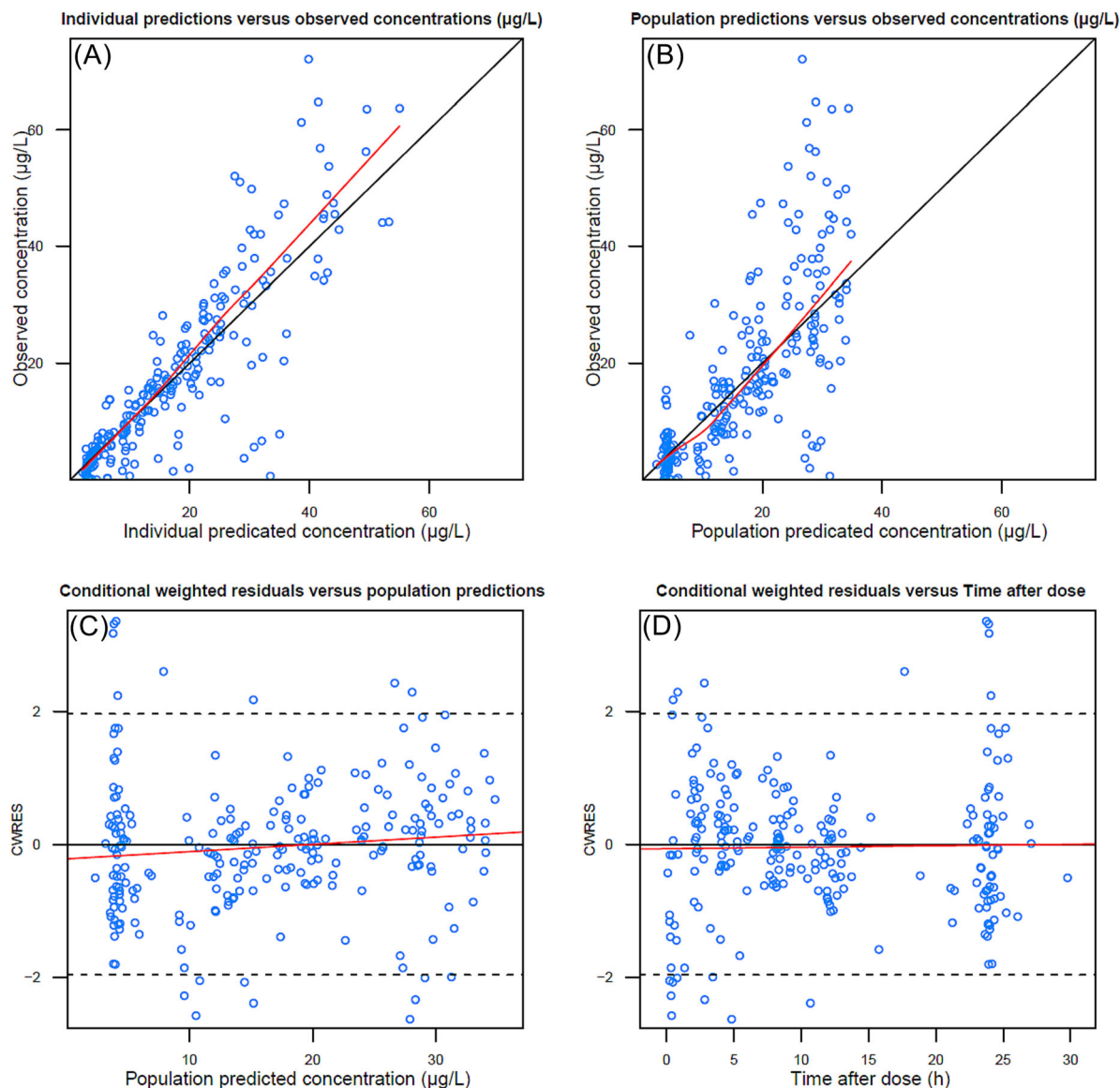


FIGURE 1 Goodness of fit plots of the final model.

concentration and with time. An additive error was added to the BLQ samples on top of the proportional error in the model. Whilst there was a high level of variability amongst the BLQ samples, and the added residual error on the BLQ observations had a high relative standard error, adding the extra error parameter improved the model ($\Delta\text{OFV} -194$) and enabled the use of these samples.

Model predicted AUC_{0-24} were compared to values obtained in previous studies, with an average AUC_{0-24} of $408 \pm 129 \mu\text{g h/L}$ from the model predictions compared to an AUC of $506 \mu\text{g h/L}$ in Wilkerson et al (based on x samples from three women, non-steady state).⁵ The model predicted C_{max} was 30.6 ± 7.02 ($13.2-55.2$) $\mu\text{g/L}$.

3.2 | Relative infant dose

The mean RID \pm standard deviation calculated from the model predicted average concentration over a dosing interval, for each individual mother-infant pair was $1.99 \pm 0.70\%$ (range 1.02–3.53). The variability in the calculated RID values was generally low, with a difference between the highest and the lowest values of less than 3.5-fold.

The observed milk concentrations of cetirizine are plotted against the individual predicted concentrations (A) and the population predicted concentrations (B). The lower two panels show the conditional weighted residuals (CWRES) plotted against the population-predicted concentration (C) and the time after dose (D).

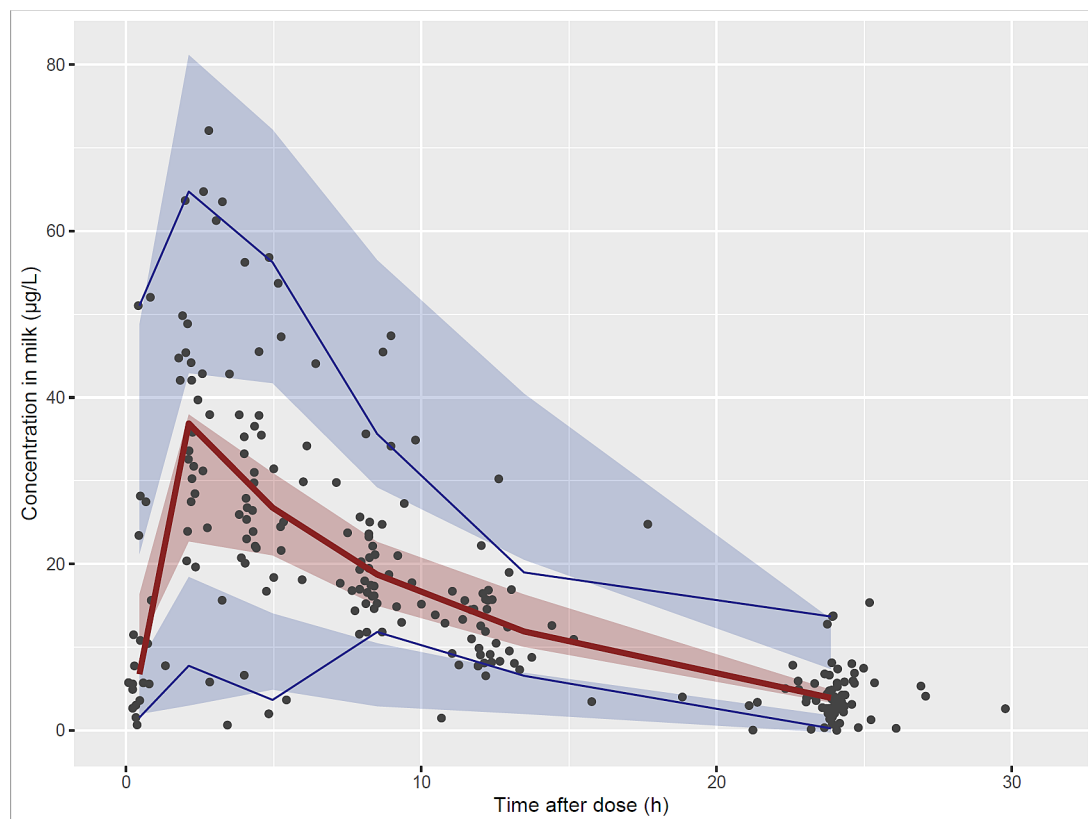


FIGURE 2 Prediction corrected visual predictive check plot, $n = 205$ samples.

TABLE 2 Relative infant dose.

	Relative infant dose (%)	SD	Range
Average concentration	1.99	0.70	1.02–3.53
C_{max}	3.36	0.77	1.65–5.21
Feed at 12 h post dose	2.02	0.41	1.34–2.93

Note: The C_{max} and 12 h time points were calculated by assuming 75% of the feed volume at the specific time point and 25% at the average concentration. Range is the range from minimum to maximum calculated RID.

Observed cetirizine concentrations are shown as black circles, with the median (solid red line), 5th and 95th percentiles (solid blue lines). The shaded areas represent the 95% confidence interval around the model-predicted median, 5th and 95th percentiles, respectively. Model-predicted T_{max} was 2.53 ± 1.09 h (range: 1.23–5.83) with a model-predicted C_{max} of 30.6 ± 7.02 $\mu\text{g/l}$ (range: 13.2–55.2).

4 | DISCUSSION

To our knowledge, this is the first study to describe a population pharmacokinetic model of cetirizine in human breast milk and calculations of RID at a population level. Demographic factors such as the maternal BMI and the age of the infant were assessed, together with sampling

parameters such as the pumping duration of the breast milk sample. The results show that the estimated amount of cetirizine ingested by the infant is low, assuming a feeding of 150 ml milk per kg per day, regardless of when the infant is fed related to the maternal drug intake. The results from a popPK approach, with the RID around 2%, align well with previous studies using traditional PK methodology^{5,12}; further strengthening the confirmation that cetirizine is unlikely to be transferred to breastmilk in amounts that could have pharmacological or toxicological effects in breastfed infants. This study thus provides evidence that supports current clinical guidelines that the use of cetirizine is compatible with breastfeeding. These results may also enable the updating of market authorisation holders' product labels and be helpful for prescribing practitioners. The WHO Working Group on Drugs and Human Lactation considers drugs as compatible with

breastfeeding when the RID is below 10%, which cetirizine is in all the tested scenarios in this study.^{18,21} There was no major difference between the RID based on average concentrations and that based on feeding separated from dose intake, suggesting that there is no need for the mother to take special care not to feed the infant for a certain time period after taking the dose.

The model-based approach also allows for the use of all available data, including data points below the limit of quantification. Since low concentrations can be expected to be common in lactation studies due to low milk-to-plasma ratios, being able to utilise all collected samples is a strength of model-based analysis.

In the covariate analysis, the only parameter that had a significant effect on the model predictions was the pumping duration, i.e., the time it took for the mother to pump the breast milk sample. A shorter pumping duration would result in a higher predicted concentration in the breast milk and thus a higher relative infant dose. A possible reason for this could be changes in the composition of milk over time. With shorter pumping durations the amount of fat in the milk is lower, whereas longer pumping durations leave more time for the milk to become richer in fat.²² Given that cetirizine is a water-soluble drug, this compositional change could lead to higher concentrations in less fatty milk.²³ This is of interest not only from a modelling perspective but also for more conventional human lactation studies. By recording the pumping duration, the effect on the concentration can be assessed, and it could help explain outliers in a dataset. To our knowledge, pumping duration has not been investigated or found to be a significant covariate in other popPK models of lactation studies.

By using a model-based approach to characterise the cetirizine concentrations in human breast milk and by determining RID based on the model-predicted concentrations, it is possible to assess the range of possible infant doses in the studied population without having to rely on abstract worst-case scenarios. This allows for risk assessment and clinical decision-making based on real data from real mother-infant pairs. It also provides us with a way to estimate the PK characteristics of the studied drug in the population without performing a large-scale clinical trial, which is often difficult to do in breastfeeding mothers. The popPK approach strengthens the understanding of drug transfer into breast milk and its potential impact on the infant, thus offering clinicians a more flexible and comprehensive framework for decision-making. Despite several strengths, the study has some potential limitations. Because the collection of breast milk was based on participants' self-sampling, we were not able to directly monitor the women and had to rely on the accuracy of their samplings and recordings. We utilised close

follow-ups and simple instructions to counteract such inaccuracies.¹² Moreover, the high number of samples included would counteract single reporting errors having a large impact on the results. Although we included a range of maternal and infant factors in the PopPK model, there were some potentially relevant covariates that were not available to us. These include factors related to milk composition (e.g. pH and lipid and protein content). We were thus unable to ascertain whether differences in milk composition impacted the predicted drug concentrations. Factors like the cytochrome P450 (CYP) genotype, diet and co-medications have little impact on cetirizine serum concentrations and are therefore not expected to affect milk concentrations.^{6,24}

This study used only milk data from the subjects as no plasma samples were collected. Whilst plasma data is useful, both for calculating the milk-to-plasma ratio, and for a more complete understanding of the time-course of the transfer from plasma to milk, the general goal of human lactation studies is to determine the RID and any potential risk to the infant. For this purpose, milk concentrations are sufficient. According to the market authorisation holder, the C_{max} in plasma is around 300 µg/l with a T_{max} at approximately 1 hour, indicating a delay in reaching maximum concentrations in breast milk which is to be expected.⁶ Whilst utilising such data to add a plasma compartment to the model could be done, it would introduce a lot of assumptions about the populations, and this study was performed without a plasma compartment to stay focused on the milk PK. To fully understand the infant exposure to cetirizine when breastfed by a mother who takes cetirizine, paediatric studies, where the infant plasma is sampled, are required. Such studies can capture the transfer of the drug to the infant via breast milk, but also the infant's absorption and elimination of cetirizine. However, they are invasive and require sampling in a clinical setting, whereas in the present study collection of the biological material could be performed by the mothers themselves taking their samples in the home, greatly simplifying the process. Previous popPK models have been developed both with and without plasma concentration data, and the choice to include plasma samples will depend on the questions the study aims to answer.^{25,26} In their draft guidance the FDA recommends performing milk-only studies unless there are specific considerations that can only be answered by other study designs.¹⁹ For example, when there is a need to determine the systemic PK of the drug, either because it is not known, or if the specific PK in lactating women needs to be studied, samples of both maternal plasma and breast milk can be collected. Studies measuring the drug in both maternal and infant plasma can be performed if the aim is to evaluate the absorption of the drug from the breastmilk into the

infant circulation and the elimination in the infant. It should be noted that because the model used in the present study only utilises milk concentrations all pharmacokinetic parameters are apparent parameters. This means that they are providing “true” physiological information but is rather an empiric description of how the concentrations of cetirizine in milk change over time. This milk-specific model does not provide information on systemic processes and purely describes the change of concentrations in breast milk. The strength of the popPK approach is that a plasma compartment could later be added to the model, should it be needed and the data in a relevant population is collected.

5 | CONCLUSION

This study provides a popPK model for cetirizine in human breast milk. The model was able to adequately fit observed data from a human lactation study and was used to calculate the RID which was low (3.53% at the highest), indicating that cetirizine use whilst breastfeeding can be considered safe. It was also found that the pumping duration when expressing the milk sample significantly impacts the estimated concentration and that it therefore would be important to monitor the pumping duration in future lactation studies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data are within the paper. Authors may not share the study data due to regulations which restrict access and distribution to those with ethical and legal permission to use the data. The study protocol was registered and is available in the HMA-EMA Catalogue. <https://redirect.ema.europa.eu/resource/43386>.

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