Single-dose Pharmacokinetics of Famciclovir in Infants and Population

Pharmacokinetic Analysis in Infants and Children

Jeffrey Blumer,¹ Adib Rodriguez,² Pablo J. Sánchez,³ William Sallas,⁴ Guenther Kaiser,⁵ and Kamal Hamed⁶*

¹University Hospitals of Cleveland, Cleveland, Ohio, USA
²Hospital Infantil de Infectologia y Rehabilitacion, Ciudad de Guatemala, Guatemala
³University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA
⁴Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA
⁵Novartis Pharma AG, Basel CH 4002, Switzerland

Running Title: Pharmacokinetics of famciclovir in infants and children

*Corresponding author. Mailing address: One Health Plaza, East Hanover, NJ 07936.
Phone: (862) 778-4780. Fax: (973) 781-6042. E-mail: kamal.hamed@novartis.com.

Key Words: famciclovir, pharmacokinetics, infants, children, herpes simplex virus, modeling
ABSTRACT

A multicenter, open-label, study evaluated single-dose pharmacokinetics and safety of a pediatric oral famciclovir (prodrug of penciclovir) formulation in infants aged 1 to 12 months with suspicion or evidence of herpes simplex virus (HSV) infection. Individualized single doses of famciclovir based on the infant’s body weight ranged from 25 to 175 mg. Eighteen infants were enrolled (1 to <3 months \( n = 8 \), 3 to <6 months \( n = 5 \), and 6 to 12 months \( n = 5 \)). Seventeen infants were included in the pharmacokinetic analysis; one infant experienced immediate emesis and was excluded. Mean \( C_{\text{max}} \) and \( AUC_{0-6h} \) values of penciclovir in infants <6 months of age were approximately 3- to 4-fold lower vs. those in the 6 to 12 months age group. Specifically, mean \( AUC_{0-6h} \) was 2.2 µg/mL•h in infants 1 to <3 months, 3.2 µg/mL•h in infants 3 to <6 months, and 8.8 µg/mL•h in infants 6 to 12 months. These data suggested that the dose administered to infants <6 months was less than optimal. Eight (44.4%) infants experienced at least one adverse event with gastrointestinal events reported most commonly. An updated pharmacokinetic analysis was conducted, which incorporated the data in infants from the current study and previously published data in children 1 to 12 years of age. An 8-step dosing regimen was derived that targeted exposure in infants and children 6 months to 12 years of age to match the penciclovir AUC seen in adults after a 500 mg dose of famciclovir.
INTRODUCTION

Manifestations, sequelae, and risk of mortality and morbidity of herpes simplex virus (HSV-1 and HSV-2) infections differ among newborns, infants, and immunocompetent vs. immunocompromised children (7, 12, 20, 23, 31, 32). At presentation, clinical symptoms range from infections limited to the skin, eye and mouth to disseminated disease and encephalitis. Acyclovir, valacyclovir, and famciclovir are effective and safe options for the treatment of HSV infections (32). Despite being considered as a gold standard, acyclovir’s pharmacokinetic profile is less than ideal for oral administration to children (e.g., limited bioavailability requires frequent dosing) (9). Administration of valacyclovir, the prodrug of acyclovir, provides higher serum levels of acyclovir (13). Valacyclovir is not approved in children less than 12 years of age for the treatment of herpes labialis and in children less than 2 years old with chickenpox. Penciclovir, the active component of the prodrug famciclovir, has activity against HSV-1, HSV-2, and varicella zoster virus (VZV) (30), and a higher affinity for viral thymidine kinase than acyclovir (4, 8). Viral thymidine kinase phosphorylates penciclovir or acyclovir to a monophosphate, which is then converted by cellular kinases to the respective triphosphate. The triphosphate inhibits viral replication (8). Penciclovir triphosphate has a longer intracellular half-life in infected cells compared with acyclovir triphosphate (7 to 20 h vs. 1 h, respectively) (8). The pharmacokinetics of penciclovir in earlier studies with adults show that peak penciclovir concentration and exposure (AUC) increase linearly with dose after administration of famciclovir (10, 16). Famciclovir is approved for use in immunocompetent adults based on findings from clinical trials for herpes zoster,
An experimental famciclovir oral formulation (i.e., “sprinkle” hard gelatin capsules containing famciclovir oral granules) was developed for use in pediatric trials. The capsules were to be opened and the granules sprinkled on OraSweet syrup vehicle before the mixture was ingested. Sáez-Llorens et al (19) recently reported the findings of single-dose pharmacokinetic and multiple-dose safety evaluations with the pediatric famciclovir formulation in HSV- and VZV-infected children aged 1 to 12 years. In brief, these studies revealed that the average systemic exposure to penciclovir was similar (6- to 12-year-olds) or slightly lower (1- to <6-year-olds) than that in adults receiving a 500 mg dose of famciclovir. The pharmacokinetic data in children 1 to 12 years old provided initial information to guide dose selection for an exploratory single-dose pharmacokinetic study in infants.

The current paper has two main purposes: 1) to describe the pharmacokinetics, safety and tolerability of a single dose of famciclovir in infants 1 to 12 months of age who are at risk of, or who have HSV infection and 2) to present an updated population pharmacokinetic model of penciclovir in infants and children with HSV or VZV infection. The updated model, which combined data in children aged 1 to 12 years with those from infants 1 to 12 months, was used to derive a new dosing scheme for infants and children to match exposure in adults.
PATIENTS AND METHODS

Study design and treatment. A multicenter, open-label, single-dose trial was conducted to evaluate the pharmacokinetics of famciclovir following administration to infants aged 1 to 12 months. Infants could have been hospitalized or dosed as outpatients.

The individualized single dose of famciclovir was based on the infant’s body weight (BW; Table 1). The dosing algorithm used was based on pharmacokinetic data recently obtained in children aged 1 to 12 years (19), and took into account physiological changes of renal function with age. The contents of the appropriate number of capsules, provided as 25 mg and 100 mg sprinkle capsules, were mixed with 5 mL of OraSweet just prior to dosing and administered within 1 h. Study site personnel administered and supervised famciclovir dosing. The infant’s intake of food and beverages was restricted. Administration of up to 90 mL (3 oz) of one of the following was permitted up to 1 h prior to dosing: breast milk, formula, or a suitable milk substitute. Water was allowed ad libitum. Normal feeding was permitted 1 h post-dose. Infants could be re-dosed 12 h following the initial administration of study drug if they did not ingest the entire dose, or significant emesis occurred within 30 min of dosing. While an 8 h washout of current antiviral therapy was recommended, concomitant use of antiviruses nucleoside analogue treatments was permitted if deemed appropriate by the investigator.

Approval of the study protocol and consent form was obtained from each investigator’s independent ethics committee or institutional review board and the Ministry of Health (Guatemala), and all study activities were conducted in accordance with good clinical
practice and the Declaration of Helsinki. The parent or legal guardian provided written informed consent.

Study population. Infants were enrolled and stratified by age (1 to <3 months, 3 to <6 months, and 6 to 12 months); age grouping was used for recruitment purposes to ensure an approximately even distribution of infants across the age range. The study population consisted of a representative group of infants who had active, suspected or latent HSV-1 or HSV-2 infection, and who were candidates for antiviral therapy, regardless of their immune status. Infants who were starting or using acyclovir therapy were eligible for the study.

Infants were excluded from study participation if they were aged 1 month to <3 months with a gestational age <35 weeks or 3 to 12 months with a gestational age <32 weeks; were unable to swallow (e.g., infants who had extensive gingivostomatitis in whom drinking was impaired); had a history of malabsorption or previous gastrointestinal surgery, or history of radiation therapy that could affect drug absorption or metabolism; had clinically significant hepatic or renal disorders; or had any of the following age-adjusted clinical or hematologic laboratory and blood chemistry abnormalities: aspartate aminotransferase or alanine transaminase level >3 times the upper limit of normal (ULN), total bilirubin level >2-fold the ULN, serum creatinine level >2-fold the ULN, absolute white blood cell count of <4,000/mm³, platelet count of <50,000/mm³, hemoglobin level of <7 gm/dL, or a significant blood volume loss (>3% of calculated blood volume) in the
previous 30 days. Probenecid use was prohibited due to its effects on renal physiology and because of its propensity to elevate plasma levels of penciclovir.

Acceptability, tolerability and safety assessments. Immediately after swallowing the formulation, the caregiver and the person who administered the drug rated the apparent acceptability of the formulation using a 5-point subjective scale (1 = very badly/unalcceptable, 2 = badly but accepted, 3 = neither good nor bad, 4 = well accepted, 5 = very well accepted). The study personnel who administered the dose also rated tolerability 30 minutes after dosing using a 4-point scale (1 = significant emesis occurred, 2 = infant spit out most of the dose ingesting less than half of what was administered, 3 = infant spit out some of the dose, but ingested at least 50% of what was administered, 4 = infant was able to ingest and retain the dose administered).

Safety assessments consisted of monitoring and recording all adverse events (AEs), serious AEs, physical examination, and vital sign measurements. AEs were recorded at serial times up to 8 h post-dose, at 24 h after completion of therapy if the infant prematurely withdrew, did not ingest the full dose, or underwent significant emesis and was not re-dosed, and at the time of the Day 8 or 38 follow-up telephone call. Clinical laboratory (e.g., hematology, clinical chemistry) tests were performed for all infants at screening, at 24 h after completion of therapy for infants specified above, and if a repeat follow-up visit was required. Laboratory toxicity grading (1 to 4) was based on modified Division of Microbiology and Infectious Diseases (November 2007) and Division of AIDS (December 2004) pediatric toxicity criteria.
Pharmacokinetic assessment and analysis. Blood samples (1.0 mL each) were drawn for measurement of penciclovir concentrations at 0.5, 1, 4, and 6 h following the famciclovir dose using tubes containing EDTA as the anticoagulant; a 0 time sample was not obtained in order to minimize the amount of blood withdrawn. Plasma was separated using centrifugation and kept frozen at -20°C until analysis. Penciclovir and 6-deoxypenciclovir concentrations in plasma were determined using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. The intra- and inter-batch precision of the method as characterized by the coefficient of variation (CV) ranged between 1.2% and 5.4% for plasma samples spiked with penciclovir or 6-deoxypenciclovir (pre-study assay validation). In spiked quality control samples analyzed together with the study samples, the CV ranged between 1.1% and 5.9%. The limit of quantification was 0.15 µg/mL for each compound. 6-deoxypenciclovir is an inactive metabolite of famciclovir and the precursor of the active metabolite penciclovir (10, 22).

Plasma drug concentration-time data were used to derive the following pharmacokinetic parameters of penciclovir: $C_{\text{max}}$ (maximum concentration), $T_{\text{max}}$ (time to $C_{\text{max}}$), and $AUC_{0-6}$ (area under the plasma drug concentration-time curve from time zero to 6 h). Pharmacokinetic calculations were performed using WinNonlin Professional Version 5.2 (Pharsight Corporation, Mountain View, CA) and noncompartmental methods. Since no pre-dose plasma sample was collected, the 0 h concentration of penciclovir was assumed to be zero for calculation of $AUC_{0-6}$. 
Population pharmacokinetic modeling. An updated population pharmacokinetic model for penciclovir in pediatric patients was generated based on pooled pharmacokinetic data from the infant study described in this paper and two previous studies in older children ages 1 to 12 years (19). A weight-based dose table for infants and children that would provide AUC exposures comparable to adults was subsequently derived.

Model building was performed using DOUBLE PRECISION NONMEM Version VI Level 1.3 with METHOD = 1 INTERACTION. A one-compartment model with first-order input and parameters to be estimated for apparent clearance (CL), apparent volume (V), and input rate constant (kₐ) was selected for the population pharmacokinetic analysis based on a previous interim analysis reported in children 1 to 12 years of age (19). CL and V are used here synonymously with CL/F and V/F, where F is the oral bioavailability. An input lag time (ALAG1) equal to 0.21 h, and clearance and volume allometrically scaled by BW to the 0.75 and 1.0 power (2), respectively, were assumed as in the previous analysis.

The population model added random effects for the pharmacokinetic parameters in order to recognize differences among individuals and similarities across observations corresponding to the same subject. Intersubject random effects for CL, V, and kₐ (η₁, η₂, and η₃, respectively) were assumed normally distributed with means of zero and with η₁ correlated with η₂, but both uncorrelated with η₃. The individual pharmacokinetic parameter for clearance was represented in terms of its typical value (TV) – TVCL as CL = TVCL * exp(η₁). Other pharmacokinetic parameters used similar representations. A
combined residual error model was adopted in this analysis. In this case, the residual error is normally distributed with mean 0 and variance $\sigma_1^2 + \sigma_2^2 C^2$, where $C$ is the individual predicted plasma penciclovir concentration at a specific time point, $\sigma_1$ is the approximate standard deviation of the residual error when $C$ is small, and $\sigma_2$ is the approximate residual coefficient of variation (CV) when $C$ is large.

The likelihood function and diagnostic plots, including a visual predictive check, were used to suggest refinements to the model and to assess goodness of fit. Successful convergence was declared if NONMEM reported “MINIMIZATION SUCCESSFUL” with number of significant digits at least 3.0. For the visual predictive check using NONMEM, 1000 replicates of the penciclovir concentration data were simulated based on covariate data and actual mg doses and times of doses and samples in the actual data set. Final population parameters were fixed at their final estimates in the simulation (i.e., assuming no uncertainties in the population parameters), but incorporating variability in individual parameters and observational (residual) error. SAS PROC UNIVARIATE was used to compute the 5th, 50th, and 95th percentiles of the simulated penciclovir concentrations by three weight groups (>3 to 7 kg, >7 to 12 kg, and >12 kg) and elapsed time after dose. Finally, S-Plus was used to display the visual predictive check with observed data superimposed over the percentiles.

The final model was used to predict pharmacokinetic exposure measures (AUC, the area under the plasma concentration-time curve from time zero to infinity, and $C_{\text{max}}$) and related pharmacokinetic parameters for penciclovir for each patient in the population.
pharmacokinetic analysis population using actual doses as well as various proposed
alternative dosing tables designed to match AUC for infants and children with adults.
SAS Release 8.2 was used for all non-graphical descriptive summaries. S-Plus version
6.2 was used for all graphical analyses.

Sample size and statistical methods. For this single-dose study, 18 infants were planned
with a sample size of 6 participants per group based on common practice for
pharmacokinetic studies in pediatric participants.

Descriptive summaries of demographics, medical history, pharmacokinetics, safety, and
medication acceptability were provided. Safety data were analyzed by Biometrical
Practice BIOP AG (Basel, Switzerland), using SAS 8.2 or Windows XP. No inferential
analyses were performed.

RESULTS

Participants. A total of 18 infants were enrolled, all of whom completed the study
(safety population). One infant, exactly 12 months of age, was enrolled and included in
the analysis. Sixteen of the infants were inpatients and 2 were outpatients. The full dose
was administered to 16 infants (88.9%) and ranged from 25 to 175 mg. One infant in the
6 to 12 months group took a dose of 175 mg instead of 200 mg and another infant (1 to
<3 months group) did not receive the full dose secondary to significant emesis (re-dosing
was not attempted and pharmacokinetic samples were not taken). Demographic and
disease characteristics are outlined in Table 2. Approximately two-thirds of infants had
confirmed HSV at baseline, with confirmation most commonly by PCR. Regarding HSV
disease, 6 had meningoencephalitis, 1 unspecified congenital herpes, 3 eczema
herpeticum, 1 gingivostomatitis, and 7 unspecified HSV infection. Two infants were
immunocompromised, both in the 1 to <3 months group, (1 with myeloproliferative
disorder and the second with unspecified immune system disorder). The remaining 16
infants were immunocompetent. A total of 16 patients (89.0%) received concomitant
acyclovir therapy including 8 patients in the 1 to <3 months group, 4 patients in the 3 to
<6 months group, and 4 patients in the 6 to 12 months group.

Pharmacokinetics. Seventeen infants were included in the pharmacokinetic analysis.
Blood samples for penciclovir concentrations were available from 7 patients in the 1 to
<3 months group, 5 patients in the 3 to <6 months group, and 5 patients in the 6 to 12
months group. The mean famciclovir dose administered to groups 1, 2 and 3 was
6.6 mg/kg, 9.4 mg/kg and 13.5 mg/kg, respectively.

Mean plasma concentration time profiles of penciclovir and 6-deoxy penciclovir for the
three age groups are shown in Figure 1. Concentrations of 6-deoxy penciclovir were
lower than those of penciclovir and were below the limit of quantification at 4 h after
dosing in 16 of the 17 infants. A summary of pharmacokinetics parameters for
penciclovir by age group is presented in Table 3. Mean $C_{\text{max}}$ and $\text{AUC}_{0-6\text{h}}$ values of
penciclovir in the infants below 6 months of age were approximately 3- to 4-fold lower
compared with those in the 6 to 12 months group.
In Figure 2, the individual AUC\(_{0-6h}\) values of penciclovir are plotted against BW (upper graph) or age (lower graph) of the infants of each age group; infants in both the 1 to <3 months and 3 to <6 months groups had a lower exposure to penciclovir than infants in the 6 to 12 months group. As mentioned previously, 1 infant in the 6 to 12 months group received an incorrect dose (i.e., 175 mg instead of 200 mg, according to BW [11.5 kg]). The AUC\(_{0-6h}\) of penciclovir in this infant was 8.45 \(\mu\)g/mL•h. Assuming exposure proportionally increased with dose, the AUC\(_{0-6h}\) for the correct dose (200 mg) would have been 9.66 \(\mu\)g/mL•h, which is still well below the upper limit of the exposure range in this age group.

**Acceptability, tolerability and safety.** A total of 8 (44.4%) infants experienced at least one adverse event. All adverse events occurred within 8 days, with the majority occurring 3 or more days, after single-dose famciclovir administration except for one (fever), which was reported 31 days after study drug administration. No infants discontinued the study or treatment because of adverse events. Among 17 individual adverse events reported, the most common were vomiting in 3 infants, and diarrhea, pyrexia, and dehydration in 2 infants each. All other adverse events were reported in 1 infant each. A total of 3 infants (16.7%) had at least one mild adverse event, 4 infants (22.2%) had at least one moderate adverse event and 1 infant (5.6%) had a severe adverse event. The infant with a severe event was immunocompromised with oral candidiasis and was reported to have worsening HSV encephalitis. The infant’s deterioration began after 18 of 21 days of intravenous acyclovir therapy and was reported on Day 3 of famciclovir single-dose
administration. The encephalitis was not considered to be related to famciclovir therapy per the investigator’s judgment.

One infant was reported by the investigator to have a possible drug-related adverse event. The infant had vomiting of moderate intensity on Day 1 soon after taking the medication, which resolved on the same day without intervention.

A 4-month-old male with eczema herpeticum, experienced 2 serious adverse events, which led to hospitalization: dehydration and worsening of constitution both reported on Day 2 of the study. The infant was treated with intravenous fluids; each event resolved after 15 days. Neither of these events was suspected to be related to study medication.

There were no meaningful changes from baseline in vital signs. For hematology and clinical chemistry tests, changes from baseline were generally small and not clinically meaningful overall. A 1-month-old male shifted from normal at baseline for hemoglobin to Grade 3 toxicity post-treatment. The same patient shifted from abnormal at baseline for neutrophils to Grade 3 toxicity post-treatment. No changes to Grades 3 or 4 toxicities were reported for clinical chemistry values.

Most infants appeared to like the taste of the famciclovir formulation administered. After the first dose was given, the majority of caregivers (66.6%; 12 of 18) indicated that the medication was ‘well accepted’ or ‘very well accepted’ by the infant. Three caregivers rated the medication as being of neutral acceptability. Two caregivers stated that the
medication was taken ‘badly but accepted’ or ‘very badly, unacceptable’ (one in the 1 to 3 months group and the second in the 6 to 12 months group). Similar results were seen in the acceptability responses from study personnel. Overall, 17 patients (94.4%) were considered by study personnel to have been able to ingest the study medication and retain the dose. One patient as mentioned above had significant emesis after receiving the single dose.

**Updated pediatric population pharmacokinetic model.** A total of 67 patients (50 children 13 months to 12 years, 5 infants 6 to 12 months and 12 infants <6 months) comprised the dataset, which included 316 post-dose penciclovir plasma concentrations. Children averaged 4.26 years (median 3.67 years, range: 0.09 years to 11.94 years); BW averaged 17.5 kg (median 15.4 kg, range: 3.2 - 61.7 kg) and was correlated with age. Males slightly outnumbered females 35 (52.2%) to 32 (47.8%). Racial diversity prevailed: 21 (31.3%) Caucasian, 18 (26.9%) Black, 3 Native American (4.5%), 1 (1.5%) Asian, and 24 (35.8%) mixed or other. Each patient contributed 3 to 5 blood samples to the pharmacokinetic analysis.

The one compartment model was fitted with clearance and volume allometrically scaled by BW to the powers 0.75 and 1.0, respectively, as had been done in the previous pediatric study (19). Diagnostics plots for the model (Model 1) indicated clearances in infants needed no adjustment, but the $k_a$ was smaller in infants than in older children.

A new model was proposed (Model 2) which incorporated two additional parameters for
the effect of a maturation factor (MF) on TVKA as follows:

\[ MF = \frac{PCA^{\theta_7}}{\theta_8^{\theta_7} + PCA^{\theta_7}} \]

\[ TVKA = \theta_3 \cdot MF \]

Full maturity is indicated by \( MF = 1 \). MF increases from 0 to 1 based on a sigmoid \( E_{\text{max}} \) model parameterized in terms of \( \theta_7 \), the sigmoidicity parameter, and \( \theta_8 \), the post-conceptional age to reach half of full maturity. Model 2 was fitted and its goodness of fit as measured by the log likelihood function was significantly better than Model 1

\( (\chi^2 = 586.463 - 541.555 = 44.908, p < 0.0001) \).

Models with additional parameters (Model 3, Model 4, Model 5, and Model 6) were proposed, but the additional parameters were not statistically significant. Three parameters to estimate the bioavailability fraction (F1) as a function of MF (2 parameters for the MF and 1 parameter for the variance of the random effect related to F1) were not significant when added to Model 1 or Model 2 (Model 3 vs. Model 1: \( \chi^2 = 543.361 - 541.555 = 1.806, p > 0.2 \); Model 4 vs. Model 2: \( \chi^2 = 586.552 - 586.463 = 0.089, p > 0.2 \)). Two parameters added to Model 2 for a separate MF on CL were not statistically significant (Model 5 vs. Model 2: \( \chi^2 = 586.499 - 586.463 = 0.036, p > 0.2 \)). An added parameter to estimate the exponent for BW in the expression for clearance was estimated as 0.767 and was not statistically significant different than the assumed value of 0.75 (Model 6 vs. Model 2: \( \chi^2 = 586.681 - 586.463 = 0.218, p > 0.2 \)). Model 2 was adopted as the final model based on these statistical comparisons (Table 4). The coefficient of variation for unexplained intersubject variability in apparent clearance was 21%. The residual coefficient of variation ranged from 13% to 18% at expected concentrations from
5.0 µg/mL to 0.5 µg/mL.

The visual predictive check by BW groups (≥3 to 7 kg, >7 to 12 kg, and >12 kg) showed good agreement of the observed concentration data and model with the data centered near the 50th percentile (median) and about 10% of the 316 observations outside the 90% prediction intervals. Estimates of pharmacokinetic exposure (i.e., AUC and $C_{\text{max}}$) subsequently were computed using Model 2 (Table 5). Model-based estimates of penciclovir exposure in infants <6 months averaged less than one-half (AUC) or one-third ($C_{\text{max}}$) of that for all other age groups for infants and children. Infants <6 months (n = 12) had a mean AUC = 3.69 ± 1.19 µg/mL•h and mean $C_{\text{max}}$ = 0.79 ± 0.31 µg/mL.

The final model (Model 2) depended upon BW in units of kg and post-conceptional age in units of months (PCA) assuming a full-term birth at 9 months post-conception. The population TV of the pharmacokinetic parameters (CL, V and $k_{\text{a}}$) of penciclovir were expressed in terms of the famciclovir dose and were estimated in the final model as follows:

\[
TV_{\text{CL}} = 29.6 \cdot \left(\frac{\text{BW}}{20}\right)^{0.75} \text{L/h} \quad \text{(equation 1)}
\]

\[
TV_{\text{V}} = 55.7 \cdot \left(\frac{\text{BW}}{20}\right) \text{L}
\]

\[
TV_{k_{\text{a}}} = 5.48 \cdot \text{MF h}^{-1}, \text{ where } \text{MF} = \frac{\text{PCA}^{3.87}}{\left(21.1^{3.87} + \text{PCA}^{3.87}\right)}
\]

\[
\text{PCA} = \left(\frac{9}{12} + \text{AGE}\right) \cdot 12 \text{ month and AGE is in units of years}
\]

In the above equations, TVCL and TVV are expressed in terms of the famciclovir dose. MF, the maturation factor on $k_{\text{a}}$, increases from 0 to 1, based on a sigmoid $E_{\text{max}}$ model, parameterized in terms of 3.87, the sigmoid parameter and 21.1, the PCA to reach half of
The model can be re-expressed in terms of the penciclovir equivalent dose by multiplying both TVCL and TVV by 0.7884 to adjust for difference in molecular weight (MW) between famciclovir (321.3 g/mol) and penciclovir (253.3 g/mol). Thus, the model-based oral clearance (CL/F) of penciclovir is given by the equation:

$$\frac{CL}{F} = \frac{MW(\text{penciclovir})}{MW(\text{famciclovir})} \times TVCL = 0.7884 \times TVCL$$

$$= 23.3 \times (BW/20)^{0.75} \text{ L/h}$$  (equation 2)

and CL/F of penciclovir for a typical 20 kg child is predicted to be 23.3 L/h.

The relationship between the oral clearance of penciclovir (model-based) and BW in all 67 pediatric patients included in the population pharmacokinetic analysis is illustrated in Figure 3. The data were fitted to an empirical power model ($\frac{CL}{F} = A \times BW^B$) resulting in the following equation:

$$\frac{CL}{F} = 2.3873 \times BW^{0.7658}$$  (equation 3)

As seen in Figure 3, this function is practically superimposing equation 2 ("modeled CL/F"). By dividing both sides of equation 3 by BW, weight normalized oral clearance (L/h/kg) is seen to be inversely related to BW. Penciclovir weight normalized oral clearance generally increased when BW decreased (Figure 4).

**Updated Dosing Recommendations.** As presented above, the infants younger than 6 months showed considerably lower exposure than those between 6 and 12 years of age. To match the exposure (penciclovir AUC) seen in adults after a single 500 mg dose (8.94
of famciclovir was not established in patients below 6 months of age, the updated
dosing scheme of famciclovir for pediatric patients covers the age range from 6 months to
12 years.

Based on the presented pharmacokinetic data above and the population pharmacokinetic
model, an 8-step dosing scheme was developed for pediatric patients between 6 months
and 12 years of age, aiming to achieve the target exposure (i.e., the exposure seen in
adults after a single 500 mg dose). Starting from equation 1 and substituting TVCL by
famciclovir dose/penciclovir AUC, the theoretical famciclovir dose to match the adult
AUC (8.94 µg/mL·h) is given by:

\[
\text{Famciclovir dose (mg)} = 29.6 \cdot (\text{BW/20})^{0.75} \cdot 8.94 \quad \text{(equation 4)}
\]

These theoretical doses are listed in Table 6 for the lower and upper BW limits of each of
the eight BW groups, together with the proposed doses. The proposed dose is at the lower
limit of the theoretical dose range for the lowest BW group (6 to 8 kg) and near the
middle of the theoretical range of doses for all other BW groups.

Subsequently, all 55 patients between 6 months and 12 years included in the population
pharmacokinetic analysis were assumed to receive a famciclovir dose according to the 8-
step dosing scheme shown in Table 6 and the model-based individual AUC values of
penciclovir for these doses were calculated. In Figure 5, these AUCs are plotted against
BW. The graph also shows the target AUC (i.e., mean and range of AUCs observed in healthy adult volunteers after a single 500 mg dose of famciclovir). The individual values are equally distributed around the target mean and 51 (93%) of the 55 patients show values within the range seen in adults.

DISCUSSION
The current single-dose famciclovir pharmacokinetic study extends previous investigations to infants 1 to 12 months of age. The basis for dosing famciclovir in infants originated from data accumulated in older children (19), wherein BW was shown to be the most important factor in penciclovir pharmacokinetics. This is in keeping with expected characteristics of a drug with low protein binding that distributes in total body water and is predominantly renally excreted (17), as is the case for penciclovir (10). For children 1 to 12 years old, famciclovir dosing was calculated based on the established relationship between penciclovir clearance and BW in order to achieve the target exposure (i.e., the penciclovir AUC seen in adults after a 500 mg dose of famciclovir) (19). It was subsequently assumed that clearance of penciclovir in infants younger than 12 months of age would be lower than extrapolated from the relationship between penciclovir clearance and BW in older children due to their physiologically immature kidneys (11, 25, 28). Glomerular filtration and active tubular secretion are involved in the renal elimination of penciclovir (10) and both processes have been reported to be immature at birth, reaching adult levels during the first year of life (11, 25). As such, a renal MF was introduced in the equation describing the relationship between penciclovir clearance and the infant’s BW. Accordingly, the infant dosage algorithm derived from the
modified model and used in the current single dose study resulted in relatively lower
doses (mg) per BW (kg) in the infants below 6 months of age (mean 6.6 and 9.4 mg/kg,
see Table 3) than in the older infants (13.5 mg/kg), as well as in the children of the
previous study that comprised three age groups (12.2 to 13.0 mg/kg) (19).

Actually, penciclovir concentrations in infants aged 6 to 12 months were similar to those
observed in children aged 1 to 12 years and in adults following a single 500 mg dose of
famciclovir (19). The mean estimate of AUC was 8.59 µg/mL•h in the 6 to 12 months
group compared with mean estimates between 7.81 and 9.62 µg/mL•h in the age groups
between 1 and 12 years (Table 5). In adults, mean AUC was 8.94 µg/mL•h. In contrast,
systemic exposure to penciclovir in infants 1 month to <6 months of age was
considerably lower, the AUC estimate being 3.69 µg/mL•h (Table 5). In addition, the
penciclovir concentration-time profiles were relatively flat in these infants, without a
distinct peak in most profiles (Figure 1). These observations suggest that unlike acyclovir
(28), the apparent oral clearance of penciclovir is not reduced in young infants due to an
immature kidney function, thus disproving the assumption that a renal MF is needed for
deriving dosages in the 1 to <6 months age group.

In order to optimize the dose of famciclovir in the pediatric population, we conducted a
series of population pharmacokinetic analyses of penciclovir using data from children
and most recently infants. The first analysis included 41 children with HSV and VZV
infections (aged 1 to 12 years) from the study reported by Sáez-Llorens (19). This model
estimated the typical oral clearance of penciclovir as a function of BW (i.e., CL/F = 23.8
• \([\text{BW}/20]^{0.75}\), which was used to predict famciclovir doses to match the targeted penciclovir AUC. An 8-step dosing regimen was subsequently derived for pediatric patients aged 1 to 12 years and was used in the multiple-dose phase of the study reported by Sáez-Llorens (19). The subsequent analysis reported herein combined the data obtained in older children (19) with the 17 infants described in the first part of this paper. The typical oral clearance of penciclovir in the latest model \((\text{CL/F} = 23.3 \times ([\text{BW}/20]^{0.75}))\) was nearly identical to that described in the first model and also supported that a relationship between clearance and BW was close to proportional. Importantly, the updated model found no effect of renal maturation on apparent oral clearance. However, the updated model included a MF on the input rate \(k_a\), which depended upon post-conceptual age: MF increased from 0 to 1, being 0.05 and 0.21 for an infant aged 1 month or 6 months, respectively. Full maturity was reached at about 6 years of age (MF = 0.99). The effect of MF on the concentration-time profile of penciclovir in infants and children 1 month to 12 years of age is illustrated in Figure 6. The profile is getting flatter and \(T_{\text{max}}\) is being shifted to later times the younger the subject.

Conversion of the prodrug famciclovir to the active metabolite penciclovir occurs in two steps (i.e., deacetylation of famciclovir to 6-deoxy penciclovir, followed by oxidation of the intermediate metabolite to penciclovir). In adults and children 1 to 12 years of age, it has been shown that famciclovir is rapidly absorbed and extensively metabolized to penciclovir (10, 15, 19, 22). Plasma concentrations of 6-deoxy-penciclovir were typically lower than that of penciclovir, and detectable only for a short period after dosing (15, 19). As shown in Figure 1, this observation is also valid for the infants in our study.
Despite the apparent similarities of 6-deoxypenciclor to penciclovir ratios between the pediatric age groups, it is worthwhile to consider the enzymes involved in the conversion of famciclovir to penciclovir. The deacetylation is catalyzed by esterases, the oxidation by aldehyde oxidase (10). There are reports that activity of these enzymes is reduced in infants (25, 26). Tayama recently reported that aldehyde oxidase activity rapidly increases with the patient’s age up to about 1 year (26). Thus, conversion of famciclovir to penciclovir could be affected in infants, resulting in a delayed appearance of penciclovir in plasma and, potentially, also in a reduction of the amount of penciclovir reaching the systemic circulation. The first effect was actually observed, as discussed above (i.e., effect of MF on \( k_a \)). The second effect (i.e., smaller amount converted) may have been compensated by a somewhat slower renal elimination of penciclovir in the very young infants, so that the net affect is close to zero and apparent oral clearance is not dependent on a MF. The latter may also explain the difference in the disposition of penciclovir and acyclovir in very young infants, since acyclovir is not dependent on metabolic activation.

Another factor which could have contributed to the observed differences in the disposition kinetics of penciclovir between young infants and children is slow gastric emptying in neonates and young infants, resulting in a slower rate at which orally administered drugs are absorbed in these populations compared to older infants/children or adults (11, 25, 27). Thus, in young infants treated with famciclovir, famciclovir absorption as well as its conversion to penciclovir could be delayed to a certain extent,
resulting in a delay of the time to achieve the maximal plasma concentration, as observed in our study.

The population pharmacokinetic analysis has led us to recommend an 8-step dosing scheme for oral famciclovir in pediatric patients aged 6 months to 12 years, one that targets the mean AUC in adults (i.e., 8.94 µg/mL•h) after a 500 mg dose (Table 6). The recommended dosage regimen is expected to achieve optimal penciclovir concentrations, as illustrated in Figure 5. While the model would allow us to derive doses also for infants below 6 months of age and weighing less than 6 kg, we currently cannot recommend such doses since they would be considerably higher than those actually tested in our study.

The proposed dosages for infants and children 6 months to 12 years of age remain to be tested in prospective clinical trials, however, exploratory efficacy data in children with active HSV and VZV infections has been encouraging (19).

Recently Ogungbenro et al (14) reported another population pharmacokinetics analysis of penciclovir, which was done to develop optimal sampling windows for future pediatric studies. The authors used pharmacokinetic data from studies in 46 adults and 23 children aged 2 to 17 years. The children were either immunocompromised or had hepatitis B infection. The population model shows some differences to our model. It is a 2-compartment model and includes bioavailability as a separate model parameter. The clearance of penciclovir depends on body weight, age and the creatinine clearance of the patient, whereas in our model penciclovir clearance depends only on body weight (see equations 1 to 3). Nonetheless, the two models seem to give similar results when used to
predict penciclovir clearance for a given individual. For an 8.1-year-old-child with a body weight of 29.5 kg and a creatinine clearance of 58.2 mL/min (mean values for the children in the Ogungbenro paper (14), CL/F of penciclovir is 29.7 L/h, whereas our model (equation 2) predicts a CL/F value of 31.2 L/h.

Famciclovir was well tolerated in infants 1 to 12 months of age. Similar to adults and older children (1, 3, 5, 6, 19, 24), the most frequent adverse events in the 18 infants given famciclovir were vomiting, diarrhea, pyrexia, and dehydration. No infants discontinued famciclovir for safety reasons and none of the infants had serious drug-related adverse events. There were no signals of significant CNS, hepatic or hematologic toxicities, nor unexpected changes in hematology or clinical chemistry parameters and no trends indicative of hepatic or renal toxicities, or neutropenia or thrombocytopenia. A one-month-old male infant experienced a shift from normal at baseline to Grade 3 toxicity for hemoglobin, although of questionable clinical relevance. Infants between the ages of 1 and 12 months tolerated the single-dose oral famciclovir sprinkle formulation well. Similar to that observed in older children given the oral sprinkle famciclovir formulation (19), the majority of caregivers and study personnel considered the famciclovir pediatric formulation to be well or very well accepted by the infants.

In summary, a single dose of famciclovir oral pediatric formulation was safe and well tolerated in infants 1 to 12 months of age with active, suspected, or latent HSV infection. Combining single-dose data in infants with those of older children allowed us to derive an 8-step weight-based dosage scheme for infants and children between 6 months and 12
years, which achieve a target exposure similar to adults after a 500 mg dose. Famciclovir oral sprinkle formulation appears suitable for use in infants who require treatment for HSV infections.
The Famvir Study Group

United States. Dr. Basim Asmar, Detroit, Michigan; Dr. Jeffrey Blumer, Cleveland, Ohio; Dr. David Kimberlin, Birmingham, Alabama; Dr. Pablo Sánchez, Dallas, Texas; Dr. Ram Yoge, Chicago, Illinois.

Germany. Dr. Uwe Schauer, Bochum, Germany; Dr. Peter Hoeger, Hamburg, Germany; Dr. Jorg Doetsch, Erlangen, Germany; Dr. Volker Schuster, Leipzig, Germany.

Guatemala. Dr. Adib Rodriguez, Ciudad de Guatemala, Guatemala.
ACKNOWLEDGMENTS

We thank the volunteers, coinvestigators, and study coordinators including Luz Muniz, for their participation in this study. Editorial support for preparation of the manuscript was provided by Teresa Tartaglione (IDP Communications). Funding for editorial support and for the study was provided by Novartis.

This study was registered with www.ClinicalTrials.gov; trial’s identifier NCT00448227.

This study was supported in part by the National Institute of Child Health and Human Development Pediatric Pharmacology Research Unit (University of Texas Southwestern Medical Center grant 1U10-HD046000-06 to PJ Sánchez and University of Cleveland Hospitals grant 5U10-HD031323-15 to J Blumer).
Table 1. Famciclovir Dosing Regimen by Body Weight

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4.5</td>
<td>25</td>
</tr>
<tr>
<td>4.6 - 5.4</td>
<td>25</td>
</tr>
<tr>
<td>5.5 - 6.4</td>
<td>50</td>
</tr>
<tr>
<td>6.5 - 7.4</td>
<td>75</td>
</tr>
<tr>
<td>7.5 - 8.4</td>
<td>100</td>
</tr>
<tr>
<td>8.5 - 9.4</td>
<td>125</td>
</tr>
<tr>
<td>9.5 - 10.4</td>
<td>150</td>
</tr>
<tr>
<td>10.5 - 11.4</td>
<td>175</td>
</tr>
<tr>
<td>11.5 - 13.4</td>
<td>200</td>
</tr>
</tbody>
</table>
Table 2. Demographic and baseline characteristics by age group for infant single-dose study (Safety Population)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 to &lt;3 months</td>
<td>3 to &lt;6 months</td>
<td>6 to 12 months</td>
<td>N = 18</td>
</tr>
<tr>
<td>n</td>
<td>n = 8</td>
<td>n = 5</td>
<td>n = 5</td>
<td></td>
</tr>
<tr>
<td>Confirmed HSV infection, n (%)</td>
<td>5 (62.5)</td>
<td>3 (60.0)</td>
<td>4 (80.0)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>HSV identification confirmation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>3 (37.5)</td>
<td>2 (40.0)</td>
<td>–</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Culture</td>
<td>1 (12.5)</td>
<td>1 (20.0)</td>
<td>1 (20.0)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Clinical diagnosis only</td>
<td>1 (12.5)</td>
<td>–</td>
<td>3 (60.0)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Immunocompromised, n (%)</td>
<td>2 (25.0)</td>
<td>–</td>
<td>–</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>No (%) male</td>
<td>5 (62.5)</td>
<td>3 (60.0)</td>
<td>3 (60.0)</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>Age (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1 (1 - 2)</td>
<td>3 (3 - 4)</td>
<td>8 (7 - 12)</td>
<td>3 (1 - 12)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>4 (50.0)</td>
<td>3 (60.0)</td>
<td>1 (20.0)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>n (%)</td>
<td>Median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------</td>
<td>----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (37.5)</td>
<td>4.0 (3.2 - 6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>–</td>
<td>5.9 (5.5 - 7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (12.5)</td>
<td>7.9 (6.9 - 11.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>1 (12.5)</td>
<td>4.0 (3.2 - 6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (12.5)</td>
<td>5.9 (5.5 - 7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (75.0)</td>
<td>7.9 (6.9 - 11.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weight (kg)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>n (%)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>3 (37.5)</td>
<td>4.0 (3.2 - 6.0)</td>
</tr>
<tr>
<td>Native American</td>
<td>–</td>
<td>5.9 (5.5 - 7.7)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (12.5)</td>
<td>7.9 (6.9 - 11.5)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>1 (12.5)</td>
<td>4.0 (3.2 - 6.0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>–</td>
<td>5.9 (5.5 - 7.7)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (75.0)</td>
<td>7.9 (6.9 - 11.5)</td>
</tr>
</tbody>
</table>
Table 3. Pharmacokinetic parameters of penciclovir in infants after administration of single dose famciclovir

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1 (1 to &lt;3 months)</th>
<th>Group 2 (2 to &lt;6 months)</th>
<th>Group 3 (6 to 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n = 7</td>
<td>n = 5</td>
<td>n = 5</td>
</tr>
</tbody>
</table>

**Pharmacokinetic parameter, mean ± SD**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (1.00 - 5.17)</th>
<th>Group 2 (1.0 - 4.17)</th>
<th>Group 3 (0.58 - 1.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.00</td>
<td>4.00</td>
<td>1.02</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>0.69 ± 0.41</td>
<td>0.74 ± 0.17</td>
<td>3.24 ± 1.01</td>
</tr>
<tr>
<td>$\text{AUC}_{0-6}$ (µg/mL•h)</td>
<td>2.22 ± 1.23</td>
<td>3.16 ± 0.68</td>
<td>8.77 ± 2.14</td>
</tr>
</tbody>
</table>

**Body weight (BW) adjusted dose (mg/kg), mean ± SD**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.6 ± 1.4</td>
<td>9.4 ± 2.1</td>
<td>13.5 ± 2.0</td>
</tr>
</tbody>
</table>

*Values reported as median (range)*
Table 4. Pharmacokinetic models and their goodness of fit

<table>
<thead>
<tr>
<th>Model number and description</th>
<th>No. parameters</th>
<th>Model description</th>
<th>-2 x ln(likelihood)</th>
</tr>
</thead>
</table>
| 1. No maturation factor (MF) | 9              | \( \begin{align*} 
CL & = \theta_1 (BW/20)^{0.75} \times \exp(\eta_{CL}) \\
V & = \theta_2 (BW/20) \times \exp(\eta_V) \\
k_a & = \theta_3 \times \exp(\eta_{ka}) 
\end{align*} \) | -541.555 |
| 2. TVKA depends on MF       | 11             | CL and V as in Model 1 \( MF = PCA^{\theta_7}(\theta_8^{\theta_7} + PCA^{\theta_7}) \) \( k_a = \theta_3 \times MF \times \exp(\eta_{ka}) \) | -586.463 |
| 3. Bioavailability fraction (F1) depends on MF and a random effect | 12             | CL and V as in Model 1 \( MF = PCA^{\theta_7}(\theta_8^{\theta_7} + PCA^{\theta_7}) \) \( F1 = MF \times \exp(\eta_{F1}) \) | -543.361 |
| 4. \( k_a \) and F1 depend on separate MFs | 14             | CL, V, \( k_a \) as in Model 2 \( MFF1 = PCA^{\theta_9}(\theta_{10}^{\theta_9} + PCA^{\theta_9}) \) | -586.552 |
5. $k_a$ and CL depend on separate MFs

F1 = MFF1 $\times \exp(\eta_{F1})$

5 and $k_a$ as in Model 2

MFCL = PCA$^{\theta_9} / ( \theta_{10} + PCA^{\theta_9} )$

CL = $\theta_1 \times MFCL \times (BW/20)^{0.075} \times \exp(\eta_{CL})$

6. Model 2 with exponent for body weight (BW) estimated for clearance

V = $\theta_2 \times (BW/20) \times \exp(\eta_V)$

MF = PCA$^{\theta_7} / ( \theta_{8} + PCA^{\theta_7} )$

$\theta_3 = \theta_1 \times MF \times \exp(\eta_{\theta_3})$

$-586.499$

CL = $\theta_1 \times (BW/20)^{0.08} \times \exp(\eta_{CL})$

V = $\theta_2 \times (BW/20) \times \exp(\eta_V)$

MF = PCA$^{\theta_7} / ( \theta_{8} + PCA^{\theta_7} )$

$-586.681$

$\theta_3 = \theta_1 \times MF \times \exp(\eta_{\theta_3})$
Table 5. Estimates of penciclovir pharmacokinetic exposure measures by age group using the population pharmacokinetic model

<table>
<thead>
<tr>
<th>Age group</th>
<th>N</th>
<th>Mean AUC (µg/mL•h)</th>
<th>SD</th>
<th>Mean C_{max} (µg/mL)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>12</td>
<td>3.69</td>
<td>1.19</td>
<td>0.79</td>
<td>0.31</td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>5</td>
<td>8.52</td>
<td>1.74</td>
<td>3.04</td>
<td>0.92</td>
</tr>
<tr>
<td>13 months to &lt;2 years</td>
<td>10</td>
<td>7.77</td>
<td>2.28</td>
<td>3.41</td>
<td>0.61</td>
</tr>
<tr>
<td>2 to &lt;6 years</td>
<td>23</td>
<td>7.86</td>
<td>1.77</td>
<td>3.21</td>
<td>0.79</td>
</tr>
<tr>
<td>6 to &lt;12 years</td>
<td>17</td>
<td>9.62</td>
<td>1.68</td>
<td>3.49</td>
<td>0.77</td>
</tr>
</tbody>
</table>
Table 6. Theoretical doses of famciclovir to achieve the target exposure in pediatric patients aged 1-12 years and proposed dose according to 8-step dosing scheme

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Theoretical dose * (mg)</th>
<th>Dose according to 8-step dosing scheme (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 to 8</td>
<td>100 - 139</td>
<td>100</td>
</tr>
<tr>
<td>9 to 11</td>
<td>139 - 175</td>
<td>150</td>
</tr>
<tr>
<td>12 to 15</td>
<td>175 - 219</td>
<td>200</td>
</tr>
<tr>
<td>16 to 20</td>
<td>219 - 270</td>
<td>250</td>
</tr>
<tr>
<td>21 to 26</td>
<td>270 - 327</td>
<td>300</td>
</tr>
<tr>
<td>27 to 33</td>
<td>327 - 390</td>
<td>350</td>
</tr>
<tr>
<td>34 to 40</td>
<td>390 - 449</td>
<td>425</td>
</tr>
<tr>
<td>≥41</td>
<td>≥449</td>
<td>500</td>
</tr>
</tbody>
</table>

*Theoretical dose = 29.6 • (BW/20)^0.75 • AUC, where BW = body weight and AUC defines the mean exposure seen in adults (n = 24) after a single 500 mg dose of famciclovir (mean AUC = 8.94 µg•h/mL; minimum-maximum: 6.31-11.84 µg•h/mL). The lower (upper) BW limit used in the computation of the theoretical dose range begins at -0.5 kg (+0.5 kg) from the integer weight limit.
Figure Legends

FIG. 1. Mean (± SD) plasma concentration-time profiles of penciclovir and 6-deoxy-penciclovir after a single oral famciclovir dose administered to infants stratified by age. Group 1: 1 to <3 months; Group 2: 3 to <6 months, Group 3: 6 to 12 months. Symbols: ■ Penciclovir; ○ 6-Deoxy-penciclovir.

FIG. 2. Relationship between AUC_{0-6} of penciclovir and body weight or age. Infant 0511_0001 received incorrect dose, i.e. 175 mg instead of 200 mg. (Upper) Observed AUC_{0-6} vs. body weight after single oral famciclovir dose. (Lower) Observed AUC_{0-6} vs. age after single oral famciclovir dose. Group 1: 1 to <3 months; Group 2: 3 to <6 months, Group 3: 6 to 12 months.

FIG. 3. Relationship between penciclovir oral clearance (CL/F) and body weight for 67 infants and children aged 1 month to 12 years old. Individual values represent the model-based CL/F values. Modeled CL/F represents the equation 2 (CL/F = 23.3 • (BW/20)^{0.75}). Power (individual values) shows the fit of an empirical power model to the individual data: CL/F = 2.3873 • BW^{0.7658}.

FIG. 4. Relationship between model-based penciclovir oral clearance normalized to a body weight of 70 kg (CL/F/70 kg body weight) for 67 infants and children aged 1 month to 12 years old. The curve is a local regression model (LOESS).
FIG. 5. Model-based estimates of AUC of penciclovir versus body weight in pediatric patients (n = 55) between 6 months and 12 years given a single dose of famciclovir according to the proposed 8-step dosing table. The squares represent the model-based individual values. The middle, lower and upper horizontal lines represent the mean (8.94 µg/mL•h), minimum (6.31 µg/mL•h) and maximum AUC (11.84 µg/mL•h), respectively, in adults (n = 24) after a single 500 mg dose (19).

FIG. 6. Simulated typical penciclovir concentration-time profiles after a single theoretical dose to match adult exposure (AUC = 8.94 µg/mL•h) in infants and children 1 month to 12 years of age.
FIG. 1.

Cohort 1, n=7

Cohort 2, n=5

Cohort 3, n=6
FIG. 2.

AUC<sub>0-∞</sub> vs. body-weight

AUC<sub>0-∞</sub> vs. age
FIG. 3.
FIG. 4.

[Graph showing the relationship between Penciclovir CL/F (L/h/70kg body weight) and Body weight (kg).]
FIG. 5.
FIG. 6.

Time (h)
Penciclovir concentration (mg/L)

2 years, 12kg
6 years, 20kg
1 year, 9kg
12 years, 40kg
6 months, 7kg
3 months, 5kg
1 month, 3.5kg
References


AUC₀-₆h vs. body weight

Body weight [kg] vs. AUC [(µg/mL)h]

Subject 0511_00001