

**Rapporteur's  
Public Paediatric Assessment Report  
for paediatric studies submitted in accordance  
with Article 46 of Regulation (EC) No1901/2006, as  
amended;**

**Famvir and associated names  
famciclovir**

**DE/W/005/pdWS/001**

**Marketing Authorisation Holder:  
Novartis Pharma GmbH**

<b>Rapporteur:</b>	Germany
<b>Finalisation procedure (day 120):</b>	26.05.2010
<b>Date of finalisation of PAR</b>	05.08.2010

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	FAMVIR
INN (or common name) of the active substance(s):	Famciclovir
MAH:	Novartis Pharma GmbH
Currently approved Indication(s)	<ul style="list-style-type: none"><li>- Herpes zoster</li><li>- primary and recurrent genital herpes</li></ul>
Pharmaco-therapeutic group (ATC Code):	J05A B09
Pharmaceutical forms and strengths:	Film-coated tablets, 25 mg and 100 mg

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## I. EXECUTIVE SUMMARY

In accordance with Article 46 of Regulation 1901/2006 the Marketing Authorisation Holder of Famvir (and associated names), Novartis Pharma GmbH, submitted information about paediatric studies. A Community worksharing procedure was started on 04 May 2009 to evaluate data presented by Novartis.

Altogether, three studies have been submitted, two in children aged 1 to 12, infected either with Varicella zoster or Herpes simplex virus (HSV), and one in infants with HSV-infections from one month up to one year of age.

The studies investigated primarily the pharmacokinetics and the safety of a paediatric dosage form. Also, acceptability of the formulation was investigated. Since studies were uncontrolled, efficacy was assessed descriptively only.

The studies showed overall comparable pharmacokinetic characteristics as compared with adults when dosed according to weight bands. No new safety concerns arose. However, a comparison of the safety profile with that in adults is currently missing. Also, it was shown that the overall acceptability of the paediatric formulation “sprinkle capsules” (gelatine hard capsules) mixed with “Orasweet®” syrup is good. Symptoms of disease improved and were resolved in most cases by the end of the studies.

In this report the MAH’s responses to the Request for Supplementary Information (issued on 29 June 2009), submitted in January 2010, are summarized and assessed (from page 25 onward).

## II. RECOMMENDATION

The data from the submitted studies are considered clinically relevant. Especially, in view of different pk/pd characteristics compared with aciclovir, the only antiherpetic drug currently licensed for treatment of children (less than 12 years of age), famciclovir may be a valuable alternative. In contrast to this, the MAH states that no extension of the indication to include also treatment of children is planned.

Upon the Request for Supplementary Information a critical discussion (expert statement) on this decision has been provided (RSI no.1). In conclusion, the MAH’s reasoning for not pursuing the paediatric formulation/indication remains still disputable, as a therapeutic alternative to aciclovir in this population for the treatment of HSV may be valuable. Especially, the need for less frequent dosing may be a considerable advantage for patients and their caregivers.

***For a final decision/recommendation on this issue as well as on the final wording of the SPC the assessment of data submitted within the article 45 procedure of famciclovir will have to be awaited.***

The other more specific issues on the submitted studies (RSI no. 2 to 7) were appropriately addressed by the MAH and can be considered resolved.

## III. INTRODUCTION

Famvir® (famciclovir) is the oral prodrug of the antiviral nucleoside analogue penciclovir, which has activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV).

Famvir was first registered in United Kingdom on 10 December 1993 by SmithKline Beecham for the treatment of herpes zoster with subsequent registrations in many EU Member States and worldwide. Further approvals included those for treatment of first and recurrent episodes of genital herpes, suppression of recurrent genital herpes, treatment of ophthalmic zoster, and treatment of herpes zoster or herpes simplex infections in immunocompromised patients. In December 2000, marketing authorisations for Famvir have been transferred to Novartis in most countries.

Novartis is currently the marketing authorisation holder in 69 countries worldwide including 19 countries in EU/EEA. Famvir is not registered in the following EU countries: Belgium, Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Slovenia, Slovak Republic, Romania, and one EEA country, Norway. De-

registration of Famvir was initiated in February 2009 in Poland and Portugal. The reason for the requested de-registration is not related to any safety concerns, but only based on marketing considerations.

In the EU/EEA, Famvir is registered only via national procedures (NPs). Renewals have been performed. Last cluster of member states received renewal documentations in March 2007.

Currently an Article 30 procedure for harmonisation of the SPC is ongoing.

The product is not licensed for the treatment of children and adolescents. In the SPC it is stated that famciclovir is not recommended for use in children due to a lack of sufficient safety and efficacy data.

On June 12, 2008, the MAH submitted reports of two completed paediatric studies for Famvir (report nos: FAM810B2303, FAM810B2304), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. On April 3, 2009, a critical expert overview on another study was submitted (study no: CFAM810B2301).

The MAH stated that he neither intends to register the studied formulation nor to apply for changes in the indication or patient population. Moreover, he stated that the submitted paediatric studies do not influence the benefit risk for Famvir and that there is no consequential regulatory action.

**Assessor's comment:**

*Unfortunately, a study report of study CFAM810B2301 has not been submitted.*

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the studies**

Due to the potential utility of famciclovir in paediatric populations, Novartis Technical Research and Development (TRD) developed a new paediatric formulation, i.e. a 25 mg and a 100 mg 'sprinkle' gelatine hard capsules containing granules of the tablet formulation. The composition of this paediatric formulation is the same as that of the tablet formulation, except for the film-coating of the tablet. The bioavailability characteristics of sprinkle granulate are expected to be similar to that of the marketed tablet. The contents (granules) of the capsules are to be sprinkled in a food vehicle such as OraSweet® for easy consumption.

**Assessor's comment:**

*It is not clear whether a bioequivalence study comparing the film-coated tablets and the sprinkle hard gelatine capsules has been conducted.*

### **IV.2 Clinical aspects**

#### **1. Introduction**

Infections due to herpes simplex viruses (HSV-1 and HSV-2) are very common. Although more common in adults, paediatric populations also are impacted by them. Infections in healthy hosts are frequently asymptomatic or have relatively benign courses; however, these infections can lead to mortality and morbidity in neonates and in immunocompromised hosts. Significant morbidity is also seen in immunocompetent infants when infections of the mouth and gums interfere with normal eating and drinking.

In neonates, HSV infections can have devastating consequences. There are approximately 1500 neonatal herpes cases per year in the US. Disseminated infection and encephalitis have a high mortality rate even with intravenous antiviral therapy, whereas infection limited to the skin, eye and mouth has a higher rate

(~7%) of neurological impairment if associated with three or more recurrences of vesicles. Suppressing oral therapy for 6 months with an aciclovir suspension effectively reduced the number of children with recurrences to 19% from 46% in untreated children, but was associated with a high rate of neutropenia (46% with an absolute neutrophil count < 1000 cells/mm<sup>3</sup>).

Herpetic gingivostomatitis is a common manifestation of a primary HSV infection in immunocompetent children, with a peak incidence in the 1 to 3 year age group. The patients present with painful oral lesions on the buccal and gingival mucosa and the tongue. The clinical manifestations last about 12 days, during which time eating and drinking are impaired. In one study, 8% of the children required rehydration by parenteral fluids, while in another the disease was responsible for 0.6% of all admissions to a paediatric hospital. Therapy with oral aciclovir suspension has been shown to reduce the duration of clinical manifestations, but the 5 times daily recommended dosing regimen is inconvenient.

In children with immunosuppression due to haematologic malignancy, an increased risk of development of severe mucocutaneous HSV infection is apparent. When oral therapy is possible, aciclovir has been widely used in paediatric patients because of the commercial availability of a suspension. The limited and variable bioavailability of aciclovir, however, requires frequent dosing, and may not provide maximum therapeutic benefit since immunocompromised hosts require higher plasma levels of antiviral agents. Consequently, it is desirable to find new effective therapies with increased bioavailability for patients suffering from diseases related to HSV infection.

Penciclovir, a nucleoside analogue, possesses potent antiviral activity against HSV-1, HSV-2 and VZV. Famciclovir, the orally bioavailable prodrug of penciclovir, is available in Europe for the treatment of genital herpes and herpes zoster infections in immunocompetent and immunocompromised adult patients.

Famciclovir is a potentially interesting alternative to aciclovir therapy in paediatric patients because of the higher and more consistent bioavailability, the longer intracellular half-life of the active metabolite in infected cells, and the possibility of less frequent dosing than aciclovir. However, there is only limited information concerning the safety, efficacy and pharmacokinetics (PK) of penciclovir in children.

In one study in immunocompromised children due to bone marrow transplantation or chemotherapy, 9 children received i.v. penciclovir 5 mg/kg t.i.d. for 5 days. Of these, 5 patients were 2 to 6 years of age and 4 patients were 7 to 12 years of age. Only one of these patients, age 7, received oral famciclovir tablets at 10 mg/kg t.i.d. for 5 days. The PK data suggest that the terminal half-life (t<sub>1/2</sub>) of penciclovir was somewhat shorter in these patients than in adults (1.5 hours vs. 2.0-2.3 hours).

As part of a program to determine the safety and efficacy of famciclovir in patients with chronic hepatitis B, PK measurements were made in adults and children with hepatitis B.

Adults receiving 500 mg (average dose, 7.5 mg/kg) had C<sub>max</sub>, t<sub>1/2</sub> and AUC<sub>0-∞</sub> values of penciclovir of 3.9 µg/ml, 2.2 h, and 12 µg.h/ml, respectively, similar to that observed in patients with HSV or varicella zoster virus (VZV) infections. Five children aged 10 to 11 years weighing more than 33 kg received famciclovir tablets at a dose of 500 mg (average dose 12.5 mg/kg) and had C<sub>max</sub>, t<sub>1/2</sub> and AUC<sub>0-∞</sub> values of 5.6 µg/ml, 1.5 h, and 12 µg.h/ml, respectively. Nine children aged 6 to 10 years weighing less than 33 kg received a 250 mg dose (average dose, 10.3 mg/kg) and had C<sub>max</sub>, t<sub>1/2</sub> and AUC<sub>0-∞</sub> values of 5.0 µg/ml, 1.4 h, and 8.9 µg.h/ml, respectively.

Due to the potential utility of famciclovir in paediatric populations, Novartis Technical Research and Development (TRD) developed a new paediatric formulation, i.e. 'sprinkle' gelatine hard capsules containing granules of the tablet formulation. The composition of this paediatric formulation is same as that of the tablet formulation, except for the film-coating of the tablet. The bioavailability characteristics of sprinkle granulate are expected to be similar to that of the marketed tablet. The contents (granules) of the capsules are to be sprinkled in a food vehicle such as OraSweet® for easy consumption.

The PK, safety and tolerability of famciclovir in the sprinkle-capsule formulation have been evaluated in paediatric patients in three studies. These studies were designed and discussed with the FDA.

Two protocols were developed to facilitate recruitment of the two disease populations. Study CFAM810B2303 in patients with HSV infection, and CFAM810B2304 in patients with VZV infection, both conducted in paediatric patients 1 to 12 years of age, divided into three cohorts:

- Cohort 1: 1 to <2 years of age

- Cohort 2: 2 to <6 years of age
- Cohort 3: 6 to 12 years of age.

The protocols consist of a two-step design. Part A is a single-dose PK study in the respective age cohorts to validate that the chosen dose will produce blood levels and exposures which have been shown to be safe and effective in adults. Part B is designed to obtain safety data using the dosing scheme developed from results of Part A.

Detailed PK modelling and simulation methods were used to develop an initial dosing scheme for the paediatric formulation of famciclovir. The outcome of the initial work was a linear dosing algorithm of 12.5 mg/kg for children up to 40 kg, and 500 mg doses for children  $\geq 40$  kg.

This dosing algorithm was used in Part A of studies CFAM810B2303 and CFAM810B2304.

**Table 1: Model-based predictions of oral clearance and AUC of penciclovir by age, body weight and dose**

Age (years)	Body weight (kg)	Apparent clearance <sup>1</sup> (L/h)	Dose of famciclovir (mg)	Molecular weight adjustment	Adjusted dose <sup>2</sup> (mg)	AUC <sub>0-∞</sub> <sup>3</sup> (µg/mL·h)
2	12	16.2	150	0.7884	118	7.3
6	20	22.5	250	0.7884	197	8.8
12	40	34.8	500	0.7884	394	11.3
14	50	40.1	500	0.7884	394	9.8
16	60	44.8	500	0.7884	394	8.8
18	70	49.1	500	0.7884	394	8.0
35	70	42.3	500	0.7884	394	9.3
55	70	34.2	500	0.7884	394	11.5

<sup>1</sup>The population pharmacokinetic model estimated oral clearance (CL/F, L/h) as a function of age (AGE, years) and body weight (WT, kg) as follows:  $CL/F = 27.7 \cdot (140 - AGE) / 105 \cdot (WT/70)^{0.7} / 0.655$  (Appendix 3: Implementation of a population pharmacokinetic model of penciclovir after administration of Famvir for study design optimization and dosage recommendations in children and infants, 25 November 2002)

<sup>2</sup>Equivalent dose in terms of penciclovir (=dose of famciclovir • 0.7884, where 0.7884 is the ratio of the molecular weight of penciclovir (253.3 g/mol) to famciclovir (321.3 g/mol)

<sup>3</sup> AUC<sub>0-∞</sub> = adjusted dose / apparent clearance

The third study (CFAM810B3201) investigated the PK and safety of a single, body-weight adjusted dose of famciclovir in infants 1 month to < 1 year of age with active, suspected or latent herpes simplex infection. Also, in this study patients were divided into three age cohorts.

## 2. Clinical studies

According to the MAH these clinical studies were designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/83/EC and US Code of Federal Regulations Part 21), and with the ethical principles laid down in the Declaration of Helsinki.

**Title of study:** A multicenter, open-label, single-arm, two-step study to evaluate the safety and single dose pharmacokinetics of famciclovir and multiple-dose safety after administration of famciclovir oral pediatric formulation to children 1 to 12 years of age with herpes simplex infection (CFAM810B2303).

**Study centers:** Part A: USA (6 centers)

Part B: USA (8 centers), Panama (2 centers)

**Study period:** First patient enrolled: 05-Feb-2005  
Last patient completed: 07-Dec-2007

**Title of study:** A multicenter, open-label, single-arm, two-step study to evaluate the safety and single dose pharmacokinetics of famciclovir and multiple-dose safety after administration of famciclovir oral pediatric formulation to children 1 to 12 years of age with varicella zoster infection (CFAM810B2304).

**Study centers:** Part A: 2 centers (1 in Panama, 1 in Costa Rica)  
Part B: 4 centers (2 in Panama, 1 in Costa Rica, 1 in Guatemala)

**Study period:** First patient enrolled: 14-Jul-2005  
Last patient completed: 30-Jul-2007

Since these two studies were very similar in their design, the main features are described only once.

**Objectives:**

Part A:

Primary: The primary objectives were to evaluate the safety and tolerability, and pharmacokinetics (PK) of a single dose of famciclovir oral paediatric formulation in children from 1 to 12 years of age with herpes simplex virus (HSV) infection (study -03)/varicella zoster infection (study -04), in order to define the dose in this age group which gives a similar exposure to a 500 mg dose in adults.

Secondary: The secondary objective was to assess patient acceptability of the paediatric formulation.

Part B:

Primary: The primary objective was to evaluate the safety and tolerability of multiple doses of famciclovir paediatric formulation administered twice-daily for 7 days in patients from 1 to 12 years of age who had HSV infection/varicella zoster infection.

Secondary: The secondary objective was to assess acceptability of the paediatric formulation by the patients.

An exploratory analysis was performed to assess overall response to treatment in each patient.

The study was completed as planned.

**Assessor's comment:**

*Investigation of the PK also in part B after changing the dosing regimen/strategy, e.g. by means of population PK analyses, could have been reassuring.*

**Methodology:**

This was an open-label, single-/ multiple-dose, single-arm study with a two-step design (Part A and Part B). A screening period of 1 to 3 days was used to assess patients' eligibility.

Patients were stratified by age (1 to <2 years, 2 to <6 years, 6 to 12 years).

Two adolescent patients were enrolled in Part A of study -03 (13 to 18 years) under amendment 2 of the protocol (in compliance with the FDA Pediatric Written Request (PWR) issued 08-Aug-2006). These patients were dosed based upon the derived optimized dose established for Part B with a maximum single dose of 500 mg. Amendment 3 excluded further enrolment of adolescent patients in compliance with the final PWR (19-Apr-2007).

In Part A each patient received a single dose of famciclovir, and safety and pharmacokinetics were assessed.

In Part B multiple-dose safety and tolerability was evaluated for famciclovir given b.i.d. for 7 days. Part B started only after the PK data from Part A had been reviewed with the FDA, and the FDA concurred with the proposed dosing scheme for Part B. Part A patients may have been included in Part B.

The current study was originally designed to meet the requirements specified in the FDA's PWR issued in December 2003.

**Number of patients:**

Part A: It was planned to recruit 26 patients in 3 cohorts: 6 (1 to <2 years), 12 (2 to <6 years) and 8 (6 to 12 years).

Part B: It was planned to recruit approximately 50 patients (enrolment of patients to be evenly distributed across the age groups).

Study -03: The number of patients who entered Part A were 4 (1 to <2 years), 13 (2 to <6 years) and 8 (6 to 12 years). Prior to Amendment 3, two adolescent patients were enrolled in Part A of this study (13 to 18 years). All patients were included in the safety population and PK analysis.

A total of 47 patients entered Part B: 13 (1 to <2 years), 16 (2 to <6 years) and 18 (6 to 12 years). All patients were included in the safety population.

Study -04: The number of patients who entered Part A were 6 (1 to <2 years), 11 (2 to <6 years) and 9 (6 to 12 years). Prior to Amendment 3, two adolescent patients were enrolled in Part A of this study (13 to 18 years). All patients were included in the safety population and PK analysis.

A total of 53 patients entered Part B: 18 (1 to <2 years), 19 (2 to <6 years) and 16 (6 to 12 years). All patients were included in the safety population.

### **Indication and main criteria for inclusion:**

The study population consisted of patients with active HSV/VZV infection from 1 to 12 years of age, with clinical evidence or who were suspected of having an infection with HSV or who had laboratory evidence of HSV/VZV infection, and who were expected to survive more than 4 weeks.

For Part A only, the protocol recommended that patients on oral, i.v. or topical antiviral therapy should ideally have had a washout period of minimum 12 hours prior to study medication administration, and those who required episodic antiviral treatment should be treated prior to enrollment.

For Part B, concomitant therapy with oral or i.v. antivirals was at the discretion of the investigator, depending on the patient's underlying condition. Key exclusion criteria were inability to swallow (i.e. unconscious/coma due to encephalitis, history of any condition (e.g. malabsorption, gastrointestinal surgery, radiation therapy) that could affect drug absorption, distribution, metabolism or excretion, significant hepatic or renal abnormalities, AST or ALT >3x ULN, total bilirubin >2x ULN, serum creatinine >ULN, absolute WBC count <4,000 /mm<sup>3</sup>, platelets count <50,000 /mm<sup>3</sup>, haemoglobin <7 g/dl and a significant blood volume loss (>3% of calculated blood volume) in the previous 30 days. In Part B, patients with a body weight <9 kg were excluded.

For study -03 also patients with extensive gingivostomatitis were excluded (only if drinking was impaired).

### **Investigational drug:**

Famciclovir sprinkle capsules, 25 mg and 100 mg, using OraSweet® syrup vehicle.

Patients in Part A received famciclovir single-doses of approximately 12.5 mg/kg with a maximum dose of 500 mg. Patients weighing ≥ 40 kg received a famciclovir dose of 500 mg.

Patients in Part B were given famciclovir sprinkle capsules in OraSweet® twice-daily, approximately 12 hours apart (b.i.d.) for 7 days. The maximum single-dose was 500 mg for patients weighing ≥40 kg. Patients with a body weight <40 kg were assigned to one of the weight categories described in the protocol.

The daily doses ranged in 8-step increments from 150 mg b.i.d. to 500 mg b.i.d., depending on the patient's body weight. Batch and formulation numbers for study medication are presented below:

<b>Product name</b>	<b>Batch number</b>	<b>Formulation number</b>
Bottles for Part A:		
Famciclovir 25 mg capsules	AEUS/2004-0138	6001532.001
Famciclovir 100 mg capsules	AEUS/2004-0116	6001492.001
Blister Card for Part B:		
Famciclovir 25 mg capsules	AEUS/2005-0288	6001532.003
Famciclovir 100 mg capsules	AEUS/2005-0289	6001492.002

**Reference therapy:**

No reference therapy was used in this study.

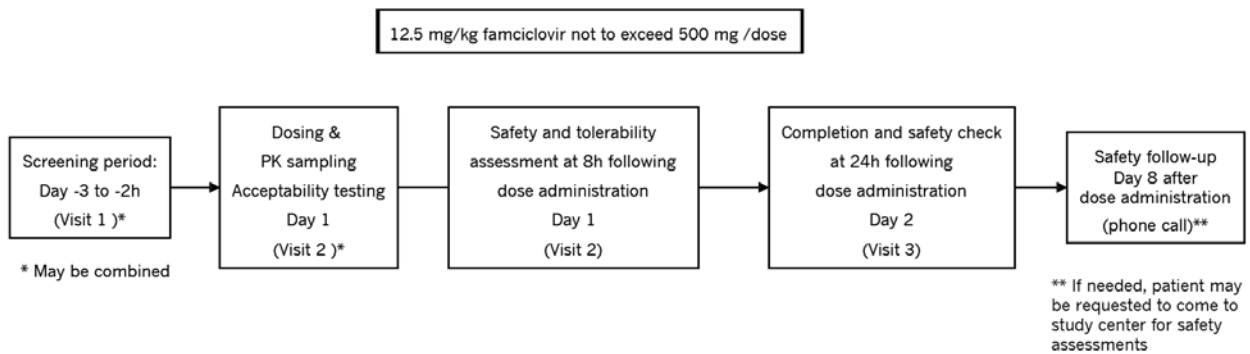
**Duration of treatment:**

In Part A, patients received a single dose of famciclovir. They were followed up for 24 hours after dosing, with a follow-up telephone call 7 days after dosing.

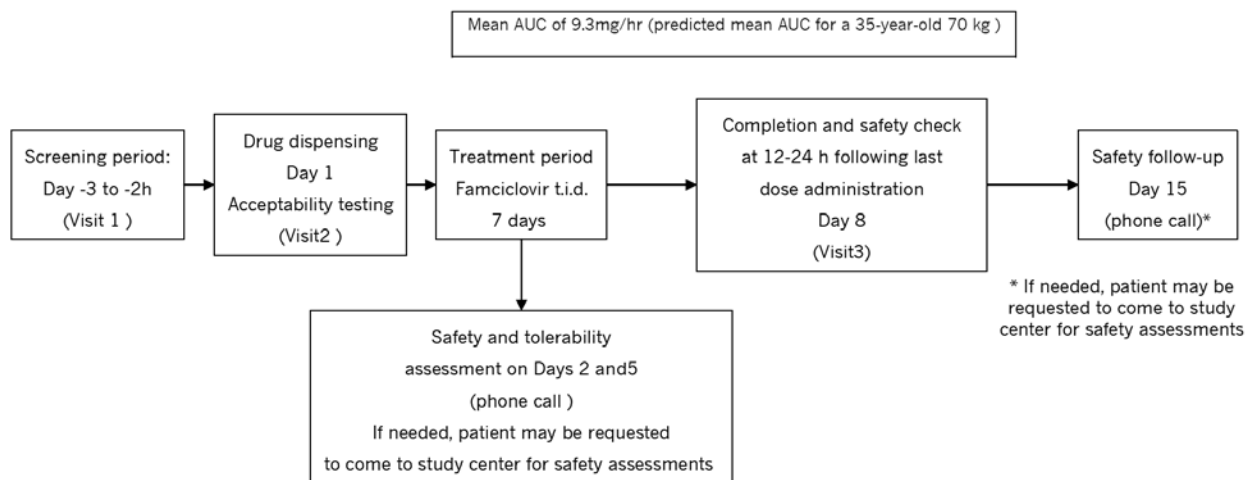
In Part B, patients received famciclovir for 7 days.

**Figure 1: Study outline**

**PART A**



**PART B**



**Criteria for evaluation**

**Efficacy (exploratory):** No efficacy assessments were carried out for Part A. For Part B the overall response to treatment was assessed for exploratory purposes.

**Safety:** Safety assessments consisted of monitoring and recording of all adverse events (AEs), serious adverse events (SAEs), pregnancy test results, physical examination and vital signs, and laboratory evaluations (haematology and clinical chemistry).

**Acceptability of the study medication:** A modified, 5-point facial hedonic scale, for the taste in the mouth was used. Depending on the patient's age either patients (when > 5 years of age) or caregivers/legal

guardians were asked to complete an assessment of study medication. This questionnaire was filled post dose 1 in the clinic, post dose 1 at home and at the end of study (day 8) or early termination.

**Pharmacokinetics:** Plasma samples were collected (from 1 ml blood) pre-dose and at 1, 2, 3, 4, and 5 hours after dosing. Penciclovir and 6-deoxy penciclovir (BRL42359, precursor of penciclovir) plasma concentrations were determined by liquid chromatography/tandem mass spectrometry. The limit of quantification was 0.15 µg/ml for both compounds. Plasma concentration-time data were used to calculate the following pharmacokinetic parameters of penciclovir: C<sub>max</sub> (maximum concentration), t<sub>max</sub> (time to C<sub>max</sub>), AUC<sub>0-tlast</sub> (area under the plasma concentration time curve from 0 up to the last quantifiable concentration), AUC<sub>0-∞</sub> (AUC up to infinity), t<sub>1/2</sub> (apparent terminal elimination half-life) and Cl/F (apparent oral clearance).

In accordance with the study protocol, pharmacokinetic parameters were only determined for penciclovir. Calculations were performed in WinNonlin using noncompartmental methods.

### Statistical methods

Descriptive summaries of clinical data as well as pharmacokinetic data were generated. No inferential analyses were performed.

For part A, the planned number of approximately 26 patients in cohorts 1 to 3 and a sample size of 6 to 12 patients per cohort (depending on age group) for the PK profiles was based on common practices for PK studies in paediatric patients. Furthermore, simulations based on the initial population PK model which were presented to the FDA, predict that a sample size of 26 patients would allow apparent clearance of penciclovir to be predicted with a precision of approximately 20%.

For part B, in case no AE of a certain type was observed in 50 patients, one could exclude an incidence of more than 6% for this event (based on the 95% confidence interval for the rate).

### Populations:

PK population: Patients were considered for PK evaluation if they had evaluable penciclovir concentration data with no protocol deviations affecting the PK results.

The safety population consisted of all patients that received any dose (including partial dose) of study drug and had at least one post-baseline safety or acceptability assessment. The statement that a patient had no AEs constitutes a safety assessment.

The intent-to-treat (ITT) population included all patients enrolled into the study. There was no requirement on the minimum amount of study drug intake for inclusion into the ITT population.

The modified intent-to-treat (mITT) population included all ITT patients who had at least one dose of study drug intake, and whose VZV infection was confirmed by PCR, immunofluorescence of specimens, or viral culture.

For Part A the analysis was carried out for the PK and the safety populations.

For Part B the analysis was carried out for the safety, ITT and mITT populations.

## Results

### Study CFAM810B 2303

#### **Patient disposition and baseline characteristics:**

All patients completed Part A of this study with no premature discontinuations and provided evaluable penciclovir concentration data. Therefore the safety and PK populations are identical.

**Table 2: Patient disposition by age group (Safety population, Part B)**

Disposition Reason	1 to <2 years N=13 n (%)	2 to <6 years N=16 n (%)	6 to ≤12 years N=18 n (%)	Total N=47 n (%)
Completed	13 (100.0)	16 (100.0)	17 (94.4)	46 (97.9)
Discontinued				
Protocol deviation	0 (0.0)	0 (0.0)	1 (5.6%)	1 (2.1)

Protocol variations were mostly minor and were not regarded as impacting the pk and safety analyses. With respect to the mITT-population for the efficacy analysis two patients were excluded due to missing clinical and laboratory evidence of HSV infection.

**Table 3: Analysis populations by age group (All patients, Part B)**

	1 to <2 years N=13 n (%)	2 to <6 years N=16 n (%)	6 to ≤12 years N=18 n (%)	Total N=47 n (%)
Included in safety population	13 (100.0)	16 (100.0)	18 (100.0)	47 (100.0)
Immunocompetent	12 (92.3)	16 (100.0)	16 (88.9)	44 (93.6)
Immunodeficient	1 (7.7)	0 (0.0)	1 (5.6)	2 (4.3)
Receiving concomitant anti-herpes therapy	1 (7.7)	1 (6.3)	1 (5.6)	3 (6.4)
Not receiving concomitant anti-herpes therapy	12 (92.3)	15 (93.8)	16 (88.9)	43 (91.5)
Included in the intent-to-treat population	13 (100.0)	16 (100.0)	18 (100.0)	47 (100.0)
Included in the modified intent-to-treat population	13 (100.0)	15 (93.8)	17 (94.4)	45 (95.7)

**Part A:** Sixty-three percent of the patients were female, participants' mean age was 6 years and the mean weight was 26.9kg. Most patients were Black (48.1) or Caucasian (40.7%).

**Part B:** Fifty-one percent of the patients were female, participants' mean age was 5 years and the mean weight was 21.7 kg. Most patients were Caucasian (44.7%) or of "Other" racial origin (29.8%). 44.7% had active disease, which was mild in 21.3% and moderate in 23.4% (none had severe disease). Overall, patients took 97.7% of the doses.

**Efficacy (exploratory; in Part B only):** Two patients took aciclovir during this study phase. Twenty-one patients had active disease at baseline. At the end of the study, symptoms were resolved in the majority of patients with active disease at baseline, 10 (90.9%) in the 1 to <2 years age group, 4 (80.0%) in the 2 to <6 years age group, and 5 (100.0%) in the 6 to 12 years age group. For the 2 patients (1 in the 1 to <2 years age group and 1 in the 2 to <6 years age group) where symptoms did not resolve, the disease did not progress to dissemination. The severity of the disease that was still present in these 2 patients was mild (unchanged from baseline). Disease related complications were reported for one patient (0509/01002) in the 1 to <2 years age group. This patient also had disease related complications at baseline.

**Assessor's comment:**

*The MAH should clarify, whether "the end of the study" means end of therapy (as summarized in the conclusions) or the last study visit.*

**Safety:** In Part A of the study there were no deaths, SAEs, or discontinuations for safety reasons. A total of 5 patients (18.5%) had AEs in Part A: 2 (15.4%) in the 2 to <6 years age group, 1 (12.5%) in the 6 to 12 years age group and 2 (100.0%) in the 13 to 18 years age group. No meaningful abnormalities were observed in vital signs.

In Part B of the study, there were no deaths, SAEs, or discontinuations due to AEs. The most frequent AEs overall were vomiting (5 patients [10.6%]), diarrhoea and headache (each occurring in 4 patients [8.5%]). All headache AEs occurred in the 6 to 12 years age group. AEs suspected to be study medication related occurred in ≤2 patients for any given preferred term and age group and were nausea, flatulence, vomiting, clumsiness, and pruritus. There were no strong trends by age group, although shifts in absolute counts for the some white blood cell types generally occurred in the youngest age group. Shifts from normal at baseline were noted for haemoglobin (5/40 patients shifting from normal to low), WBC (4/39 patients shifting from normal to high) and platelets (7/34 patients shifting from normal to high). The few patients who entered the study with values outside the normal range generally shifted to normal or remained unchanged at the end of the study.

There were neither consistent changes in renal markers, such as BUN and creatinine, nor in hepatic markers, such as AST, ALT, bilirubin, total protein and albumin constituting a signal of concern for any patient. Changes from baseline in renal and hepatic markers were small. There were no meaningful changes from baseline in vital signs.

**Assessor's comment:**

*Overall, the safety profile appears reassuring. Nevertheless, vomiting reported in more than 10% of the patients may be a concern in clinical practice when considering medication adherence. The safety profile of famciclovir in children should be put into perspective with data from a comparable adult population (with respect to disease characteristics).*

**Table 4: Number (%) of patients with AEs by preferred term (Safety population, Part B)**

	1 to <2 years N=13 n (%)	2 to <6 years N=16 n (%)	6 to ≤12 years N=18 n (%)	Total N=47 n (%)
Patients with AEs	6 (46.2)	8 (50.0)	12 (66.7)	26 (55.3)
Preferred term				
Vomiting	2 (15.4)	1 (6.3)	2 (11.1)	5 (10.6)
Diarrhea	1 (7.7)	1 (6.3)	2 (11.1)	4 (8.5)
Headache	0 (0.0)	0 (0.0)	4 (22.2)	4 (8.5)
Nausea	1 (7.7)	0 (0.0)	2 (11.1)	3 (6.4)
Cough	1 (7.7)	1 (6.3)	1 (5.6)	3 (6.4)
Abdominal pain upper	0 (0.0)	1 (6.3)	1 (5.6)	2 (4.3)
Pyrexia	2 (15.4)	0 (0.0)	0 (0.0)	2 (4.3)
Flatulence	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)
Gingival bleeding	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.1)
Chest pain	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.1)
Irritability	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.1)
Vessel puncture site hematoma	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)
Conjunctivitis viral	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.1)
Gastroenteritis	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.1)
Otitis media	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.1)
Arthropod bite	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.1)
Contusion	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.1)
Skin laceration	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)
Blood uric acid increased	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.1)
Hypokalaemia	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.1)
Clumsiness	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.1)
Psychomotor hyperactivity	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)
Somnolence	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.1)
Dysphonia	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)
Nasal congestion	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.1)
Pharyngolaryngeal pain	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)
Rhinorrhoea	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)
Blister	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.1)
Dry skin	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.1)
Pruritus	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.1)
Flushing	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)
Haematoma	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.1)

**Acceptability of the study medication:**

In **Part A**, overall the study medication was considered to be well or very well accepted by 51.8% of respondents, with 22.2% considering the medication as neither good nor bad. One respondent (3.7%) regarded the medication as unacceptable and 22.2% of respondents categorized the medication as 'badly but accepted'.

In **Part B**, better responses were obtained 2 to 5 minutes after swallowing study medication compared to those immediately after swallowing. Overall, the majority of respondents categorized the study medication as at least neither good nor bad: 53.2% at Day 1 post-first dose in the clinic, 61.6% at Day 1 post-first dose at home and 63.7% at Day 8 post-last dose at home.

### Pharmacokinetics:

Pharmacokinetic samples were available from 4 patients in the 1 to <2 years age group, 13 patients in the 2 to <6 years age group, 8 patients in the 6 to 12 years age group, and 2 patients in the 13 to 18 years age group. The following table presents a summary of PK parameters for penciclovir by age and shows historical data for adult healthy volunteers given a single dose of 500 mg famciclovir:

**Table 5: Penciclovir PK parameters by age group**

Parameter	Study B2303 Pediatric age group				Study A2401
	Cohort 1 1 to <2 years N=4	Cohort 2 2 to <6 years N=13	Cohort 3 6 to ≤12 years N=8	Cohort 4 13 to ≤18 years N=2	Healthy Adults N=24
$t_{max}$ (h)					
Median (Range)	1.21 (1.00 - 1.50)	1.07 (1.00 - 4.03)	1.00 (1.00 - 2.07)	1.47 (0.97 - 1.97)	0.75 (0.5 - 1.50)
$C_{max}$ (µg/mL)					
Mean ± SD (Range)	2.84 ± 1.25 (1.42 - 4.47)	2.44 ± 0.94 (0.42 - 3.81)	2.82 ± 0.65 (1.52 - 3.79)	1.89 <sup>a</sup> (1.06 - 2.72)	3.45 ± 0.82 (1.88 - 5.82)
$AUC_{0-t_{last}}$ ((µg/mL)·h)					
Mean ± SD (Range)	5.73 ± 2.34 (3.02 - 8.45)	5.71 ± 1.75 (1.63 - 8.17)	6.98 ± 1.14 (4.72 - 8.66)	4.81 <sup>a</sup> (3.57 - 6.06)	8.54 ± 1.70 (5.80 - 11.40)
$AUC_{0-∞}$ ((µg/mL)·h)					
Mean ± SD (Range)	6.17 ± 2.42 (3.43 - 8.99)	6.85 ± 1.55 <sup>b</sup> (3.19 - 9.12) <sup>b</sup>	8.15 ± 1.01 (6.49 - 9.71)	5.93 <sup>a</sup> (4.84 - 7.01)	8.94 ± 1.69 (6.31 - 11.84)
$t_{1/2}$ (h)					
Mean ± SD (Range)	1.09 ± 0.08 (1.01 - 1.18)	1.36 ± 0.20 <sup>b</sup> (1.10 - 1.70) <sup>b</sup>	1.60 ± 0.25 (1.30 - 2.11)	1.86 <sup>a</sup> (1.60 - 2.12)	1.89 ± 0.28 (1.27 - 2.39)
CL/F (L/h)					
Mean ± SD (Range)	20.8 ± 8.5 (11.0 - 28.8)	25.1 ± 4.3 <sup>b</sup> (18.1 - 33.3) <sup>b</sup>	43.7 ± 9.6 (32.4 - 60.8)	68.8 <sup>a</sup> (56.2 - 81.5)	45.7 ± 9.0 (33.3 - 62.5)
Body weight adjusted dose (mg/kg) <sup>c</sup>					
Mean ± SD (Range)	12.7 ± 0.4 (12.3 - 13.3)	12.8 ± 1.7 (7.3 - 13.7)	11.7 ± 1.7 (8.1 - 12.9)	6.6 <sup>a</sup> (6.2 - 7.1)	6.7 ± 0.8 (5.8 - 8.7)

<sup>a</sup> SD not reported since N=2; <sup>b</sup> N=12; <sup>c</sup> Body weight adjusted dose was calculated using the baseline body weights

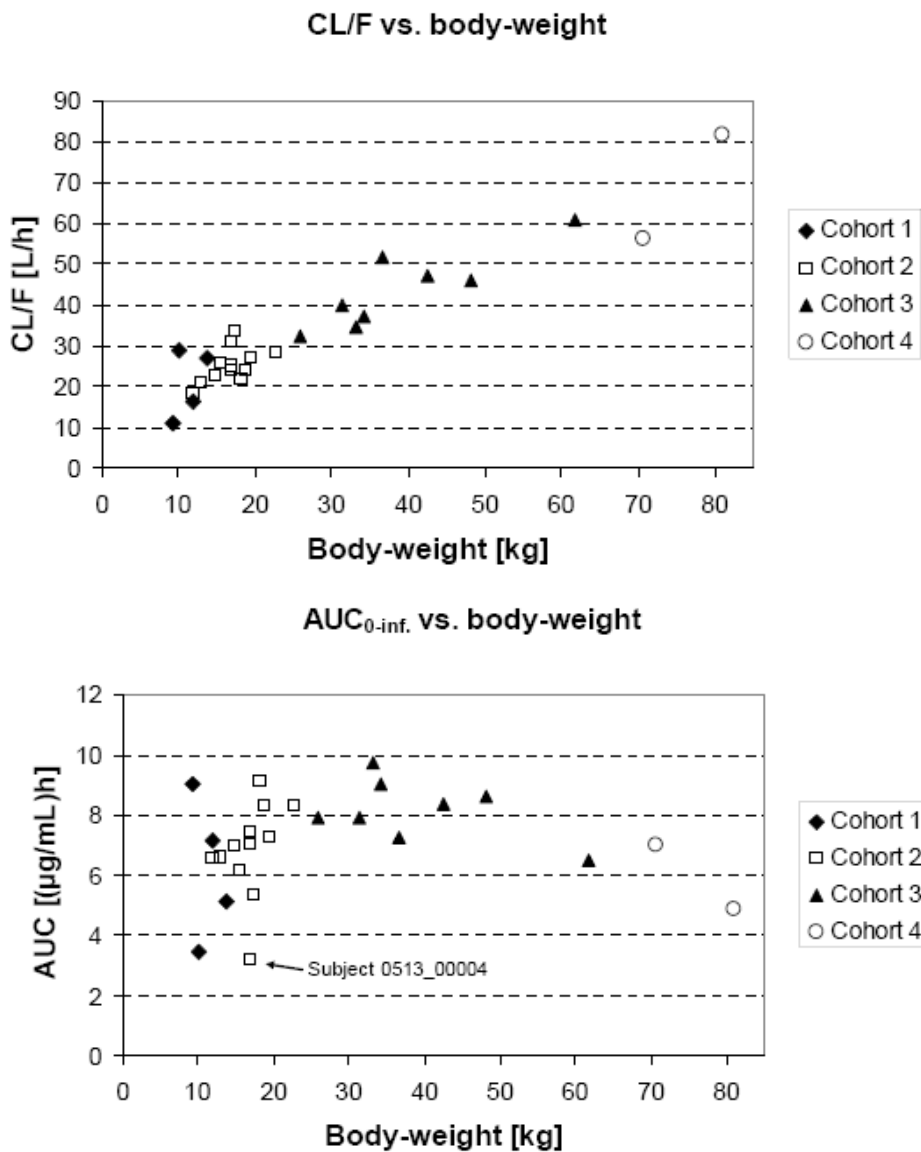
The paediatric dose (in mg/kg) was about 2-fold higher than the adult dose. With these doses, the mean exposure metrics  $C_{max}$ ,  $AUC_{0-t_{last}}$  and  $AUC_{0-∞}$  of penciclovir in the age groups up to 12 years were

similar or slightly below those observed in adults. Since only two patients were recruited in the 13 to 18 years age group, the comparison of means for this cohort with those for younger children and adults is not conclusive. However, the individual C<sub>max</sub> and AUC values in the two patients in the 13 to 18 years age group were in the ranges of values observed in the younger children. Clearance increased with body weight, confirming that dose adjustment dependent on body weight is necessary to achieve a similar systemic exposure to penciclovir in children of different body weight ranges (figure 1). For part B, the dosing was adjusted to body weight. (figure 3)

**Assessor's comment:**

The MAH should give a scientific rationale for not including adolescents (in this and also in study -04).

**Figure 2: Relationship between CL/F and AUC<sub>0-∞</sub> of penciclovir and body weight**



**Figure 3: The 8-step dosing scheme for Part B**

Bodyweight (kg)	Dose (mg)
9 to ≤11	150
>11 to ≤14	200
>14 to ≤19	250
>19 to ≤24	300
>24 to ≤29	350
>29 to ≤34	400
>34 to ≤39	450
≥40	500

### Conclusions

- This study fulfills the FDA request for development of a paediatric-appropriate formulation of famciclovir, and characterization of the pharmacokinetics and safety of this formation in patients 1 to 12 years of age with HSV infection.
- Following administration of famciclovir oral paediatric formulation to patients 1 to 12 years of age with HSV infection, using a linear dosing scheme up to 40 kg body weight (12.5 mg/kg), the average systemic exposure to penciclovir was similar (6 to 12 years) or slightly lower (1 to <6 years) than that in adults receiving a safe and effective 500 mg dose of famciclovir.
- Pharmacokinetic analyses and modeling, with the agreement of the FDA, addressed the underexposure in patients with a lower body weight and simplified the dosing scheme to 8 steps. This weight-based dosing scheme was used in Part B of the study.
- Single-dose and multiple-doses (b.i.d. for 7 days) of famciclovir oral paediatric formulation were well-tolerated in paediatric patients 1 to 12 years of age with HSV infection.
- There were no unexpected or new safety findings, with no safety signals indicative of clinically important toxicity of any major organ system.
- Overall, famciclovir oral paediatric formulation was considered acceptable. The formulation is therefore suitable for use in a paediatric population.
- Following treatment with famciclovir oral paediatric formulation, disease symptoms were resolved in the majority of patients by the end of the 7-day treatment period.

### Results

#### Study CFAM810B 2304

#### **Patient disposition and baseline characteristics:**

All patients completed Part A of this study with no premature discontinuations and provided evaluable penciclovir concentration data. Therefore the safety and PK populations are identical.

**Table 6: Patient disposition by age group (Safety population, Part B)**

Disposition Reason	1 to <2 years	2 to <6 years	6 to ≤12 years	Total
	N=18 n (%)	N=19 n (%)	N=16 n (%)	N=53 n (%)
Completed	16 (88.9)	18 (94.7)	14 (87.5)	48 (90.6)
Discontinued	2 (11.1)	1 (5.3)	2 (12.5)	5 (9.4)
Adverse event(s)	0 (0.0)	0 (0.0)	2 (12.5)	2 (3.8)
Abnormal laboratory value(s)	1 (5.6)	1 (5.3)	0 (0.0)	2 (3.8)
Lost to follow-up	1 (5.6)	0 (0.0)	0 (0.0)	1 (1.9)

Protocol variations were mostly minor and were not regarded as impacting the pk, safety or efficacy analyses. None of the deviations caused a patient to be excluded from any analysis population.

**Table 7: Analysis populations by age group (All patients, Part B)**

	1 to <2 years N=18 n (%)	2 to <6 years N=19 n (%)	6 to ≤12 years N=16 n (%)	Total N=53 n (%)
Included in safety population	18 (100.0)	19 (100.0)	16 (100.0)	53 (100.0)
Immunocompetent	17 (94.4)	19 (100.0)	16 (100.0)	52 (98.1)
Immune deficient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Receiving concomitant anti-herpes therapy	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Not receiving concomitant anti-herpes therapy	17 (94.4)	19 (100.0)	15 (93.8)	51 (96.2)
Included in the intent-to-treat population	18 (100.0)	19 (100.0)	16 (100.0)	53 (100.0)
Included in the modified intent-to-treat population	6 (33.3)	0 (0.0)	1 (6.3)	7 (13.2)

**Part A:** Forty-two percent of the patients were female, participants' mean age was 4.8 years and the mean weight was 19.5 kg. Most patients were of "Other" racial origin (73.1%) or Caucasian (15.4%).

**Part B:** Forty-nine percent of the patients were female, participants' mean age was 4.2 years and the mean weight was 19.1 kg. Most patients were Caucasian (60.4%) or of "Other" racial origin (39.6%). All patients had active disease, which was moderate in the majority of cases (62.3%) and mild or severe in 18.9%. Overall, patients took 94.1% of the doses.

**Efficacy (exploratory; in Part B only):** One patient took aciclovir during this phase of the study. All patients had active disease at baseline. At the end of the study, symptoms were resolved in the majority of patients, 15 (83.3%) in the 1 to <2 years age group, 18 (94.7%) in the 2 to <6 years age group and 16 (100.0%) in the 6 to 12 years age group. For the 3 patients in the age groups 1 to <2 years and 2 to <6 years where the symptoms did not resolve, the disease did not progress to dissemination. The severity of the disease that was still present in these patients was mild (2 patients) to moderate (one patient). Disease status was improved compared to disease status at enrollment for 51 (96.2%) patients overall (including all patients in the 2 to <6 years and 6 to 12 years age groups). Disease status was similar to baseline in one patient in the 1 to <2 years age group. No patients had a worsening of disease status at the end of the study. One patient in the 2 to <6 years age group was reported to have had disease related complications at the end of the study. The investigator commented that the patient had impetigo on the face that was treated with amoxicillin. This patient did not have disease related complications at baseline

**Assessor's comment:**

*The MAH should clarify, whether "the end of the study" means end of therapy (as summarized in the conclusions) or the last study visit.*

**Safety:** In **Part A** of the study there were no adverse events reported after single-dose drug administration. No meaningful abnormalities were observed in vital signs.

In **Part B** of the study there were no deaths or SAEs. Two patients discontinued study medication due to AEs. Both events leading to discontinuation were abdominal pain of moderate severity. The most common AEs were diarrhoea (in 6 patients, 11.3%), vomiting (in 5 patients, 9.4%) and pyrexia (in 4 patients, 7.5%).

All vomiting AEs were reported for the 1 to <2 years age group. Those related to study medication lasted one day only and were mild in severity. The most frequent AEs suspected by the investigators to be related to study medication were diarrhoea and vomiting. There were no unexpected changes in haematology or clinical chemistry parameters. There were no meaningful changes from baseline in vital signs.

The most frequent AEs overall suspected to be study medication related were diarrhoea (5 patients) and vomiting (4 patients).

One case of eosinophilia was reported and it was suspected by the investigator to be related to study medication. It was reported as mild and began on Day 8 and was ongoing. No further action was taken. The patient had a medical history of bronchial hyper-reactivity (not active), lymphadenopathy (active) and diarrhoea (not active).

Two patients, both in the 6 to 12 years age group, discontinued study medication due to AEs in Part B of the study, in both cases for moderate abdominal pain that had lasted for 4 days and was suspected by the investigator to be related to study medication.

Few haematological parameters showed notable numbers of patients shifting from normal to either high or low values. Greatest numbers of patients shifting from normal at baseline were noted for platelets (17/34 patients shifting from normal to high) and absolute lymphocyte counts (5/44 patients shifting from normal to high). Absolute neutrophil counts shifted from normal to low in 1/42 patients. The few patients who came into the study with abnormal values generally shifted to normal or remained unchanged at the end of the study.

No patient shifted from normal or abnormal baseline values to  $\geq$  Grade 2 toxicity for any parameter.

There were neither consistent changes in renal markers, such as BUN and creatinine, nor in hepatic markers, such as AST, ALT, bilirubin, total protein and albumin constituting a signal of concern for any patient. Changes from baseline in renal and hepatic markers were small.

There were no meaningful changes from baseline in vital signs.

**Table 8: Number (%) of patients with AEs by preferred term (Safety population, Part B)**

	1 to <2 years N=18 n (%)	2 to <6 years N=19 n (%)	6 to ≤12 years N=16 n (%)	Total N=53 n (%)
Patients with AEs	7 (38.9)	10 (52.6)	7 (43.8)	24 (45.3)
Preferred term				
Diarrhea	2 (11.1)	1 (5.3)	3 (18.8)	6 (11.3)
Vomiting	5 (27.8)	0 (0.0)	0 (0.0)	5 (9.4)
Pyrexia	2 (11.1)	1 (5.3)	1 (6.3)	4 (7.5)
Abdominal pain	0 (0.0)	0 (0.0)	2 (12.5)	2 (3.8)
Nausea	0 (0.0)	1 (5.3)	1 (6.3)	2 (3.8)
Cellulitis	0 (0.0)	1 (5.3)	1 (6.3)	2 (3.8)
Headache	0 (0.0)	0 (0.0)	2 (12.5)	2 (3.8)
Pruritus	1 (5.6)	0 (0.0)	1 (6.3)	2 (3.8)
Eosinophilia	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Lymphadenitis	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Abdominal pain upper	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Constipation	1 (5.6)	0 (0.0)	0 (0.0)	1 (1.9)
Gastritis	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Bronchitis	1 (5.6)	0 (0.0)	0 (0.0)	1 (1.9)
Impetigo	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Influenza	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Lice infestation	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Pharyngitis	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Skin infection	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Staphylococcal skin infection	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Varicella	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Anorexia	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Groin pain	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Pain in extremity	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Radiculitis	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Somnolence	0 (0.0)	1 (5.3)	1 (6.3)	1 (1.9)
Cystitis haemorrhagic	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)
Asthma	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Bronchospasm	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.9)
Rash	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.9)

**Assessor's comment:**

*Overall, the safety profile appears reassuring (see table below). Nevertheless, vomiting reported in almost 10% of the patients may be a concern in clinical practice when considering medication adherence. The safety profile of famciclovir in children should be put into perspective with data from a comparable adult population (with respect to disease characteristics).*

**Acceptability of the study medication:**

In **Part A**, overall the study medication was considered to be well or very well accepted by 76.9% of respondents, with 11.5% considering the medication as neither good nor bad, and another 11.5% of the respondents considering it as 'badly but accepted'. No respondents regarded the medication as unacceptable.

In **Part B**, better responses were obtained 2 to 5 minutes after swallowing study medication compared to those immediately after swallowing. Overall, the majority of respondents categorized the study medication as at least neither good nor bad or liked the medication (88%).

By the final evaluation, 26/53 (49.1%) respondents described it as sweet, while 14/53 (26.4%) described it as bitter, and 12/53 (22.6%) described it as 'other'.

### Pharmacokinetics:

Pharmacokinetic samples were available from 6 patients in the 1 to <2 years age group, 11 patients in the 2 to <6 years age group, and 9 patients in the 6 to 12 years age group. The following table presents a summary of PK parameters for penciclovir by age and shows historical data for adult healthy volunteers given a single dose of 500 mg famciclovir.

**Table 9: Penciclovir PK parameters by age group**

Parameter	Study B2304			Study A2107	Study A2401
	Pediatric age group			Adults	Adults
	1 to <2 years N=6	2 to <6 years N=11	6 to ≤12 years N=9	Herpes zoster N=7	Healthy N=24
$t_{max}$ (h)					
Median	1.08	1.07	1.00	1.00	0.75
Range	(1.00 - 1.42)	(0.93 - 3.03)	(1.00 - 1.17)	(1.00 - 2.00)	(0.5 - 1.50)
$C_{max}$ (µg/mL)					
Mean ± SD	3.21 ± 1.02	3.17 ± 0.78	3.95 ± 0.90	3.19 ± 0.88	3.45 ± 0.82
(Range)	(2.27 - 5.08)	(1.79 - 4.86)	(2.80 - 5.41)	(2.24 - 4.92)	(1.88 - 5.82)
$AUC_{0-t_{last}}$ ((µg/mL) h)					
Mean ± SD	7.05 ± 2.48	7.01 ± 1.77	8.88 ± 1.51	8.95 ± 2.03	8.54 ± 1.70
(Range)	(5.24 - 11.97)	(5.53 - 11.85)	(6.66 - 11.41)	(6.50 - 12.27)	(5.80 - 11.40)
$AUC_{0-∞}$ ((µg/mL) h)					
Mean ± SD	7.82 ± 2.97	7.81 ± 2.33*	10.38 ± 1.81	10.88 ± 2.18	8.94 ± 1.69
(Range)	(5.63 - 13.74)	(5.83 - 13.20)*	(7.69 - 13.65)	(7.18 - 13.42)	(6.31 - 11.84)
$t_{1/2}$ (h)					
Mean ± SD	1.27 ± 0.17	1.16 ± 0.17*	1.65 ± 0.28	2.34 ± 0.81	1.89 ± 0.28
(Range)	(1.08 - 1.53)	(0.83 - 1.38)*	(1.16 - 1.99)	(1.57 - 3.59)	(1.27 - 2.39)
CL/F (L/h)					
Mean ± SD	13.9 ± 4.3	23.7 ± 4.4*	26.8 ± 6.2	37.8 ± 8.9	45.7 ± 9.0
(Range)	(5.7 - 17.5)	(17.0 - 31.0)*	(16.6 - 37.2)	(29.4 - 54.9)	(33.3 - 62.5)
<b>Body weight adjusted dose (mg/kg)<sup>a</sup></b>					
Mean ± SD	13.2 ± 0.9	12.9 ± 0.5	12.6 ± 0.5	6.9 ± 1.3	6.7 ± 0.8
(Range)	(12.0 - 14.3)	(12.2 - 13.7)	(12.0 - 13.2)	(5.6 - 8.8)	(5.8 - 8.7)

\* N=8

<sup>a</sup> Body weight adjusted doses were calculated using the baseline body weights (summarized in [Table 7-4](#))

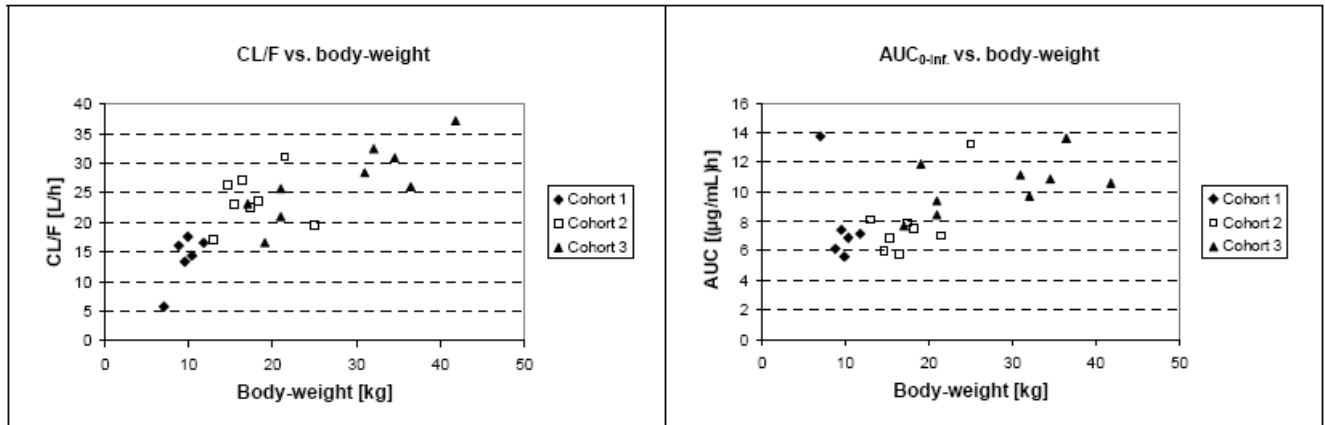
The paediatric dose (in mg/kg) was about 2-fold higher than the adult dose. With these doses, the mean exposure metrics  $C_{max}$ ,  $AUC_{0-t_{last}}$  and  $AUC_{0-∞}$  of penciclovir in the age groups up to 12 years were similar or slightly below those observed in adults.

Clearance increased with body weight, confirming that dose adjustment dependent on body weight is necessary to achieve a similar systemic exposure to penciclovir in children of different body weight ranges (figure 4)

However, with the linear dosing algorithm of 12.5 mg/kg used in Part A of the study, exposure in terms of  $AUC_{0-∞}$  appeared to be generally lower in the smaller children compared to the larger children as shown in the right side of figure 3.

Therefore a dosing regimen according to weight bands was applied for part B. (figure 5).

**Figure 4: Relationship between CL/F and AUC<sub>0-∞</sub> of penciclovir and body weight**



Cohort 1: 1 to < 2 years; Cohort 2: 2 to < 6 years; Cohort 3: 6 to ≤12 years

**Figure 5: The 8-step dosing scheme for Part B**

Bodyweight (kg)	Dose (mg)
9 to ≤11	150
>11 to ≤14	200
>14 to ≤19	250
>19 to ≤24	300
>24 to ≤29	350
>29 to ≤34	400
>34 to ≤39	450
≥40	500

### Conclusions

- This study fulfills the FDA request for development of a paediatric-appropriate formulation of famciclovir, and characterization of the pharmacokinetics and safety of this formation in patients 1 to 12 years of age with VZV infection.
- The pharmacokinetic profiles of penciclovir following administration of famciclovir oral paediatric formulation to patients 1 to 12 years of age with VZV infection are similar to those in adults receiving a safe and effective 500 mg of famciclovir. Exposure using the linear dosing scheme specified in Part A was decreased in the youngest patients (with the lowest body weights).
- Pharmacokinetic analyses and modelling, with the agreement of the FDA, addressed the under-exposure in patients with a lower body weight and simplified the dosing scheme to 8 steps. This weight-based dosing scheme was used in Part B of the study.
- Single-dose and multiple-doses (t.i.d. over 7 days) of famciclovir oral paediatric formulation were well-tolerated in paediatric patients 1 to 12 years of age with VZV infection.
- There were no unexpected or new safety findings, with no safety signals indicative of clinically important toxicity of any major organ system.
- Overall patient acceptability of the famciclovir oral paediatric formulation was good. The formulation is therefore suitable for use in a paediatric population.
- Following treatment with famciclovir oral paediatric formulation, disease symptoms were resolved in the majority of patients by the end of the 7-day treatment period.

**Title of study:** A multicenter, open-label, single-arm study to evaluate the single-dose pharmacokinetics, acceptability and safety of famciclovir oral pediatric formulation in infants 1 month to <1 year of age with herpes simplex virus infection (CFAM810B2301).

**Study centers :** Germany (4 centers), Guatemala (1 center), United States (5 centers)

**Study period:** First patient enrolled on 25-Oct-2007;  
Last patient completed on 17-Nov-2008

### **Objectives**

The primary objective of the study was to evaluate the pharmacokinetics of a single dose of famciclovir in infants 1 month to <1 years of age who have herpes simplex infection.

The secondary objectives of the study were to:

- assess the safety of the single dose of famciclovir; and
- assess tolerability/acceptability of the paediatric formulation.

The study was completed as planned.

### **Methodology**

This study was stratified by age (1 to <3 months, 3 to <6 months, 6 to <12 months) and dosed by body weight according to a dosing algorithm.

### **Number of patients**

It was planned to include a total of 18 patients, approximately evenly distributed across the three cohorts studied. A total of 18 patients were enrolled in the study (8 in the 1 to <3 months age group, 5 in the 3 to <6 months age group, and 5 in the 6 to <12 months age group). All patients were included in the safety population.

### **Indication and main criteria for inclusion:**

Key inclusion criteria were male and female patients from 1 month to <1 year of age, regardless of their immune status, who had active, suspected or latent herpes simplex infection who were at risk of developing herpes simplex virus infection, and who were candidates for antiviral therapy.

Patients could be starting or currently using aciclovir. Patients on oral, i.v. or topical antiviral therapy (aciclovir, valaciclovir, ganciclovir) ideally should have had a wash-out period of =8 hours prior to study drug administration. The investigator carefully assessed the impact of discontinuing standard therapy before enrollment. If the investigator felt that discontinuation of current antiviral was not indicated, then the patient could be enrolled without a washout period. Patients who required episodic antiviral treatment (aciclovir or valaciclovir) should have been given their final dose =8 hours prior to dosing.

Patients had to have the expectation to survive more than 4 weeks and to demonstrate no abnormalities that would make the study medically hazardous to them.

Key exclusion criteria were patients with a gestational age <32 weeks, those unable to swallow, a history of malabsorption or previous gastrointestinal surgery, or history of radiation therapy that could effect drug absorption or metabolism, or any other disorder or history of a condition that could interfere with drug absorption, distribution, metabolism, or excretion, a clinically significant abnormality of the hepatic and renal systems, any of the following age-adjusted clinical or haematological laboratory and blood chemistry abnormalities: AST/SGO T or ALT/SGPT greater than 3x ULN, total bilirubin greater than 2x ULN, serum creatinine greater than 2x ULN, absolute WBC count less than 4000/mm<sup>3</sup>, platelet counts less than 50,000/mm<sup>3</sup>, hemoglobin less than 7.0 g/dl, a known hypersensitivity to famciclovir or penciclovir or drugs with similar chemical structures, concomitantly using probenecid.

## Investigational Product

Famciclovir sprinkle capsules of 25 mg and 100 mg, dosed as a suspension using OraSweet® as a vehicle. The individualized dose of famciclovir, based on the patient's body weight, was administered on Day 1. The measured body weight was rounded to the closest value as indicated in the following table. Patients were assigned to one of the weight categories and received the single doses given in (Table 11).

**Table 10: Dose for infants 1 month to <1 year of age based on body weight**

Body weight (kg) (range of weights included)	Dose (mg)
<5 (=4.5)	25
5 (4.6 - 5.4)	25
6 (5.5 - 6.4)	50
7 (6.5 - 7.4)	75
8 (7.5 - 8.4)	100
9 (8.5 - 9.4)	125
10 (9.5 - 10.4)	150
11 (10.5 - 11.4)	175
12-13 (11.5 - 13.4)	200

### Assessor's comment:

*The rationale for the dose recommendations has not been submitted and should be provided.*

## Duration of treatment

Patients received a single dose of famciclovir. Safety checks were performed at 8 hours and 24 hours following drug administration. Patient's caregivers were contacted by telephone on Day 8 and Day 38 to determine if any serious adverse events had occurred. Study completion was defined as Day 38.

## Acceptability/tolerability

Acceptability of the study medication was assessed by the patient's caregiver or the study personnel. The following questions were answered:

- How did your child accept the medication? (Caregiver)
- How did the infant accept the medication? (Study personnel)

Tolerability was assessed the study personnel 30 minutes after dosing by answering the following question:

- How did the infant tolerate the medication? (30 minutes after dosing, by study personnel)

## Pharmacokinetics

Plasma samples were collected (from 1 ml blood) at 0.5, 1, 4 and 6 hours after dosing. Penciclovir and 6-deoxypenciclovir (BRL42359, precursor of penciclovir) plasma concentrations were determined by liquid chromatography/tandem mass spectrometry. The limit of quantification was 0.15 µg/ml for both compounds. Plasma concentration-time data were used to calculate the following pharmacokinetic parameters of penciclovir: C<sub>max</sub> (maximum concentration), T<sub>max</sub> (time to C<sub>max</sub>), AUC<sub>0-tlast</sub> (area under the plasma concentration-time curve from 0 up to the last quantifiable concentration), and AUC<sub>0-6h</sub> (AUC up to 6 hours post dose). In accordance with the study protocol, pharmacokinetic parameters were only determined for penciclovir. Calculations were performed in WinNonlin using noncompartmental methods.

## Results

### Efficacy

Not applicable.

## Safety

There were no deaths during the study. One patient, a 4-month-old male, had 2 SAEs (dehydration and aggravated condition [worsening of constitution]) reported on Day 2, each event lasting 15 days. Neither SAE was suspected to be related to study medication. Four patients had AEs requiring concomitant medication, none of which were suspected to be related to study medication.

The most frequent AEs were vomiting (3 patients [16.7%]), diarrhoea (2 patients [11.1%]), pyrexia (2 patients [11.1%]), and dehydration (2 patients [11.1%]). Only one AE, vomiting in a 1 month old female, was suspected to be study medication related. There were no unexpected changes in haematology or clinical chemistry parameters. There were no meaningful changes from baseline in vital signs.

## Acceptability/tolerability

After the first dose intake, the majority of caregivers (66.6%) responded that the medication was ‘well accepted’ or ‘very well accepted’ by the patient. Three patients (16.7%) were considered by the caregiver to be neutral (neither good nor bad) regarding the acceptability of the medication. One caregiver responded that the medication was ‘badly but accepted’ by a patient in the 6 to 12 months age group and one caregiver responded that the medication was ‘very badly / unacceptable’ by a patient in the 1 to <3 months age 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, a 1-month-old female, was reported to have had significant emesis (vomiting) after the first dose intake.

## Pharmacokinetics

Pharmacokinetic samples were available from 7 patients in the 1 to <3 months age group, 5 patients in the 3 to <6 months age group, and 5 patients in the 6 to 12 months age group.

Concentrations of 6-deoxypenciclovir were lower than those of penciclovir and were below the limit of quantification at 4 hours after dosing in 16 out of the 17 patients. Table 11 presents a summary of pharmacokinetic parameters of penciclovir and the body weight adjusted dose for penciclovir by age group.

**Table 11: Penciclovir pharmacokinetic parameters by age group**

Parameter	Cohort 1 1 to <3 months N=7	Cohort 2 3 to <6 months N=5	Cohort 3 6 to 12 months N=5
$T_{max}$ (h)			
Median	1.00	4.00	1.02
(Range)	(1.00 - 5.17)	(1.00 - 4.17)	(0.58 - 1.10)
$C_{max}$ (µg/mL)			
Mean ± SD	0.69 ± 0.41	0.74 ± 0.17	3.24 ± 1.01
(Range)	(0.25 - 1.52)	(0.51 - 0.98)	(1.83 - 4.47)
$AUC_{0-t_{last}}$ ((µg/mL)•h)			
Mean ± SD	2.09 ± 1.38	3.16 ± 0.68	8.68 ± 2.09
(Range)	(0.28 - 4.30)	(2.36 - 4.12)	(5.42 - 11.15)
$AUC_{0-6h}$ ((µg/mL)•h)			
Mean ± SD	2.22 ± 1.23	3.16 ± 0.68	8.77 ± 2.14
(Range)	(0.71 - 4.30)	(2.36 - 4.12)	(5.42 - 11.15)
Body weight adjusted dose (mg/kg)			
Mean ± SD	6.6 ± 1.4	9.4 ± 2.1	13.5 ± 2.0
(Range)	(4.8 - 8.3)	(7.8 - 13.0)	(10.9 - 15.8)

Penciclovir concentrations in the 6 to 12 months age group were in the range observed previously in children 1 to <2 years of age. Patients in the 1 to <3 months and 3 to <6 months age groups had a lower exposure to penciclovir than patients in the 6 to 12 months age group.

### **Conclusion**

- This study characterizes the pharmacokinetics and safety of a paediatric-appropriate formulation of famciclovir in patients 1 to 12 months of age with HSV infection.
- With the famciclovir doses used in this study, systemic exposure to penciclovir in the infants below 6 months of age was on average 21% to 36% of that in the 6 to 12 months age group.
- Comparison with results from previous studies in children studies showed that penciclovir concentrations in the 6 to 12 months age group were in the range observed in children 1 to <2 years of age and were similar to those in adults following a 500 mg dose of famciclovir.
- A single dose of famciclovir oral paediatric formulation was well-tolerated in paediatric patients 1 to 12 months of age with active, suspected, or latent HSV infection.
- There were no unexpected or new safety findings, with no safety signals indicative of clinically important toxicity of any major organ system.
- Famciclovir oral paediatric formulation was considered acceptable and well-tolerated in the infant population studied.

### **Overall conclusion**

At this stage Novartis does not intend to apply for a marketing authorization of a paediatric indication in the EU. Therefore, no SPC changes are necessary based on the results of this infant study.

## **V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

### **➤ Overall conclusion**

The submitted data appear promising with respect to the development of a suitable paediatric dosage form and weight-based dosing regimen. Some data/analyses from the studies are missing and should be provided (see section VI). Most importantly, no reasoning for not applying for an extension of the indication to include children has been given. In light of the potential usefulness of famciclovir in the paediatric population, this should be presented.

Due to the currently missing information no final conclusion can be given, but the MAH's response to the RSI has to be awaited.

### **➤ Recommendation**

Due to the currently missing information no recommendation can be given, but the MAH's response to the RSI has to be awaited.

Based on the data submitted, the MAH should provide supplementary information as part of this worksharing procedure (see section VI "Request for Supplementary Information").

## VI. REQUEST FOR SUPPLEMENTARY INFORMATION

1. The MAH should provide a critical discussion on the usefulness of /medical need for famciclovir in children (expert statement). The pk/pd profile, up-to-date resistance data ([lack of], cross-resistance with aciclovir) as well as the current position of the MAH should be taken into consideration.
2. The MAH should clarify whether a bioequivalence study comparing the film-coated tablets and the sprinkle hard gelatine capsules has been conducted.
3. The MAH should clarify, whether the point in time: “the end of the study” used for the efficacy assessment in studies -03 and -04 means end of therapy or the last study visit.
4. Overall, the safety profile appears reassuring. However, it should be put into perspective with data from a comparable adult population (with respect to disease characteristics).
5. A scientific rationale for not including adolescents into studies -03 and -04 should be provided.
6. The rationale for the dose recommendations in children less than 1 year of age (study -01) should be provided. And the MAH could propose a more suitable dosing regimen for the very young (i.e. less than 6 months of age) based on the results of this study.

### **MAH's response to the Request for Supplementary information as submitted on January 20, 2010**

#### **Overview**

According to information presented in this response to the Request for Supplementary Information, Novartis considers that there is no scientific support for pursuing paediatric indications for Famvir. The decision not to seek paediatric registration is in line with Paragraph 2 of Article 46 of Regulation (EC) No 1901/2006, as amended.

The safety and pharmacokinetic (PK) profile of an experimental paediatric formulation (oral granules) of famciclovir (prodrug of penciclovir) were evaluated in three open-label studies in infants and children with either herpes simplex virus (HSV) or varicella zoster virus (VZV) infection (i.e. herpetic gingivostomatitis or varicella). These studies were successful in identifying a body weight-adjusted dosing scheme for paediatric patients between the ages of 6 months and 12 years that would provide a similar exposure to that in adults following a famciclovir dose of 500 mg. Additionally, the studies in children aged 1 to 12 years found that multiple-dose regimens, b.i.d. (HSV infection) or t.i.d. (VZV infection) for 7 days, were well tolerated. However, the efficacy data were insufficient to support the use of famciclovir in paediatric patients for the treatment of HSV infection or varicella. Clinical (efficacy) information gathered in the open-label paediatric trials is limited. Moreover, extrapolation of efficacy data from adult patients is not appropriate as the diseases in adults and children are different (i.e. there are no data in adult patients with diseases similar to those evaluated in the paediatric studies). For this reason, Famvir was not indicated for treating paediatric patients with HSV or VZV infection by the United States FDA who had requested the three completed paediatric studies.

In addition, Novartis does not intend to seek registration of the experimental paediatric famciclovir formulation for the following reasons:

- The paediatric population needing an antiherpes antiviral is small and may become smaller with the widespread introduction of varicella vaccination.

- The greatest medical need is in neonates and hospitalized immunocompromised paediatric patients where intravenous antiviral administration is required. (Note: there is no available intravenous formulation of penciclovir.)
- The current medical need is addressed by approved paediatric formulations of aciclovir (intravenous and oral).
- Resistance to aciclovir is rare and not increasing. Moreover, HSV or VZV resistant to aciclovir will likely be cross resistant to penciclovir.

**Request for supplementary information No. 1**

***The MAH should provide a critical discussion on the usefulness of /medical need for famciclovir in children (expert statement). The pk/pd profile, up-to-date resistance data ([lack of], cross-resistance with aciclovir) as well as the current position of the MAH should be taken into consideration.***

**Summary of MAH response:**

**Medical need for famciclovir in infants and children**

Disease caused by HSV-1 or HSV-2 infections and herpes zoster (shingles) are relatively uncommon or rare in infants and children and their clinical courses are typically mild when compared to adults. Varicella (chickenpox), which is also typically a mild and self-limiting disease during childhood, has markedly decreased in incidence in countries that adopted varicella vaccination as part of the routine immunization schedule. Manifestations, sequelae, and risk of morbidity or mortality are increased for neonates and immunocompromised children. To evaluate the medical need for famciclovir in infants and children, each infection will be discussed in terms of prevalence, clinical presentation and current management drawing from information provided by published literature.

**HSV infections in infants and children**

Serologic surveys have been one of the best means of studying the epidemiology of HSV infections. HSV-1 is more markedly widespread than HSV-2. HSV-1 is typically transmitted during childhood through infected saliva, whereas HSV-2 is usually sexually transmitted.

Worldwide, the seroprevalence of HSV-1 infection is generally >25% by age 6 years and increases with age to up to > 80%. Furthermore, seroprevalence rates vary by country and population.

Overall, HSV-2 prevalence in the paediatric population is low, with a seroprevalence ranging between 11% in 1 to 5 year-old children (Africa, Rashida tribe) to 0% in most of the other countries, for which respective studies are available.

Herpetic gingivostomatitis represents the most common clinical manifestation in children infected with HSV-1, reported to occur in up to 40% of children aged up to 6 years (*Auvin et al 2004*).

Gingivostomatitis is usually asymptomatic, with symptomatic outbreaks being mild and selflimited (*Bacon et al 2002*). The typical patient presents with painful lesions on the buccal and gingival mucosa and the tongue. The clinical manifestations last about 12 days, during which time eating and drinking may be impaired. The disease is responsible for 0.6% of all admissions to a paediatric hospital. Recurrence rarely occurs in immunocompetent patients.

HSV infection in neonates (congenital HSV infection) can be grave with significant morbidity and mortality. The incidence of neonatal herpes has been difficult to quantify, but a number of studies suggest that it is low. A wide variation exists in the published rates of infection in different geographic areas. For example, *Brown et al 2003* reported 31.2/100,000 incidence of neonatal herpes in a Seattle community (Seattle, WA, USA), a statistic that is widely used as the incidence of disease in the USA. In 1989 a national surveillance conducted by the Centers for Disease Control and Prevention found an incidence of 4/100,000 (*Stone et al 1989*). In the 5-year study period from 1999 to 2003, researchers at the University of Texas Southwestern Medical Center (Dallas, TX, USA) identified an incidence of 5.1/100,000 (95% CI: 1.4/100,000 – 13.1/100,000) (*Mahnert et al 2007*). Similar low rates of neonatal herpes (less than 5.1/100,000) are reported in other developed countries (*Mahnert et al 2007*).

Most cases of neonatal herpes result from infant exposure to HSV in the birth canal at delivery (*Kimberlin 2004*). Neonatal herpes can present in one of three forms: disseminated infection, encephalitis, or skin, eye and mouth disease. Complications are common and include cognitive impairment, severe neurological disease, organ dysfunction, and death. In the pre-antiviral era, 85% of patients with disseminated HSV disease and 50% of patients with central nervous system (CNS) disease died by the age of 1 year. With current antiviral therapy the 12-month mortality rate has been reduced to 29% for disseminated neonatal herpes and to 4% for CNS disease. Improvement of morbidity rates with antiviral therapy, while not as dramatic as with mortality, have been achieved. The proportion of survivors of disseminated disease who have normal neurological development has improved from 50% in the pre-antiviral era to 83% today. In contrast to disseminated or CNS disease, the rate of morbidity in patients having skin, eye or mouth disease has improved dramatically during the antiviral era.

Before antiviral therapy, 38% of patients experienced developmental difficulties at 12 months of age.

Today, fewer than 2% of aciclovir recipients show developmental difficulties.

Aciclovir is the best studied antiviral agent for HSV infections in infants and children (*Dwyer and Kesson 1997*). Intravenously administered aciclovir is the drug of choice for neonates with any form of HSV infection and for children with HSV encephalitis (*Dekker and Prober 2001*). Treatment of primary gingivostomatitis in paediatric patients using oral aciclovir at 600 mg/m<sup>2</sup>/dose administered four times a day for 10 days decreases the time to cessation of symptoms by 30% to 50% and the time to lesion healing by 20% to 25% (*Amir et al 1997*).

Immunocompromised children with moderate to severe HSV infections should be treated with intravenous aciclovir.

### **Varicella and herpes zoster in infants and children**

Serologic prevalence of VZV infection across Europe is greater than 90% in children aged 10 years and older (*Bonanni et al 2009, Guillén et al 2009*). Varicella, which is caused by VZV, used to be a highly common childhood disease. However, the incidence has decreased since countries have adopted varicella vaccination as part of the routine immunization schedule (*Centers for Disease Control and Prevention 2008*).

Since the vaccine was first approved in the USA, the majority of the published studies have been conducted there. The incidence varies depending on age, study population, and exposure to varicella vaccine. Compared to the non-vaccinated areas, where lifetime incidence of varicella may be close to 100% (*Guillén et al 2009*), the incidence in vaccinated areas reported in the literature is low, ranging from 0% to 2% (*Seward et al 2002, Centers for Disease Control and Prevention 2003, Jumaan et al 2005, Yih et al 2005*).

States with higher vaccination coverage implemented with childcare and/or school entry requirements had lower incidence (*Centers for Disease Control and Prevention 2003*).

Varicella is typically a mild and self-limiting disease. However, serious complications of varicella can develop in those with impaired immune response. In the EU the annual incidence of hospitalization for varicella ranged from 1.3 to 4.5/100,000 with an average duration of hospital stay ranging from 3 to 8 days (*Bonanni et al 2009*).

Herpes zoster is due to a reactivation of the VZV and is uncommon in childhood (*Smith and Glaser 1996*). Its incidence increases with age. In Europe the annual incidence is 0.3/1,000 in children <10 years of age and increases to an incidence of 10/1,000 in adults >80 years of age (*Volpi et al 2005*). Overall, before and after introduction of varicella vaccination, the incidence rate of herpes zoster has not changed.

These rates (which include USA, France, Corsica, and Iceland) are consistent worldwide. The observed incidence ranged from 0.07% in the age group 0 to 2 years (*Mullooly et al 2005*) to 0.23% in the age group 10 to 14 years (*Petursson et al 1998*).

The cases and anticipated growth of herpes zoster for several European countries and the USA is presented in table 12.

**Table 12: Cases of herpes zoster paediatric patients up to 14 years (Decision Resources)**

	2008	2018	2008 – 2018 Growth (%/10 years)
Europe Total	50,720	49,020	-3%
France	11,740	11,620	1%
Germany	12,400	11,400	-8%
Italy	8,630	8,020	-7%
Spain	6,710	7,180	7%
United Kingdom	11,240	10,800	-4%
USA	66,600	69,280	4%

Herpes zoster in healthy children is relatively mild, and prognosis for these children is excellent (*Smith and Glaser 1996*). Pain and pruritus can occur, but significant pain is uncommon. Postherpetic neuralgia, a common problem for elderly patients, is very rare in children. Systemic reactions such as fever, headache and regional lymphadenopathy are common in the paediatric age group. Although rare, complications may occur in immunocompromised children.

The value of aciclovir in the treatment of severe varicella and herpes zoster in immunocompromised children is well established. Its role in treating chickenpox in otherwise healthy children is debatable given the relatively mild self-limiting illness and the lack of effect if used after 24 hours of rash onset (*Dwyer and Kesson 1997, Dekker and Prober 2001*).

Otherwise healthy children who develop varicella should be considered for treatment with oral aciclovir if they have risk factors for developing severe infection. Herpes zoster is only occasionally encountered in healthy children. In these patients, treatment with oral aciclovir is indicated only for ophthalmic zoster or when pain is moderate or severe at the onset of rash (*Dekker and Prober 2001*). Herpes zoster should be treated with intravenous aciclovir when it occurs in immunocompromised patients. Completion of therapy with oral aciclovir may be reasonable if disease is limited and response to therapy is prompt.

### **Prevalence and antiviral use in the UK, France and Germany**

European databases were used to analyze disease prevalence and prescription of antiviral drugs in the UK, France and Germany by general practitioners in patients less than 18 years of age for a period of 5 years. For the UK, The Health Improvement Network database (THIN) was used. THIN is a UK general practice research database that collects anonymous patient data, including diagnoses and prescriptions issued by the general practitioner, from practices using the Vision practice management system. Currently, the THIN dataset contains data from 220 practices with a total of over 3.4 million patients. The Cegedim Longitudinal Patient Database (LPD) was used for data from France and Germany. Office-based active general practitioners upload anonymous and coded excerpts from medical files of patients who visit them. Complete computerized clinical records are gathered in the electronic medical records.

The LPD database includes 1,600,000 patient medical records from 1,200 physicians in France and 590,000 patient medical records from 550 physicians in Germany. The limitation of these databases is that they do not include information on hospitalized patients (i.e. antiviral prescription data summarized below do not include intravenous therapy).

Two different analyses were performed (utilization and incidence):

- Number of individuals with a diagnosis code for varicella, herpes zoster, herpes simplex, gingivostomatitis and congenital herpes in one year (annual prevalence).
- Number of individuals prescribed antiherpes antivirals during one year (annual prevalence).

Both analyses will be stratified by age group and calculated annually for 2 or 5 consecutive years.

### **Annual prevalence for HSV/VZV infection in general practice in the UK, France and Germany**

In the UK there were few cases of varicella in both adults and children. So, the estimates of annual prevalence were calculated per 100,000 persons. During the 5 years of study (2003-2007) the annual prevalence for varicella ranged from 0.09 to 0.30 per 1,000 population for varicella. The annual prevalence for herpes zoster was 3.65 to 3.91 per 1,000 population. As expected, it was observed more frequently in adults. The annual prevalence of herpes simplex was 2.28 to 2.37 per 1,000 population, and the annual prevalence of gingivostomatitis was 0.04 to 0.06 per 1,000 population. In 2007, out of 641,698 children and adolescents there were only 3 children with varicella. Concerning herpes zoster the annual prevalence was greater in adults, while herpes simplex was greater in the age group 12 to <18 years, and gingivostomatitis in the age group 1 to <12 years.

In France the overall annual prevalence for varicella decreased from 7.11 in 1,000 individuals in 2004 to 5.64 per 1,000 in 2008. The age group with the highest annual prevalence was 1 to <12 years of age. The annual prevalence for herpes zoster was higher in adults (up to 3.72 per 1,000 individuals) than in individuals <18 years of age (up to 1.96 per 1,000 individuals). The annual prevalence of herpes simplex was up to 8.52 per 1,000 individuals, and was greater in adults. The annual prevalence of gingivostomatitis was up to 0.23 per 1,000 individuals.

Due to pertinence of data available, it was only possible to estimate the annual prevalence of herpes virus infections during 2 years (2007-2008) in Germany. The annual prevalence for varicella in all ages decreased from 1.56 to 1.18 per 1,000 population. In the age group 1 to <12 years, where the prevalence is higher, it decreased from 20.18 to 14.41 per 1,000 individuals. In children and adolescents the age group of 12 to <18 years had the highest annual prevalence of herpes zoster (2.97 per 1,000 individuals). As expected, it was observed more frequently in adults (annual prevalence of 6.5 per 1,000 individuals). The annual prevalence of herpes simplex in 2008 was 7.24 per 1,000 individuals, with the highest prevalence in individuals 1 to <12 years of age. The annual prevalence of gingivostomatitis in 2008 was of 1.16 per 1,000 individuals, the highest prevalence was observed in the age group 1 to <12 years.

### **Analyses of prescriptions for antiviral drugs in general practice in the UK, France and Germany**

In the UK the annual prevalence of individuals prescribed antivirals per 1,000 population decreased from 1.26 in 2003 to 0.81 in 2007 for famciclovir; increased from 2.90 in 2003 to 4.77 in 2008 for aciclovir, and remained stable for valaciclovir (range 0.25 to 0.19). Most of the famciclovir prescriptions were for adults (e.g. in 2007 n=2,301 users). There were few prescriptions for ages 1 through <18 years (e.g. in 2007 n=60 users), and no individual <1 year of age was prescribed famciclovir.

In France during the 5 years (2004-2008) of analyses, the annual prevalence of individuals prescribed antiviral drugs per 1,000 population ranged from 0.01 to 0.03 for famciclovir, 13.38 to 11.78 for aciclovir, and 5.60 to 7.76 for valaciclovir. The prescriptions have remained stable in the last 5 years. Famciclovir was not prescribed in individuals <18 years.

In Germany during the 5 years (2004-2008) of analyses, the annual prevalence of individuals prescribed famciclovir per 1,000 population ranged from 0 to 0.02, for aciclovir from 4.94 to 6.27, and for valaciclovir from 0.05 to 0.06. The prescriptions have remained stable in the last 5 years. The only antiviral prescribed in individuals <18 years was aciclovir.

#### ***Assessor's comment:***

*The data from UK GPs on the prevalence of Herpes zoster and HSV are noteworthy, as HZ has been reported at a higher frequency than HSV. At first sight this is not plausible. Possible reasons might be that patients with HSV do not consult the GP, but either use OCT medications or consult the specialist (e.g. gynaecologist).*

*The low figures of famciclovir use in children in the past years are quite expected, as the agent is not approved for use in patients < 18 years of age.*

### **Pharmacokinetic / pharmacodynamic profile of famciclovir in infants and children**

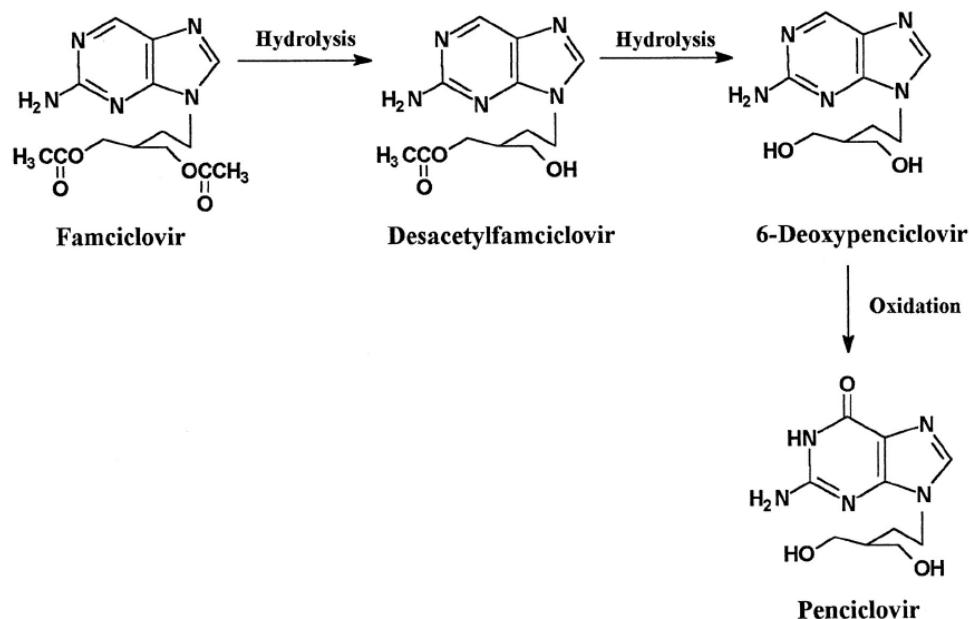
Recognizing that there can be dramatic differences in pharmacokinetics in paediatric patients of different ages, Novartis assessed the PK profile of famciclovir in infants and children defined by age cohorts and

compared the results to those in adults. The goal of this program was to define doses in infants and children that would provide a drug exposure equivalent to a 500 mg oral dose of famciclovir in adults.

### Overview of famciclovir pharmacokinetics from adult studies

The 500 mg dose of famciclovir administered either twice or three times daily is effective and recommended for treating adults with HSV or VZV infections, respectively (*Simpson and Lyseng-Williamson 2006*). Famciclovir undergoes substantial first-pass metabolism in the intestinal wall and the liver being rapidly deacetylated and oxidized to form the active metabolite penciclovir along with 6-deoxy penciclovir, the major inactive metabolite and precursor of penciclovir (Figure 06).

**Figure 06: Famciclovir major metabolic pathway in man**



Penciclovir reaches its maximum plasma concentration within 2 hour after administration.

The volume of distribution is 1.08–1.5 L/kg indicating extensive distribution into the tissues. Penciclovir and 6-deoxy penciclovir are poorly (<20%) bound to plasma proteins (*Crumpacker 1996*). The terminal elimination half-life of penciclovir is approximately 2 hours, and the primary route of elimination of penciclovir and 6-deoxy penciclovir is renal (*Crumpacker 1996*). The PK of penciclovir are linear and dose proportional, and intersubject variability was low (*Pue et al 1994*). Multiple-dose AUC values were similar to those after single doses indicating no accumulation of the drug after multiple doses.

Several PK characteristics of famciclovir are worthy of highlighting as they apply to paediatric considerations. Cytochrome P450 enzymes do not play a role in the metabolism of famciclovir, and protein binding plays a limited role in the disposition of famciclovir (*Simpson and Lyseng-Williamson 2006*). Therefore, the known changes in these categories during development should not influence famciclovir PK and impact the dosing regimen. However, deacetylation (by esterases) and oxidation (by aldehyde oxidase) is required in the transformation of the prodrug famciclovir to its active form penciclovir. There are reports that the activity of these enzymes is reduced in infants. (*Tayama et al 2007*) examined the developmental expression of aldehyde oxidase. Its activity rapidly increased after birth reaching maturity at 1 year of age. Additionally, elimination of penciclovir is dependent on renal clearance. Maturation of renal function (e.g. renal blood flow, glomerular filtration and tubular secretion) is a dynamic process that begins during fetal organogenesis and is complete by early childhood (*Kearns et al 2003*).

### Overview of the clinical development program

Novartis developed an experimental oral paediatric formulation for use in clinical trials consisting of sprinkle capsules (also referred to as oral granules).

The composition of this paediatric formulation is the same as that of the tablet formulation, except for the film-coating of the tablet. Capsules with 25 mg and 100 mg famciclovir were provided. The capsules were to be opened and the granules sprinkled on OraSweet® syrup vehicle before the mixture was ingested. This paediatric formulation was used in all three of the clinical studies described in the first assessment step of this procedure (see first part of this report). The bioavailability characteristics of sprinkle granulate were expected to be similar to that of the marketed tablet and, as evidenced below, provided drug exposures following weight-adjusted dosing in children very similar to that observed in adults following a 500 mg dose.

Prior to initiation of studies with the paediatric formulation in children 1 to 12 years of age, a population PK model for dosing was developed. The aim of the dosage algorithm was to ensure that the exposure to penciclovir in paediatric patients corresponded to the exposure “envelope” in adults following a single 500 mg dose while mitigating the risk that the smallest children would be over-dosed. The outcome of the PK simulation work was a linear dosing algorithm of 12.5 mg/kg for children up to 40 kg, and 500 mg doses for children  $\geq 40$  kg.

### Pharmacokinetics of famciclovir/penciclovir in paediatric patients, comparison to adults and derived dosing scheme for paediatric patients

In the three paediatric studies ([Study B2303], [Study B2304] and [Study B2301]) the PK of penciclovir have been evaluated in a total of 68 paediatric patients 1 month to 12 years of age with HSV or VZV infection following single-dose administration of an oral mixture of famciclovir (content of sprinkle capsules mixed with OraSweet®). In children 1 to 12 years of age, a linear dosing algorithm of 12.5 mg/kg up to a body weight (BW) of 39 kg and 500 mg at and above a BW of 40 kg was used. For infants below 1 year of age, the kidney maturation was taken into account, which resulted in proposed doses lower than 12.5 mg/kg for BW below 8 kg. All patients completed PK arm of these studies with no premature discontinuations and provided penciclovir concentration data. Protocol variations were mostly minor and were not regarded as impacting the PK analyses.

Famciclovir doses in mg/kg and PK parameters (non-compartmental data) of penciclovir are provided in Table 13 by age cohort. The historical data for adult healthy volunteers (age:  $34 \pm 7$  years) [Study A2401] given a single dose of 500 mg famciclovir (as 500 mg tablet) is also provided for comparison.

**Table 13: Penciclovir pharmacokinetic parameters (non-compartmental data) by age group**

Age cohort	Study in paediatric patients 1 to $\leq 12$ months of age			Studies in paediatric patients 1 to $\leq 12$ years of age			Healthy adults (N=24)
	1 to <3 months (N=7)	3 to <6 months (N=5)	6 to $\leq 12$ months (N=5)	1 to <2 years (N=10)	2 to <6 years (N=24)	6 to $\leq 12$ years (N=17)	
Dose (mg/kg)	6.6 ( $\pm 1.4$ )	9.4 ( $\pm 2.1$ )	13.5 ( $\pm 2.0$ )	13.0 ( $\pm 0.8$ )	12.8 ( $\pm 1.3$ )	12.2 ( $\pm 1.3$ )	6.7 ( $\pm 0.8$ )
$t_{max}$ (h)	1.00 (1.00-5.17)	4.00 (1.00-4.17)	1.02 (0.58-1.10)	1.08 (1.00-1.50)	1.07 (0.93-4.03)	1.00 (1.00-2.07)	0.75 (0.5 - 1.50)
$C_{max}$ ( $\mu\text{g/mL}$ )	0.69 ( $\pm 0.41$ )	0.74 ( $\pm 0.17$ )	3.24 ( $\pm 1.01$ )	3.06 ( $\pm 1.06$ )	2.78 ( $\pm 0.93$ )	3.41 ( $\pm 0.96$ )	3.45 ( $\pm 0.82$ )
AUC <sup>a</sup> ( $\mu\text{g}\cdot\text{h/mL}$ )	2.22 ( $\pm 1.23$ )	3.16 ( $\pm 0.68$ )	8.77 ( $\pm 2.14$ )	7.16 ( $\pm 2.75$ )	7.23 <sup>b</sup> ( $\pm 1.90$ )	9.33 ( $\pm 1.84$ )	8.94 ( $\pm 1.69$ )
$t_{1/2}$ (h)	NA	NA	NA	1.20 ( $\pm 0.16$ )	1.28 <sup>b</sup> ( $\pm 0.21$ )	1.62 ( $\pm 0.26$ )	1.89 ( $\pm 0.28$ )
CL/F (L/h)	NA	NA	NA	16.7 ( $\pm 6.8$ )	24.6 <sup>b</sup> ( $\pm 4.3$ )	34.7 ( $\pm 11.6$ )	45.7 ( $\pm 9.0$ )

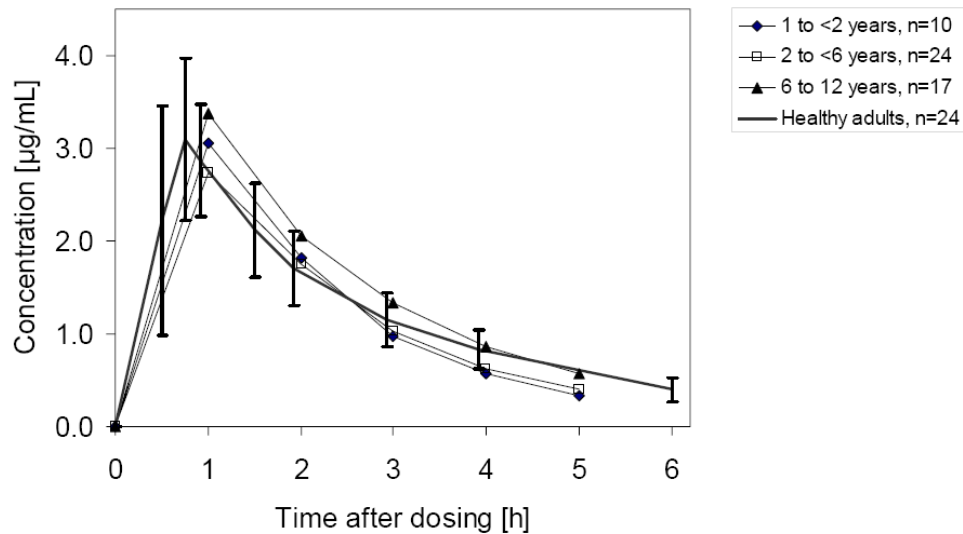
<sup>a</sup> Area under the plasma concentration-time profile, up to 6 hr post dose (i.e. AUC<sub>0-6h</sub>) for patients  $\leq 12$  months of age [Study B2301], and extrapolated to infinity (i.e. AUC<sub>0-inf</sub>) for patients between 1 and  $\leq 12$  years of age [Study B2303] [Study B2304] and healthy adult volunteers [Study A2401].

<sup>b</sup> N=20

Mean plasma concentration-time profiles of penciclovir in paediatric patients 1 to 12 years of age (pooled data of [Study B2303] and [Study B2304]) are shown in Figure 07 in comparison with historical data for adult healthy volunteers [Study A2401] given a single dose of 500 mg famciclovir. Generally, the plasma concentrations in the children age groups were in the range observed in adults.

There was, however, a trend toward a slightly faster elimination of penciclovir in children. Apparent clearance of penciclovir increased by BW to the 0.7 power, from a mean of 16.7 L/h in the 1 to <2 years age group to 34.7 L/h in the 6 to 12 years age group. Overall, exposure to penciclovir in children compared to adults was similar (6 to 12 years age group) or slightly lower (1 to <2 years and 2 to <6 years age groups).

**Figure 07: Penciclovir mean plasma concentrations in children with HSV or VZV infection compared with healthy adult volunteers**

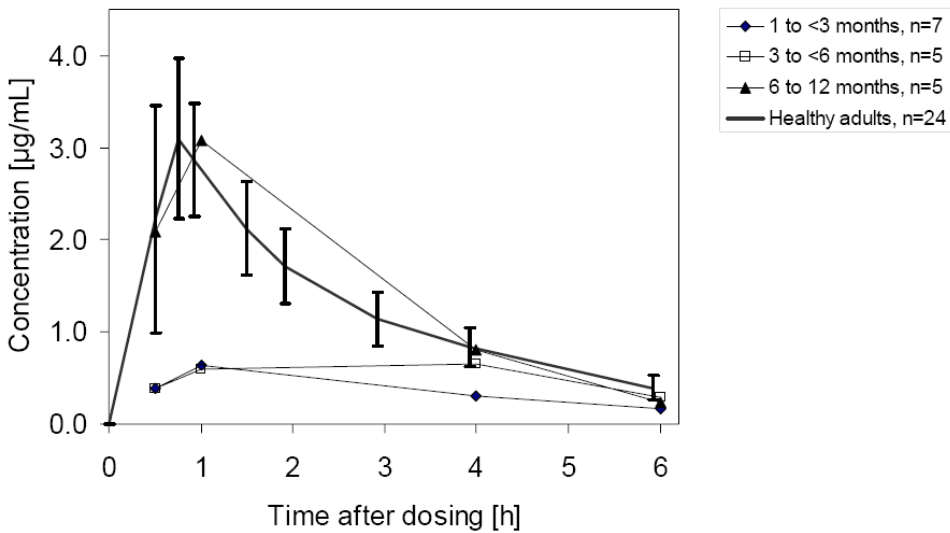


Means are shown for children, means and SD for adults. In case of identical sampling times, the adult data were shifted by 5 min.

Pharmacokinetic modeling addressed the slight underexposure in patients with lower BW and simplified the dosing scheme to eight 50 mg steps (between 150 and 500 mg). This 8-step dosing scheme was then used in the multiple-dose safety parts of [Study B2303] and [Study B2304]. Integrated PK and safety results of these two studies have recently been published (*Sáez-Llorens et al 2009*).

Figure 08 shows the mean concentration-time profiles of penciclovir in infants 1 to 12 months of age with HSV infection ([Study B2301]), again in comparison with the historical data for adult healthy volunteers [Study A2401]. Plasma concentrations of penciclovir in the 6 to 12 months age group were similar to those in adults following a 500 mg dose of famciclovir and in the range observed in children 1 to <2 years of age. However, with the doses used in this study, systemic exposure to penciclovir ( $C_{max}$ ,  $AUC_{0-6h}$ ) in the infants below 6 months was at most 36% of that in the 6 to 12 months age group.

**Figure 08: Penciclovir mean plasma concentrations in infants with HSV infection compared with healthy adult volunteers**



Means are shown for infants, means and SD for adults. In case of identical sampling times, the adult data were shifted by 5 min.

In the above studies the 6-deoxy penciclovir, an intermediate metabolite in the aldehyde oxidase catalyzed conversion of famciclovir to penciclovir, had been measured in plasma in addition to penciclovir. In all paediatric patients, the concentrations of 6-deoxy penciclovir were considerably lower than those of penciclovir and generally fell below the limit of quantitation within 2 to 4 hours after dosing, similar to findings in adult subjects (*Pue et al 1994*).

The data from [Study B2303], [Study B2304] and [Study B2301] were used to update the previous population PK model in children and to derive a final dosing scheme of famciclovir in the paediatric population [Modeling Report 2009]. Population PK modeling confirmed that BW is the most important covariate in the PK of penciclovir in the paediatric population. The final population PK model gave the following equation for the population typical apparent clearance of penciclovir in terms of the famciclovir dose:

$$CL/F [L/h] = 29.6 \cdot (BW/20)^{0.75} \text{ (equation 1)}$$

Based on the CL/F vs. BW relationship, an 8-step dosing scheme was developed for paediatric patients between 6 months and 12 years of age, aiming to achieve an exposure to penciclovir as seen in adults after a single 500 mg dose of famciclovir. Starting from equation 1 and substituting CL/F by famciclovir dose/penciclovir AUC, the theoretical famciclovir dose to match the adult penciclovir AUC (8.94 µg•h/mL, see table 13) is given by:

$$\text{Famciclovir dose (mg)} = 29.6 \cdot (BW/20)^{0.75} \cdot 8.94 \text{ (equation 2)}$$

These theoretical doses are listed in table 14 for the lower and upper BW limits of the proposed dosing scheme, together with the proposed doses. The proposed dose is at the lower limit of the theoretical dose range for the lowest BW cohort (6 to 8 kg) and near the middle of the theoretical range of doses for all other BW cohorts. The “conservative” dose for the 6 to 8 kg cohort was selected based on safety considerations.

**Table 14: Theoretical doses of famciclovir to achieve the target exposure in paediatric patients and proposed dose for patients aged 6 months to 12 years**

Body-weight (kg)	Theoretical dose (mg) <sup>a</sup>	Proposed dose (mg)
6 to 8	100 – 139	100
9 to 11	139 – 175	150
12 to 15	175 – 219	200
16 to 20	219 – 270	250
21 to 26	270 – 327	300
27 to 33	327 – 390	350
34 to 40	390 – 449	425
≥41	≥449	500

<sup>a</sup> Theoretical dose =  $29.6 \cdot (BW/20)^{0.75} \cdot AUC_{0-inf}$ , where  $AUC_{0-inf}$  defines the target exposure seen in adults after a single 500 mg dose of famciclovir ( $AUC_{0-inf} = 8.94 \mu\text{g}\cdot\text{h/mL}$ ). The lower (upper) body weight limit used in the computation of the theoretical dose range is -0.5 kg (+0.5 kg) from the integer weight limit.

As discussed below in the response to supplementary information 6, infants below 6 months of age are predicted to require 2- to 3-times higher doses than actually given in Study B2301 to achieve the target exposure seen in adults after a 500 mg dose. The safety of such doses has not been established in infants less than 6 months of age. Thus, no dose recommendations can be made for infants below the age of 6 months.

**An overview of famciclovir efficacy in children with HSV infection or varicella is provided in the first part of this AR.**

In conclusion

- The efficacy analyses undertaken in [Study B2303] and [Study B2304] were exploratory in nature (the patient populations were small and the studies were uncontrolled) and are not intended to form the basis of any efficacy claims.
- In patients with HSV infection (mucocutaneous disease, predominantly mouth lesions) and those with VZV infection (chickenpox), treatment with famciclovir was followed by improvement in disease status and resolution of symptoms in over 90% of patients. No paediatric patients with Herpes Zoster were assessed in [Study B2304].

**Resistance and cross-resistance**

**Overview (historical use, studies examining resistance)**

Novartis appreciates the concern over the development of antiviral resistance as generally there is a heightened concern for the emergence of resistance with increased use of an anti-infective agent. Aciclovir entered clinical use in the early 1980's, with penciclovir, famciclovir and valaciclovir (prodrug of aciclovir) becoming available thereafter. Over the three decades of use, many millions of patients have been successfully treated with these antiviral nucleoside analogues for HSV and VZV infections. A number of studies have addressed HSV resistance to antiviral nucleoside analogues. In particular, (*Griffiths 2009*) recently provided a perspective on this particular topic, reviewing the mechanism, prevalence and clinical management of resistance to aciclovir and penciclovir. (*Bacon et al 2003*) extensively and systematically reviewed this topic – mechanism, critique of assays for assessing resistance, prevalence of resistance in immunocompetent / immunocompromised patients (including infants) – and provided a review of mathematical models assessing future emergence of a resistant viral strain. Two publications have addressed the prevalence of resistance to either penciclovir/famciclovir as seen in clinical trials (*Sarisky et al 2003*) or aciclovir in patients with genital herpes (*Reyes et al 2003*).

A brief review of the findings from these review articles will be provided that includes the consensus opinions:

- The mechanism of action is similar for aciclovir and penciclovir.
- The spectrum of therapeutic activity and profile of resistance is similar – resistance to one agent is highly likely to be present for the second.
- The prevalence of resistance has not changed since the introduction of these antivirals.
- Resistance is unlikely to emerge in a chronically treated patient.

### **Mechanisms of Resistance**

Aciclovir and penciclovir have a similar mechanism of antiviral action against herpes viruses. Both compounds are selectively phosphorylated only within virus-infected cells expressing viral thymidine kinase. Further phosphorylation by cellular enzymes leads to the production of aciclovir or penciclovir triphosphate, both of which compete with the natural nucleotide, GTP, resulting in the selective inhibition of viral DNA polymerase. Incorporation of the analogue triphosphate into the growing DNA chain prevents continued extension of the DNA chain. *In vitro* penciclovir is more efficiently phosphorylated by viral thymidine kinase than aciclovir, and penciclovir triphosphate is also more stable than aciclovir triphosphate, resulting in prolonged intracellular half-lives in MRC-5 cells infected with HSV-1, HSV-2 or VZV (half-life [hours]: 10, 20 and 9, respectively, vs.  $\leq 1$  for these three viruses) (Bacon 1996). Aciclovir triphosphate has a greater affinity for viral DNA polymerase than penciclovir triphosphate and is an obligate DNA chain terminator. It is unclear if these *in vitro* differences impact the clinical pharmacodynamic outcomes for these two antiviral nucleosides.

Mutations with viral thymidine kinase gene or DNA polymerase gene have been implicated in mechanisms of resistance to aciclovir and penciclovir (Bacon *et al* 2003). Approximately 96% of aciclovir-resistant HSV isolates are thymidine kinase deficient. Mutants with altered DNA polymerase have also been identified, although these are infrequently reported (Morfin and Thouvenot 2003). HSV has a low inherent propensity to develop mutations within its genome because its polymerase has a proof reading mechanism (Griffiths 2009). Many replication cycles are therefore required statistically in order to generate a virus that has resistance to aciclovir/penciclovir and the potency of these drugs in inhibiting replication decreases the chance that this may occur in practice.

### **Clinical prevalence of resistant strains**

The emergence of resistant strains to antiviral nucleoside analogues has been monitored during clinical programs as well as in epidemiological post-marketing studies. The clinical programs also evaluated whether resistance emerged during treatment with antiviral agents by comparing the sensitivities of the first and last isolates obtained from patients during the course of their participation in the clinical trial. All these studies have stratified the observations according to the immune status of the recipients.

#### Surveillance in the Immunocompetent Population

A susceptibility testing program was established to determine the prevalence of resistance to penciclovir among HSV isolates collected from patients participating in 11 worldwide clinical trials involving penciclovir (topical or intravenous formulations) or famciclovir, the oral prodrug of penciclovir (Sarisky *et al* 2003). These trials included immunocompetent and immunocompromised patients receiving short-term acute (up to ten days) or chronic suppressive therapy 2 to 12 months. The prevalence of confirmed penciclovir-resistant HSV was 0.2% in immunocompetent patients (2 of 913). Phenotypic analysis of confirmed penciclovir-resistant isolates showed that they were cross-resistant to aciclovir, but sensitive to the DNA polymerase inhibitor foscarnet (PFA, phosphonoformate sodium salt). The clinical program found no evidence of reduced penciclovir sensitivity in viral isolates obtained during and after penciclovir or famciclovir therapy, when compared with those obtained during and after placebo therapy.

The historical prevalence of aciclovir-resistant HSV isolates from untreated, immunocompetent patients as detected by the plaque reduction assay is 0.3% (Sande *et al* 1998, Bacon *et al* 2002). Furthermore, there has been no detectable change over time in this prevalence based on data for isolates collected during clinical trials, from patients who had not responded well to aciclovir, and from population-based surveys (Bacon *et al* 2003, Reyes *et al* 2003).

(Fife *et al* 1994) examined the emergence of resistance following 6 years of suppressive aciclovir therapy in immunocompetent patients with recurrent genital herpes. They found that, while most patients continue to have recurrences, the selection of resistant virus has not been observed.

Recurrent mucocutaneous lesions occur in many infants after completion of antiviral therapy of neonatal HSV infection. (Sarisky *et al* 2003) examined whether viruses that had become resistant to aciclovir or vidarabine caused these recurrences, tested the antiviral susceptibilities of 22 pre-therapy and 32 post-therapy HSV isolates from 22 infants younger than 3 months of age. Sixteen had been treated with aciclovir and six with vidarabine. No reduction in sensitivity was detected to either antiviral agent as assessed by a change in the drug IC50s for the recurrent isolates compared with the isolates collected during primary infection prior to therapy. Moreover, antiviral therapy did not select for recurrences with HSV resistant to aciclovir or vidarabine.

In summary, the prevalence of confirmed penciclovir-resistant HSV was 0.2% (2 of 913 immunocompetent patients), comparable to the results for aciclovir-resistant HSV. Clinical resistance is exceptionally rare in immunocompetent patients even though resistant HSV is detectable, albeit at a low frequency, in this population. This may be the consequence of the normal immune response leading to the rapid resolution of the infection.

#### Surveillance in the Immunocompromised Population

In clinical trials with penciclovir or famciclovir, HSV isolates from 288 immunocompromised patients treated with antiviral agents or placebo were tested for susceptibility to penciclovir.

Penciclovir-resistant HSV was isolated from 2.1% of immunocompromised patients.

Treatment with penciclovir (intravenous formulation) was associated with the development of resistant HSV in only one severely immunocompromised patient (day 7 isolate IC50 = 2.01 µg/ml), although treatment was effective and resulted in the complete clearance of the lesion by day 8.

As seen for penciclovir, aciclovir-resistant HSV is more common in the immunocompromised population. Surveys in North America and Europe of HSV isolates from immunocompromised patients treated with aciclovir indicate that the prevalence of resistant HSV is generally between 4% and 7% (Bacon *et al* 2003). (Reyes *et al* 2003) examined 226 HSV-2 isolates from HIV-positive patients of which 12 (5.3%) were resistant to aciclovir (95% CI, 2.8%-9.1%). In their study, genital lesions persisted significantly longer among HIV-positive patients with aciclovir-resistant herpes than among HIV-positive patients with sensitive isolates.

In patients with defective T-cell-mediated immunity, the virus is cleared very slowly from the lesions (Whitley *et al* 1984). Consequently, the lesions tend to be more prolonged and more severe than in immunocompetent individuals (Englund *et al* 1990). Extensive viral replication occurring in the setting of prolonged antiviral therapy and immunosuppression favour the selection of resistant virus. Yet, there has been no increase in prevalence of resistant strains in this population.

#### **Clinical management of cases due to resistant strains**

In general, increasing the dose of antiviral administered is of little benefit in cases of clinical resistance, even when the route of treatment is changed from oral to intravenous (Bacon *et al* 2003). Similarly, it is very unlikely that a patient failing to respond to therapy with aciclovir or valaciclovir will respond to famciclovir, since resistance to aciclovir and penciclovir almost always maps to mutations in the HSV thymidine kinase gene with almost inevitable crossresistance between aciclovir and penciclovir (Boyd *et al* 1993). In this setting, it is necessary to use a drug whose mechanism does not depend on activation by HSV thymidine kinase such as foscarnet, which is a pyrophosphate analog that inhibits HSV DNA polymerase.

#### **MAH Position on need for famciclovir in infants and children**

- Childhood HSV infections are rare. The greatest medical need for an antiviral agent is to treat HSV infections in neonates. Famciclovir was not evaluated in neonates and a dosing scheme for infants below the age of 6 months was not identified.

- Clinical information on genital herpes in children is limited. Efficacy data from adults cannot be extrapolated to this population. Furthermore, famciclovir has not been studied in children 1 to <12 years of age with genital herpes.
- It is not clear whether orolabial or genital HSV disease in HIV adult patients is similar to that in HIV-infected children, so efficacy cannot be extrapolated from adults to children.

Varicella in children is benign, self-limiting and typically uncomplicated.

- Herpes zoster in children is rare and mostly uncomplicated. Postherpetic neuralgia is not seen in children. The greatest medical need for an antiviral agent is to treat immunocompromised children.
- The efficacy of famciclovir for the treatment of varicella has not been established in either paediatric or adult patients. Famciclovir is approved for the treatment of herpes zoster in adult patients. However, extrapolation of efficacy data from adults with herpes zoster to children with varicella would not be appropriate. Although the same virus causes varicella and herpes zoster, the diseases are different.
- Studies with famciclovir in children with gingivostomatitis and varicella were open label and had no active comparator. While no safety concerns were evident, it is unclear whether the dosing regimen provided optimal efficacy.
- Aciclovir (both intravenous and oral formulations) has been shown to be effective in treating these infections in neonates, infants, children, and adolescents.
- Resistance to the antiviral nucleoside analogues (aciclovir, penciclovir) is rare in immunocompetent patients and low in immunocompromised patients. The incidence of resistance has remained stable over the last three decades. A patient with a viral infection resistant to aciclovir would most likely also be resistant to penciclovir.
- Antiviral therapy in neonates and children is most likely administered by caregivers (parent, guardian or medical professional). In paediatric patients oral aciclovir dosing regimen for HSV (t.i.d.) and herpes zoster (q.i.d.) is not too different from famciclovir (b.i.d. and t.i.d., respectively). Therefore, the less frequent administration of oral famciclovir may not be of great advantage to caregivers.
- Given the limited size of the patient population and the current need being met by generic aciclovir, an additional antiviral agent of the same mechanism of action would not add value to the current management of these paediatric infections.

*Assessor's comment:*

*Whereas it is acknowledged that immunocompetent children may not be in need of any zoster treatment, the data on the prevalence of HSV from UK and Germany indicate that the paediatric population is mostly affected and a therapeutic alternative to aciclovir may thus be valuable. Especially, the need for less frequent dosing may be a considerable advantage for patients and their caregivers. In conclusion, the MAH's reasoning for not pursuing the paediatric indication and the further development of a paediatric dosage form is still disputable.*

**Request for supplementary information No. 2**

***The MAH should clarify whether a bioequivalence study comparing the film-coated tablets and the sprinkle hard gelatine capsules has been conducted.***

**MAH response:**

A bioequivalence study comparing the film-coated tablets and the sprinkle capsule formulation has not been conducted. A variety of data was collected regarding the bioavailability of the sprinkle capsule formulation and a previous oral suspension formulation of famciclovir. It should be noted that the composition of the new granular form is identical with that of the marketed Famvir tablet (except the film-coating of the tablet). The available data are:

1) *In vivo* systemic exposure and PK data of the sprinkle capsule formulation in the target population, i.e. infants and children up to 12 years of age have been generated in three clinical studies ([Study B2301], [Study B2303] and [Study B2304]). The dose recommendations for paediatric patients can therefore be based on the bioavailability and PK data obtained with the actual paediatric formulation, i.e. the sprinkle capsule.

2) *In vitro* dissolution data show a rapid dissolution for the sprinkle capsule and the 125 mg Famvir tablet, with more than 85% of famciclovir dissolved within 20 minutes. These data suggest similar *in vivo* performance and bioavailability of both formulations.

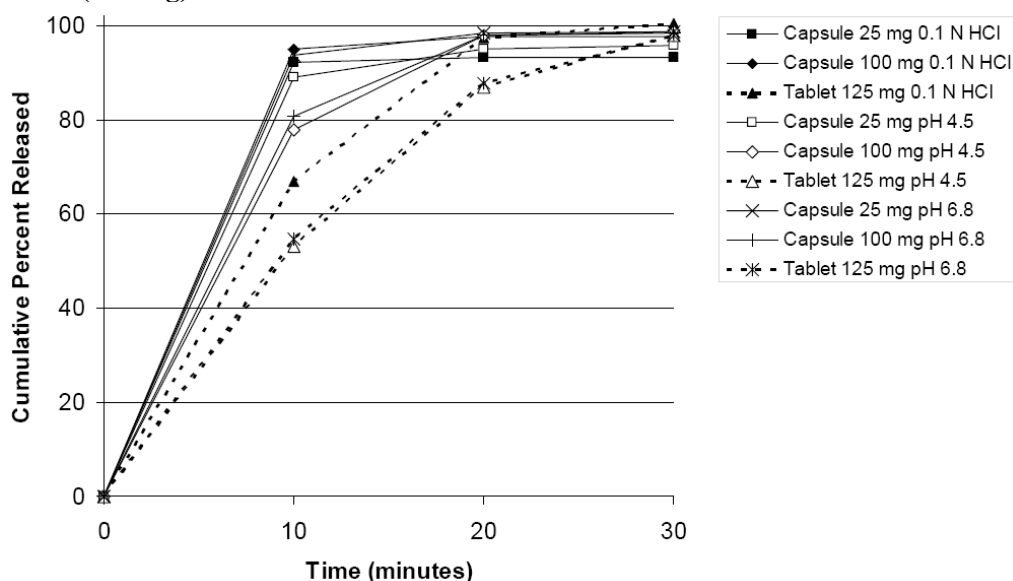
The testing was performed using the dosage form (sprinkle capsule), not the granules (granulation blend) the patient sprinkles on OraSweet as there is no standard method of measuring dissolution for powders. In acidic media (pH 1-2) the capsule shell dissolves within a few minutes. Thus performing the test with the entire capsule does not affect the dissolution result. The tests were performed in three media, i.e. in 0.1N HCl, in buffer pH 4.5 and in buffer pH 6.8.

The data is presented in figure 09. In all the dissolution curves shown in this figure, more than 85% of famciclovir was dissolved at 20 minutes for the 25 mg and 100 mg sprinkle capsules, as well as for the 125 mg Famvir tablets.

Initial dissolution sampling points of 10 minutes are not thought to be relevant from a physiological point of view since dissolution would happen in the stomach in this initial time period. As long as nearly the complete dissolved drug substance enters the upper intestine where absorption is thought to occur (Gill and Wood 1996), differences in the dissolution rate in the initial time period are unlikely to affect drug absorption. In addition, since the capsules, not the granules are used in the dissolution test, the dissolution rate in the initial time period reflects both dissolution of the capsule and dissolution of the granules, and may thus underestimate the dissolution of the granules in the *in vivo* situation.

Taken together, the *in vitro* dissolution data show a rapid dissolution for the famciclovir 25 mg and 100 mg sprinkle capsules and the 125 mg Famvir tablet, with more than 85% of famciclovir dissolved within 20 minutes. These data suggest similar *in vivo* performance and bioavailability of both formulations.

**Figure 09: Dissolution profiles of sprinkle capsules (25 mg and 100 mg) and Famvir commercial tablet (125 mg) in three media**



3) The relative bioavailability of an oral suspension of famciclovir (prepared from crushed tablets) was compared to the marketed tablets in study in adult healthy volunteers. The oral suspension was shown to be bioequivalent to the tablet with respect to penciclovir AUC<sub>0-inf</sub>. However, due to limited stability of famciclovir in oral suspension, this formulation was not used in our paediatric studies and was replaced by the sprinkle capsule formulation.

Study A2401 was conducted in healthy adult volunteers to evaluate the relative bioavailability of 500 mg/10 mL oral suspension versus 500 mg Famvir tablet and to compare the PK of famciclovir oral suspension administered with food and under fasted conditions. The study was a randomized, open-label, three-treatment, three-period, crossover study in healthy male or female volunteers. Each subject received the oral suspension form of famciclovir under both fasted (Treatment A) and fed conditions (Treatment B, high-caloric breakfast) and an oral marketed tablet under fasted conditions (Treatment C). Famciclovir was provided as 500 mg commercial tablets. The oral suspension of famciclovir (50 mg/mL) was prepared at the study site by crushing two 500 mg tablets to a fine powder and mixing the powder with 10 mL of OraPlus® suspending vehicle, and further with 10 mL of OraSweet® vehicle. In each treatment the medication (500 mg tablet or 10 mL oral suspension corresponding to 500 mg famciclovir) was administered with 240 mL of water. In Treatments A and C, food intake was Plasma samples were collected pre-dose and at 12 time points up to 24 hours after dosing. Plasma concentrations of penciclovir PK parameters of penciclovir were determined using noncompartmental methods. An analysis of variance (ANOVA) was performed on the logtransformed C<sub>max</sub>, AUC<sub>0-tlast</sub> and AUC<sub>0-inf</sub> data of penciclovir and the ratio of the geometric means together with 90% confidence intervals were computed for the comparisons of suspension fasted versus tablet fasted, suspension fed versus suspension fasted and suspension fed versus tablet fasted.

Safety assessments consisted of monitoring and recording of all adverse events (AEs), physical examination and vital signs, and laboratory evaluations (haematology and clinical chemistry).

Twenty four (24) subjects (18 males, 6 females) were enrolled and completed all study procedures. The mean ± SD age was 33.7 ± 7.1 years.

Plasma concentrations of 6-deoxy penciclovir were consistently lower than those of penciclovir and were only measurable up to 1 to 3 h after dosing in all treatments. Relative bioavailability assessments only considered the PK of penciclovir (Table 15).

**Table 15: Penciclovir pharmacokinetic parameters following single oral administration of 500 mg famciclovir as suspension (fasted and fed) and as tablet (fasted) to healthy volunteers**

Parameter	Treatment A	Treatment B	Treatment C	Ratio A/C (90% CI) <sup>a</sup>	Ratio B/A (90% CI) <sup>a</sup>	Ratio B/C (90% CI) <sup>a</sup>
	Suspension (fasted) N=24	Suspension (fed) N=24	Tablet (fasted) N=24			
t <sub>max</sub> (h)	0.50 (0.50 – 1.00)	1.00 (0.50 – 3.00)	0.75 (0.50 - 1.50)	–	–	–
C <sub>max</sub> (µg/mL)	4.19 ± 0.81	1.87 ± 0.47	3.45 ± 0.82	1.22 (1.12; 1.34)	0.44 (0.40; 0.49)	0.54 (0.49; 0.59)
AUC <sub>0-tlast</sub> (µg•h/mL)	9.11 ± 2.35	7.39 ± 1.81	8.54 ± 1.70	1.06 (0.99; 1.13)	0.81 (0.76; 0.87)	0.86 (0.81; 0.92)
AUC <sub>0-inf</sub> (µg•h/mL)	9.51 ± 2.39	7.80 ± 1.81	8.94 ± 1.69	1.05 (0.99; 1.12)	0.82 (0.77; 0.88)	0.87 (0.81; 0.92)
t <sub>1/2</sub> (h)	1.85 ± 0.26	1.81 ± 0.25	1.89 ± 0.28	–	–	–

Values are median [range] for t<sub>max</sub> and mean ± SD for other parameters.

<sup>a</sup>Ratio is test/reference ratio of geometric means (90% confidence interval) from ANOVA.

No statistical evaluation was performed for t<sub>max</sub> and t<sub>1/2</sub>.

The suspension versus tablet ratio of the geometric means was 1.05 for AUC<sub>0-inf</sub> and the 90% confidence interval was within the standard bioequivalence range of 0.80 to 1.25 (table 15). However, C<sub>max</sub> of penciclovir was 22% higher for the suspension than for the tablet. This finding is consistent with a slightly faster absorption from the suspension with shorter t<sub>max</sub>, but no difference in the extent of absorption and systemic availability of penciclovir.

Food reduced C<sub>max</sub> of penciclovir from the oral suspension by 46% when compared with administration of the tablet in the fasted state.

A total of 19 AEs were reported by 16 subjects. The majority of AEs were mild in severity (15/19) and not related to the study treatment (16/19). No serious or severe AEs were reported.

Assessor's comment:

*A formal bioequivalence study between the sprinkle capsules and the film-coated tablets has not been conducted. However, it is agreed with the MAH that the available information is supportive of a probably similar bioavailability.*

***Issue resolved.***

**Request for supplementary information No. 3**

***The MAH should clarify, whether the point in time: “the end of the study” used for the efficacy assessment in studies -03 and -04 means end of therapy or the last study visit.***

**MAH response:**

The efficacy assessment in studies B2303 and B2304 was carried out at the end of therapy. Typically this was done on day 8 or within 12 to 24 hours after the last dose of study medication (latter was administered for 7 days).

Assessor's comment:

***Issue resolved.***

**Request for supplementary information No. 4**

***Overall, the safety profile appears reassuring. However, it should be put into perspective with data from a comparable adult population (with respect to disease characteristics).***

**Summary of the MAH response:**

Novartis wishes to provide the safety information acquired from the multiple-dose paediatric and adult studies where comparable famciclovir dose regimens and duration were used (Table 16). A brief overview of the studies, their design and population studied will be reviewed.

**Table 16: Studies supporting acute treatment with famciclovir in children and adults with HSV or VZV infections**

**Safety and tolerability of an oral paediatric formulation in children ages 1 -12 years with HSV or VZV infection**

Study B2303 (Part B) [CFAM810B2303]	47	7 days	Famciclovir 150-500 mg (weight-based) b.i.d.	Dosing according to weight bands, open-label
Study B2304 (Part B) [CFAM810B2304]	53	7 day	Famciclovir 150-500 mg (weight-based) t.i.d.	Dosing according to weight bands, open-label

**Pivotal efficacy and safety studies in immunocompetent adults with genital herpes**

Study 004 [CFAM810A2207]	389	5 days	Famciclovir 250 mg t.i.d. Famciclovir 500 mg t.i.d. Famciclovir 750 mg t.i.d. Aciclovir 200 mg 5x daily	Parallel, double-blind, double-dummy, active-controlled
Study 011 [CFAM810A2211]	216	10 days	Famciclovir 125 mg t.i.d. Famciclovir 250 mg t.i.d. Famciclovir 500 mg t.i.d. Aciclovir 200 mg 5x daily	Parallel, double-blind, double dummy, active-controlled
Study 040 [CFAM810A2216]	360	10 days	Famciclovir 125 mg t.i.d. Famciclovir 250 mg t.i.d. Famciclovir 500 mg t.i.d. Aciclovir 200 mg 5x daily	Parallel, double-blind, double dummy, active-controlled
Study 035 [CFAM810A2214]	308	5 days	Famciclovir 125 mg b.i.d. Famciclovir 250 mg b.i.d. Famciclovir 500 mg b.i.d. Placebo b.i.d.	Parallel, double-blind, placebo-controlled
Study 036 [CFAM810A2215]	467	5 days	Famciclovir 125 mg b.i.d. Famciclovir 250 mg b.i.d. Famciclovir 500 mg b.i.d. Placebo b.i.d.	Parallel, double-blind, placebo-controlled

**Pivotal efficacy and safety studies in immunocompetent adults with herpes zoster**

Study 007 [CFAM810A2205]	545	7 days	Famciclovir 250 mg t.i.d. Famciclovir 500 mg t.i.d. Famciclovir 750 mg t.i.d. Aciclovir 800 mg 5x daily	Parallel, double-blind, double-dummy, active-controlled
Study 008 [CFAM810A2206]	419	7 days	Famciclovir 500 mg t.i.d. Famciclovir 750 mg t.i.d. Placebo t.i.d.	Parallel, double-blind, placebo-controlled

Two similar studies (B2303 and B2304) were conducted in children (ages 1 to 12 years). These open-label, multicenter studies with famciclovir recruited patients having either HSV or VZV infection and were designed in accordance to the FDA Paediatric Written Request.

Their protocols were similar and consisted of a two-step design. Part A was designed as a single-dose PK study in order to validate that the chosen dose would produce blood levels and exposures which have been shown to be safe and effective in adults. Part B was designed to obtain safety data using the dosing scheme developed from results of Part A. The Part B safety data will be used for this analysis. In Part B, famciclovir was dosed according to BW bands that were designed to provide the drug exposure equivalent to that achieve with 500 mg dose in adults. Patients with a BW <40 kg were assigned to one of the weight categories described in the protocol. The doses ranged in 8-step increments from 150 mg to 500 mg, depending on the patient's BW. No placebo or active comparator was included in these studies. The duration of famciclovir dosing was 7 days.

In children with herpetic gingivostomatitis [Study B2303] famciclovir was administered two times daily (b.i.d.), approximately 12 hours apart. In children with varicella [Study B2304] the dosing regimen was three times daily (t.i.d.) with doses approximately 8 hours apart. Concomitant therapy including antiviral agents was allowed. The key exclusion criteria included inability to swallow and history of any condition that might interfere with drug absorption, metabolism or elimination. The safety population consisted of all patients that received any dose (including partial dose) of study drug and had at least one post-baseline

safety or acceptability assessment. Patients were assessed on days 1 and 8 (clinic visit) as well as by telephone on days 2, 5, and 15. Safety assessments included monitoring and recording all AEs and serious adverse events (SAEs) as well as physical examination and laboratory evaluation.

In adults, five pivotal multicenter, double-blind, randomized studies were conducted in immunocompetent patients with genital herpes. Studies A2207, A2211 and A2216 were conducted with patients having first episode of genital herpes whose lesions had not progressed beyond the ulcer stage and had not been present for more than 72 hours. All three studies were similar in design, thus allowing pooling of the data. These studies included a 500 mg dose of famciclovir administered three times daily for either 5 days [Study A2207] or 10 days [Studies A2211 and A2216]. Aciclovir was the active comparator. [Studies A2214 and A2215] were conducted with immunocompetent adult patients having recurrent genital herpes. Both studies included a 500 mg dose of famciclovir administered twice daily. Placebo was the comparator. AEs and SAEs occurring during study medication and within 30 days of the end of study medication were monitored and recorded.

Studies A2205 and A2206 were pivotal studies and conducted to support the safety and efficacy claims in immunocompetent adult patients with uncomplicated herpes zoster. Both studies had a similar design conduct and analyses with a dosing duration of 7 days and a 6-month follow-up, which allowed for pooling of the data. Both Studies included a 500 mg dose of famciclovir administered three times daily. Placebo was the comparator. All these seven adult studies excluded women who were breastfeeding or not using acceptable method of birth control or were pregnant, patients with serious underlying disease including immune disorders or HIV, or patients who had received antiviral therapy within the previous 4 weeks, or who were taking corticosteroids.

### **Comparison of adverse events recorded in paediatric with those in adult studies**

In the two paediatric and 7 adult studies there was a good compliance to taking study medication. There were no deaths or SAEs observed in the paediatric studies. Two paediatric patients discontinued study medication due to abdominal pain of moderate severity.

Therefore, focus of comparison will be on reported AEs. AEs that occurred in  $\geq 2$  paediatric patients (irrespective of age) are compared to those occurring in the adult studies where similar dosing regimen was used (Table 17, ranking of the order of AEs according to the frequency seen in the paediatric studies). More extensive data for the individual pooled studies are also provided showing the AEs according to age cohort for the paediatric studies (Table 18)

Overall, the frequency of AEs reported by children taking famciclovir (50% of patients) was similar to that in adult famciclovir recipients (50.7% – 65.5%) as well as adult aciclovir recipients (40.3% – 52.5%) and somewhat less than that reported by placebo recipients (66.7% – 74.7%). Gastrointestinal events were the most commonly noted AEs in the paediatric studies representing approximately a combined total of 30% of all AEs reported. In the adult population 17% of recipients taking famciclovir 500 mg b.i.d. and approximately 23% of recipients taking famciclovir 500 mg t.i.d. reported gastrointestinal events, while 28% of adult recipients of placebo reported gastrointestinal events. In the adult studies headache was a more commonly reported AE noted by 6.6% – 27.8% of recipients taking famciclovir, 7.9% – 8.6% of aciclovir recipients and 21.1% – 23.3% of placebo recipients. In the paediatric studies headache was recorded in 6% of famciclovir recipients with all headache AEs occurring in the 6 to 12 years age group.

### **Discussion**

Part B segments of studies B2303 and B2304 were selected for this comparison as these encompassed multiple daily dosing regimens with famciclovir as opposed to the other single dose parts. Thus, the likelihood of detecting drug-related adverse events is greater. This assumption was born out by the observation that only 9% of children reported an AE in the single dose parts compared with 50% in the multiple-dose parts.

The more frequently reported AEs that occurred in 2 or more children were not always noted in the composite table from the adult studies, and this may be attributed to the cut-off criteria for most frequently noted AEs used in some of the studies (being  $\geq 5\%$  of patients). The composite tables for the adult studies A2205 and A2206 used a lower cut-off (occurring in  $\geq 2\%$  of patient). In these two combined studies there was greater overlap in the noted AEs and their frequency with the paediatric studies. It should be noted

that, in case a specific AE of a certain type was not observed in 50 paediatric patients, one could exclude an incidence of more than 6% for this event (based on the 95% confidence interval for the rate). The overall safety profile of paediatric patients in this study was similar to that described for adults. The AEs seen in paediatric studies were as expected for the class of drug as well as the symptoms for HSV infection and varicella. The reported AEs were mostly mild and transient and gave no indication of target organ toxicity. The most frequent AEs overall were vomiting, diarrhea, pyrexia, and dehydration. Gastrointestinal disorders are also common AEs in adult patients taking famciclovir. In adults no safety differences were observed for different daily doses of famciclovir with the adverse event. Moreover, there is no evidence to suggest the higher drug exposures lead to worsening safety outcomes. Some of the adult studies included a placebo arm that provides a better assessment of famciclovir's adverse event profile. It is noteworthy that the overall incidence of AEs and SAEs were generally similar between the different daily doses of famciclovir and with those reported by placebo-treated patients (for more details reference is made to table 3-21 for studies A2207, A2211, A2216 (AEs occurring at a frequency of  $\geq 5\%$ ) and table 3-22 for studies A2205 and A2206 (AEs occurring at a frequency of  $\geq 2\%$ ) in the MAH response document). There was no pattern in the SAEs or AEs leading to withdrawal that would suggest any potential for intolerance of clinical significance.

### **Conclusion**

While there were differences in the diseases being treated in paediatric and adult studies, No differences in the nature or frequency of AEs were observed for famciclovir patients across studies regardless of the mean age of enrolled patients.

**Table 17: Comparison of the more frequent adverse events reported in children with the more frequently reported adverse event in adults**

Study Number	Paediatric Studies			Adult Studies				
	B2303 / B2304	A2214 / A2215 <sup>a</sup>		A2207 / A2211 / A2216 <sup>a</sup>		A2205 / A2206 <sup>b</sup>		
Treatment	Famciclovir	Famciclovir	Placebo	Famciclovir	Aciclovir	Famciclovir	Aciclovir	Placebo
Dose Regimen	500 mg b.i.d.; 500 mg t.i.d.	500 mg b.i.d.		500 mg t.i.d.	200 mg 5x daily	500 mg t.i.d.	800 mg 5x daily	
Safety Population (N)	100	194	80	243	240	272	139	146
Patients with AEs (N (%))	50 (50.0)	127 (65.5)	120 (66.7)	138 (57)	126 (52.5)	168 (50.7)	56 (40.3)	109 (74.7)
Diarrhea	10 (10.0)	6 (3.1)	18 (10)	11 (4.5)	12 (5.0)	14 (5.2)	8 (5.8)	10 (6.8)
Vomiting	10 (10.0)			8 (3.3)	4 (1.7)	7 (2.6)	6 (4.3)	7 (4.8)
Headache	6 (6.0)	54 (27.8)	38 (21.1)	16 (6.6)	19 (7.9)	65 (23.9)	12 (8.6)	34 (23.3)
Pyrexia	6 (6.0)					6 (2.2)	2 (1.4)	6 (4.1)
Nausea	5 (5.0)	20 (10.3)	19 (10.6)	29 (11.9)	19 (7.9)	30 (11.0)	4 (2.9)	19 (13.0)
Abdominal pain	5 (5.0)	8 (4.1)	13 (7.2)	5 (2.1)	1 (0.4)	5 (1.8)	6 (4.3)	5 (3.4)
Cough	3 (3.0)			0	3 (1.2)	5 (1.8)	1 (0.7)	4 (2.7)
Pruritus	3 (3.0)					13 (4.8)	6 (4.3)	6 (4.1)
Cellulitis	2 (2.0)							
Somnolence	2 (2.0)					4 (1.5)	3 (2.2)	5 (3.4)

**Table 18: Number (%) of patients with AEs overall and by preferred term (Safety population, Part B, Studies B2303 and B2304)**

	1 to <2 years N=31 n (%)	2 to <6 years N=35 n (%)	6 to ≤12 years N=34 n (%)	2 to ≤12 years N=69 n (%)	Total N=100 n (%)
Patients with AEs	13 (41.9)	18 (51.4)	19 (55.9)	37 (53.6)	50 (50.0)
Preferred term					
Diarrhea	3 (9.7)	2 (5.7)	5 (14.7)	7 (10.1)	10 (10.0)
Vomiting	7 (22.6)	1 (2.9)	2 (5.9)	3 (4.3)	10 (10.0)
Headache	0 (0.0)	0 (0.0)	6 (17.6)	6 (8.7)	6 (6.0)
Pyrexia	4 (12.9)	1 (2.9)	1 (2.9)	2 (2.9)	6 (6.0)
Nausea	1 (3.2)	1 (2.9)	3 (8.8)	4 (5.8)	5 (5.0)
Abdominal pain upper	0 (0.0)	1 (2.9)	2 (5.9)	3 (4.3)	3 (3.0)
Cough	1 (3.2)	1 (2.9)	1 (2.9)	2 (2.9)	3 (3.0)
Pruritus	2 (6.5)	0 (0.0)	1 (2.9)	1 (1.4)	3 (3.0)
Abdominal pain	0 (0.0)	0 (0.0)	2 (5.9)	2 (2.9)	2 (2.0)
Cellulitis	0 (0.0)	1 (2.9)	1 (2.9)	2 (2.9)	2 (2.0)
Somnolence	0 (0.0)	2 (5.7)	0 (0.0)	2 (2.9)	2 (2.0)
Anorexia	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Arthropod bite	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Asthma	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Blister	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Blood uric acid increased	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Bronchitis	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Bronchospasm	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Chest pain	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Clumsiness	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Conjunctivitis viral	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Constipation	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Contusion	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Cystitis hemorrhagic	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Dry skin	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Dysphonia	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)

	1 to <2 years N=31 n (%)	2 to <6 years N=35 n (%)	6 to ≤12 years N=34 n (%)	2 to ≤12 years N=69 n (%)	Total N=100 n (%)
Eosinophilia	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Flatulence	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Flushing	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Gastritis	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Gastroenteritis	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Gingival bleeding	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Groin pain	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Hematoma	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Hypokalaemia	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Impetigo	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Influenza	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Irritability	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Lice infestation	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Lymphadenitis	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Nasal congestion	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Otitis media	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Pain in extremity	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)	0 (0.0)
Pharyngitis	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Pharyngolaryngeal pain	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Psychomotor hyperactivity	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Radiculitis	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Rash	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Rhinorrhea	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Skin infection	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)	1 (1.0)
Skin laceration	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Staphylococcal skin infection	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Varicella	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)
Vessel puncture site hematoma	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.4)	1 (1.0)

**Assessor's comment:**

*Diarrhoea, vomiting and pyrexia were observed at higher frequencies in children than in adults. Whereas diarrhoea occurred most frequently in the 6-12 year-old, vomiting and pyrexia was observed most often in the youngest age group, i.e. those aged 1 -2 years. Although in the overall paediatric population headache was reported less frequently than in adults, its frequency in the subgroup of 6 to 12 years compares well with that in adults. In conclusion, these differences are not considered of utmost clinical relevance. Only the fact that 10% of the very young suffered from vomiting might be a concern with respect to treatment compliance (adequate systemic exposure).*

***Issue resolved.***

**Request for supplementary information No. 5**

***A scientific rationale for not including adolescents into studies -03 and -04 should be provided.***

**MAH response:**

There was no scientific rationale for excluding adolescents from study B2303 and study B2304. These two studies were conducted in children 1 to 12 years of age as outlined in FDA's Paediatric Written Request.

A study in adolescents (B2305) was recently initiated.

This study, being conducted in the USA, will assess the safety and PK of famciclovir single 1500 mg dose in adolescents with recurrent herpes labialis (i.e. approved regimen in the USA for the treatment of adults with recurrent herpes labialis). As agreed with FDA, the adult marketed formulation is used in this study.

Assessor's comment:

Issue clarified/resolved.

**Request for supplementary information No. 6**

***The rationale for the dose recommendations in children less than 1 year of age (study -01) should be provided. And the MAH could propose a more suitable dosing regimen for the very young (i.e. less than 6 months of age) based on the results of this study.***

**MAH response:**

**Rationale for famciclovir doses used in infant study FAM810B2301**

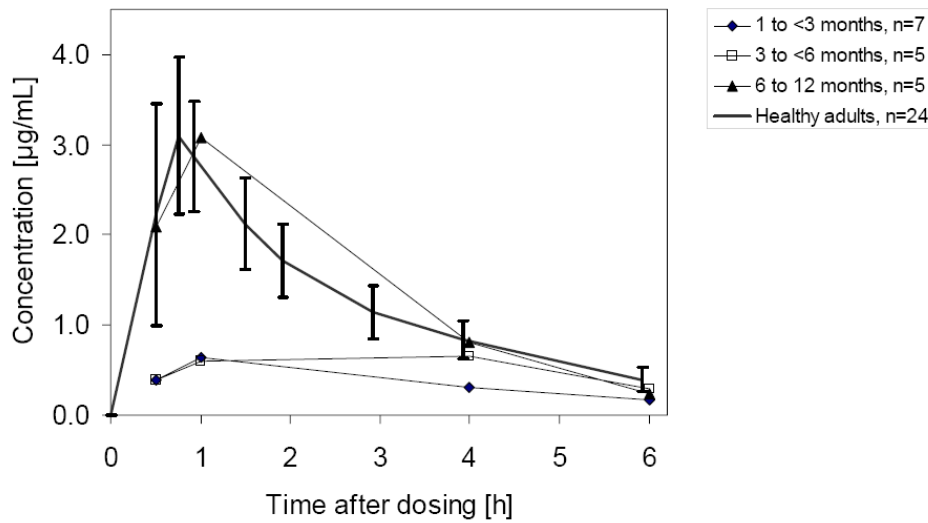
The basis for dosing famciclovir in infants below 1 year of age originated from data accumulated in older children (Study B2303, Study B2304, (Sáez-Llorens *et al* 2009)), wherein BW was shown to be the most important factor in penciclovir PK. For children 1 to 12 years old, famciclovir dosing was calculated 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) (Sáez-Llorens *et al* 2009). Since penciclovir is predominantly excreted renally (Gill and Wood 1996), it was subsequently assumed that clearance of penciclovir in infants younger than 1 year would be lower than extrapolated from the relationship between penciclovir clearance and BW in older children due to their physiologically immature kidneys. As such, a renal maturation factor was introduced in the equation describing the relationship between penciclovir clearance and the infant's BW. This resulted in the doses proposed for the infant study B2301, i.e. doses between 25 mg (BW up to 5.4 kg) and 200 mg (BW 11.5 to 13.4 kg). Consequently, the doses in mg per kg of BW were lower in the infants below 6 months of age (mean 6.6 mg/kg in 1 to <3 months age group, 9.4 mg/kg in the 3 to <6 months age group) than in the infants and children aged 6 months to 12 years (mean 12.2 to 13.5 mg/kg).

Details of the method used to define the doses in the infant study can be found on pages 289 to 293 of the Clinical Study Report of study B2301.

**Dosing regimen for infants less than 6 months of age**

Figure 10 shows the mean concentration-time profiles of penciclovir in infants 1 to 12 months of age with HSV infection (Study B2301), in comparison with historical data for adult healthy volunteers (Study A2401). Plasma concentrations of penciclovir in the 6 to 12 months age group were in the range observed in children 1 to <2 years of age in study B2303 and study B2304, and similar to those in adults following a 500 mg dose of famciclovir. However, with the doses used in this study, systemic exposure to penciclovir (C<sub>max</sub>, AUC<sub>0-6h</sub>) in the infants below 6 months was at most 36% of that in the 6 to 12 months age group. In addition, the penciclovir concentration-time profiles were relatively flat in the infants below 6 months, without a distinct peak in most profiles. The unexpectedly low systemic exposure suggests that the apparent oral clearance of penciclovir was 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.

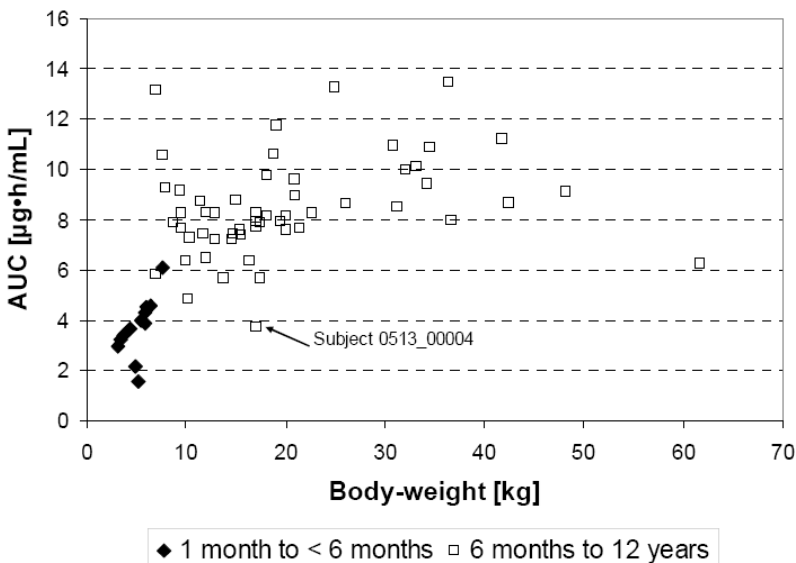
**Figure 10: Penciclovir mean plasma concentrations in infants with HSV infection compared with healthy adult volunteers**



Means are shown for infants, means and SD for adults. In case of identical sampling times, the adult data were shifted by 5 min.

The combined PK data from the three paediatric studies in 67 children 1 month to 12 years of age were included in population PK modeling (*Modeling Report 2009*). In Figure 11, the individual 67 model-based AUC<sub>0-inf</sub> values of penciclovir are plotted against BW. Eleven of the 12 patients in the age groups below 6 months showed considerably lower AUC<sub>0-inf</sub> than all patients aged 6 months and above who received the correct scheduled dose (note, one patient had received a lower dose than scheduled, and this patient defines the lower limit of the AUC<sub>0-inf</sub> range in the patients aged 6 months and above). On average, the patients in the age group below 6 months are predicted to require 2- to 3-times higher doses than actually given in study B2301 to achieve the target exposure seen in adults after a 500 mg dose. The safety of such higher doses in children less than 6 months of age was not established. Thus, famciclovir doses for children less than 6 months of age can not be recommended.

**Figure 11: Relationship between model-based AUC<sub>0-inf</sub> of penciclovir and body weight in paediatric patients with HSV and VZV infection between 1 month and 12 years of age for the doses of famciclovir actually given**



Subject 0513/00004 had received an incorrect dose, i.e. 125 mg (7.3 mg/kg) instead of the scheduled dose of 225 mg (13.2 mg/kg).

Assessor's comment:

The MAH's discussion of the data is agreed. However, it has to be clarified that the lack of a dosing recommendations for infants less than 6 months of age is due to the fact that appropriate doses, i.e. those leading to adequate systemic exposure, have not been identified (and not for known safety concerns).

**Request for supplementary information No 7**

***The MAH should confirm whether there are data available regarding the use of famciclovir granules in vehicles other than Ora-Sweet syrup (or any food likely to be used with children), as this may not be available in Europe. (UK)***

**MAH response:**

Novartis has chemical stability data up to 60 minutes in OraSweet, apple sauce, corn syrup, and Enfamil™, and recovery data in OraSweet, apple sauce and corn syrup, as vehicles for famciclovir oral granules. Vehicles other than OraSweet have not been used in clinical trials.

The stability of famciclovir in OraSweet, apple sauce, corn syrup, and Enfamil was studied to evaluate the potential use of these vehicles for drug administration. The results shown in table 22 and table 23 are for famciclovir experimental 20 mg sprinkle capsule formulation, one of the earlier development formulations. This formulation was not used in clinical trials. Stability studies performed for the 20 mg strength are valid for the 25 mg and 100 mg strengths used in clinical trials due to the use of common granulation for all strengths.

**Table 22: Stability results of famciclovir 20 mg sprinkle capsule formulation and OraSweet syrup**

Sample	Time point (minutes)	% Assay <sup>a</sup>	% Related substances <sup>b</sup>			
			BRL42359	BRL43594	Total degs	Appearance
OraSweet	Initial	97.2 – 100.4	ND	0.08	0.1	No change observed
	15	97.8 – 99.7	ND	0.08	0.1	
	30	97.6 – 100.3	ND	0.09	0.1	
	60	96.2 – 99.6	ND	0.09	0.1	
	120	97.5 – 98.4	ND	0.09	0.1	

ND = none detected

<sup>a</sup> All assay values are corrected based on the fill weight since it is known that the 20 mg dosage strength technical batch utilized for this study has a large variation in the fill weight.

<sup>b</sup> The highest related substance amount from the 3 samples/time point is being reported. No individual unspecified degradation products were found in any of the stability samples tested.

**Table 23: Stability results of famciclovir 20 mg sprinkle capsule formulation and vehicles other than OraSweet**

Sample	Time point (minutes)	% Assay <sup>a</sup>	% Related substances <sup>b</sup>			Appearance
			BRL42359	BRL43594	Total degs	
Applesauce	Initial	98.2 – 98.7	ND	0.15	0.2	No change observed
	15	99.7 – 100.2	ND	0.17	0.2	
	30	99.1 – 100.8	ND	0.16	0.2	
	60	97.0 – 101.1	ND	0.17	0.2	
Corn syrup	Initial	100.4 – 101.4	ND	0.13	0.1	No change observed
	15	99.0 – 101.3	ND	0.13	0.1	
	30	95.7 – 101.3	ND	0.14	0.1	
	60	95.4 – 99.6	ND	0.13	0.1	
Enfamil	Initial	98.2 – 98.7	1.13	1.16	2.3	No change observed
	15	99.7 – 100.2	0.50	1.09	1.6	
	30	99.1 – 100.8	0.40	1.22	1.6	
	60	97.0 – 101.1	0.48	1.21	1.7	

ND = none detected

<sup>a</sup> All assay values are corrected based on the fill weight since it is known that the 20 mg dosage strength technical batch utilized for this study has a large variation in the fill weight.

<sup>b</sup> The highest related substance amount from the 3 samples/time point is being reported. No individual unspecified degradation products were found in any of the stability samples tested.

The sample preparation for the recovery by assay of famciclovir is consistent with the instructions in the clinical trials for the administration of the dosage form to the patient. In this experiment, the prepared sample and the rinse solutions were transferred to the respective volumetric flasks to determine the delivered dose to the patient.

The recovery results for individual sprinkle capsules in OraSweet, apple sauce and corn syrup are presented in table 24. Due to the sticky nature of corn syrup two rinses were required for acceptable recovery of the drug for the 25 mg strength in corn syrup vehicle. Since individual capsule recovery was performed to be consistent with the patient dosing, the acceptance criteria was kept identical to that of the content uniformity test (85.0% – 115.0%).

Recovery results in all three vehicles met acceptance criteria.

**Table 24: Recovery results of individual sprinkle capsules in OraSweet, apple sauce and corn syrup**

Vehicle	Dose	Recovery result summary for 10 individual sprinkle capsules				
		Mean (n=10)	Minimum	Maximum	% RSD	Number of Rinses
OraSweet	20 mg	94.0	85.8	97.0	3.4	1 rise with 5 ml apple juice
OraSweet	100 mg	92.4	85.7	95.5	3.9	1 rise with 5 ml apple juice
Apple Sauce	25 mg	98.5	88.3	105.8	5.4	1 rise with 5 ml apple juice
Apple Sauce	100 mg	98.8	93.4	102.4	3.2	1 rise with 5 ml apple juice
Corn syrup	25 mg	97.8	93.1	102.4	4.5	2 rises with 5 ml apple juice
Corn syrup	100 mg	94.9	92.0	96.7	1.5	1 rise with 5 ml apple juice

## Conclusion

Based on the stability and recovery results reported, famciclovir is found to be stable for up to 60 minutes and has acceptable recovery when mixed with OraSweet, applesauce and corn syrup. However, famciclovir is found to be unstable when mixed with Enfamil. The applesauce and corn syrup are available in food grade but are variable by brand and region.

Since OraSweet is available in pharmaceutical grade, it would have been recommended as the primary vehicle for administration.

However, as Novartis will not seek registration of the experimental paediatric famciclovir formulation the above data on stability and recovery of famciclovir in various vehicles is provided for information purposes only.

Assessor's comment:

*The MAH provided a description and discussion of the available data on stability of Famciclovir sprinkle capsules formulation after mixing with different types of food.*

*Issue resolved.*

**Request for supplementary information No 8**

***The MAH should discuss if/how the safety and pharmacokinetic information generated in the provided studies could be included in the SmPC. (NL)***

**MAH response:**

Table 25 lists draft proposed amendments by SmPC section covering paediatric safety and pharmacokinetic information obtained from recently completed paediatric studies.

However, as Referral under Article 30 Directive 2001/83/EC procedure is ongoing, Novartis proposes to address inclusion of the above mentioned information in the SmPC through a separate type II variation procedure after completion of the Referral.

**Table 25: Draft proposed SmPC update regarding paediatric population**

SmPC section	Proposed text
4.2 Posology and method of administration	Paediatric population The efficacy and safety of Famvir tablets have not been established in paediatric patients. Currently available data are described in sections 5.1 “Pharmacodynamic properties and 5.2 “Pharmacokinetic properties” but no recommendation on a posology can be made.
5.1 Pharmacodynamic properties	Paediatric population The efficacy of Famvir in paediatric patients under the age of 18 years has not been established. The safety of famciclovir experimental oral granules was evaluated in 169 paediatric patients 1 month to ≤12 years of age. One hundred of these patients were 1 to ≤12 years of age and were treated with famciclovir oral granules (doses ranged from 150 mg to 500 mg) either twice (47 patients with herpes simplex virus infections) or three times (53 patients with chickenpox) daily for 7 days. The remaining 69 patients (18 patients 1 to ≤12 months, 51 patients 1 to ≤12 years) participated in single-dose pharmacokinetic and safety studies using famciclovir oral granules (doses ranged from 25 mg to 500 mg). The frequency, intensity, and nature of adverse events and laboratory abnormalities reported in the clinical trials were similar to those seen in adults.  The available data are insufficient to support the use of famciclovir for the treatment of chickenpox or infections due to herpes simplex virus in this patient population (see section 4.2 Posology and method of administration). No efficacy studies have been conducted in paediatric patients and there are no efficacy data in adults with diseases similar to the ones evaluated in the safety and pharmacokinetics paediatric studies (i.e. chickenpox or gingivostomatitis).
5.2 Pharmacokinetic properties	Paediatric population In the paediatric studies described in section 5.1 Pharmacodynamic properties, the famciclovir doses were based on the patient’s body weight and were selected to provide systemic exposures similar to the penciclovir systemic exposure observed in adults after administration of 500 mg famciclovir. Based on the pharmacokinetic data observed with these doses in children, a new weight-based dosing algorithm was designed and used in the multiple-dose safety studies in patients 1 to ≤12 years of age. Pharmacokinetic data were not obtained with the revised weight-based dosing algorithm.

**Assessor’s comment:**

*With the exception of the paragraph in section 5.1 detailed below, the wording of the respective sections of the SPC will have to be decided upon after assessment of the data submitted within the article 45 procedure for this product. The wording on the studies conducted with the sprinkle capsule formulation in section 5.1 of the SPC should read as follows:*

*“~~The safety of~~ Famciclovir experimental oral granules were evaluated in 169 paediatric patients 1 month to ≤12 years of age. One hundred of these patients were 1 to ≤12 years of age and were treated with famciclovir oral granules (doses ranged from 150 mg to 500 mg) either twice (47 patients with herpes simplex virus infections) or three times (53 patients with chickenpox) daily for 7 days. The remaining 69 patients (18 patients 1 to ≤12 months, 51 patients 1 to ≤12 years) participated in single-dose pharmacokinetic and safety studies using famciclovir oral granules (doses ranged from 25 mg to 500 mg). **None of these studies comprised a control group; therefore a conclusion on the efficacy of the investigated regimens is not possible.** The frequency, intensity, and nature of adverse events and laboratory abnormalities reported in the clinical trials were similar to those seen in adults. **However, systemic drug exposure in very young infants (> 6 months of age) was low; therefore, thus precluding any assessment of famciclovir’s safety in this age group.**”*

## V. RMS OVERALL CONCLUSIONS

The specific issues on the submitted studies (RSI no. 2 to 7) were appropriately addressed by the MAH and can be considered resolved.

*For a final decision on this procedure including the final wording of the SPC the assessment of data submitted within the article 45 procedure of famciclovir will have to be awaited.*

## VI. REFERENCES

- [Amir J, Harel L, Smetana Z, et al (1997)] Treatment of herpes simplex gingivostomatitis with aciclovir in children: a randomised double blind placebo controlled study. *BMJ* 314, 1800-3.
- [Auvin S, Imiela A, Cateau B, et al (2004)] Paediatric skin disorders encountered in an emergency hospital facility: a prospective study. *Acta Derm Venereol* 84, 451-4.
- [Bacon TH (1996)] Famciclovir, from the bench to the patient - a comprehensive review of preclinical data. *Int J Antimicrob Agents* 7, 119-34.
- [Bacon TH, Boon RJ, Schultz M, et al (2002)] Surveillance for anti-viral-agent-resistant herpes simplex virus in the general population with recurrent herpes labialis. *Antimicrob Agents Chemother* 46, 3042-4.
- [Bacon TH, Levin MJ, Leary JJ, et al (2003)] Herpes simplex virus resistance to aciclovir and penciclovir after two decades of anti-viral therapy. *Clin Microbiol Rev* 16, 114-28.
- [Becker TM, Magder L, Harrison HR (1988)] The epidemiology of infection with the human herpesviruses in Navajo children. *Am J Epidemiol* 127(5), 1071-8.
- [Bogaerts J, Ahmed J, Akhter N, et al (2001)] Sexually transmitted infections among married women in Dhaka. Bangladesh: unexpected high prevalence of herpes simplex type 2 infection. *Sex Transm Infect* 77(2), 114-9.
- [Bonanni P, Breuer J, Gershon A, et al (2009)] Varicella vaccination in Europe - taking the practical approach. *BMC Med* 7, 26.
- [Boyd MR, Safrin S, Kern ER (1993)] Penciclovir: a review of its spectrum of activity, selectivity, and cross-resistance pattern. *Anti-viral Chem Chemother* 4, 3-11.
- [Brown ZA, Wald A, Morrow RA, et al (2003)] Effect of serologic status and caesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 289, 203-9.
- [Centers for Disease Control and Prevention (2003)] Decline in annual incidence of varicella - selected states, 1990-2001. *MMWR Morb Mortal Wkly Rep* 52, 884-5.
- [Centers for Disease Control and Prevention (2008)] Chickenpox vaccine. What you need to know. Vaccine Information Statement (Internet) Available from: <<http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-varicella.pdf>> (Accessed 19 October 2009).
- [Chidiac C, Bruxelles J, Daures JP, et al (2001)] Characteristics of patients with herpes zoster on presentation to practitioners in France. *Clin Infect Dis* 33(1), 62-9.
- [Crumacker C (1996)] The pharmacological profile of famciclovir. *Semin Dermatol*, 15, 14- 26.
- [Dekker CL, Prober CG (2001)] Paediatric uses of valaciclovir, penciclovir and famciclovir. *Pediatr Infect Dis J*, 20, 1079-81.
- [Dwyer DE, Kesson AM (1997)] Advances in anti-viral therapy. *Curr Opin Pediatr* 9, 24-30.
- [Enders G, Risse B, Zauke M, et al (1998)] Seroprevalence study of herpes simplex virus type 2 among pregnant women in Germany using a type-specific enzyme immunoassay. *Eur J Clin Microbiol Infect Dis* 18, 870-2.
- [Englund JA, Zimmerman ME, Swierkosz EM, et al (1990)] Herpes simplex virus resistant to aciclovir. A study in a tertiary care center. *Ann Intern Med* 112, 416-22.

- [Fife KH, Crumpacker CS, Mertz GJ, et al (1994)] Recurrence and resistance patterns of herpes simplex virus following cessation of > or = 6 years of chronic suppression with aciclovir. *J Infect Dis* 169, 1338-41.
- [Franco E, Caprilli F, Zaratti L, et al (1987)] Prevalence of antibodies to herpes simplex virus type 1 in different population groups in Italy. *Eur J Clin Microbiol* 6(3),322.
- [García-Corbeira P, Dal-Ré R, Aguilar L, et al (1999)] Is sexual transmission an important pattern for herpes simplex type 2 virus seroconversion in the Spanish general population? *J Med Virol* 59(2), 194-7.
- [Ghebrekidan H, Rudén U, Cox S, et al (1999)] Prevalence of herpes simplex virus types 1 and 2, cytomegalovirus, and varicella-zoster virus infections in Eritrea. *J Clin Virol* 12(1), 53-64.
- [Gill KS, Wood MJ (1996)] The clinical pharmacokinetics of famciclovir. *Clin Pharmacokinet* 31, 1-8.
- [Griffiths PD (2009)] A perspective on anti-viral resistance. *J Clin Virol* 46, 3-8.
- [Guillén JM, Samaniego-Colmenero Mde L, Hernández-Barrera V, et al (2009)] Varicella paediatric hospitalizations in Spain. *Epidemiol Infect* 137, 519-25.
- [Ibrahim AI, Kouwatli KM, Obeid MT (2000)] Frequency of herpes simplex virus in Syria based on type-specific serological assay. *Saudi Med J* 21(4), 355-60.
- [Insinga RP, Itzler RF, Pellissier JM, et al (2005)] The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med* 20(8), 748-53.
- [Isacsohn M, Smetana Z, Roness ZZ, et al (2002)] A sero-epidemiological study of herpes virus type 1 and 2 infection in Israel. *J Clin Virol* 24, 85-92.
- [Jumaan AO, Yu O, Jackson LA, et al (2005)] Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992-2002. *J Infect Dis* 191(12), 2002-7.
- [Juretić M. (1966)] Natural history of herpetic infection. 21(4), 356-68.
- [Kearns GL, Abdel-Rahman SM, Alander SW, et al (2003)] Developmental pharmacology-- drug disposition, action, and therapy in infants and children. *N Engl J Med* 349, 1157-67.
- [Kimberlin DW (2004)] Neonatal herpes simplex infection. *Clin Microbiol Rev* 17, 1-13.
- [Mahnert N, Roberts SW, Laibl VR, et al (2007)] The incidence of neonatal herpes infection. *Am J Obstet Gynecol* 196, e55-6.
- [Morfin F, Thouvenot D (2003)] Herpes simplex virus resistance to anti-viral drugs. *J Clin Virol* 26, 29-37.
- [Mullooly J., Riedlinger K, Chun C, et al (2005)] Incidence of herpes zoster, 1997-2002. *Epidemiol Infect* 133, 245-53.
- [Papadopoulos AJ, Birnkrant AP, Schwartz RA, et al (2001)] Childhood herpes zoster. *Cutis* 68, 21-3.
- [Petursson G, Helgason S, Gudmundsson S, et al (1998)] Herpes zoster in children and adolescents. *Pediatr Infect Dis J* 17(10), 905-8.
- [Pue MA, Pratt SK, Fairless AJ, et al (1994)] Linear pharmacokinetics of penciclovir following administration of single oral doses of famciclovir 125, 250, 500 and 750 mg to healthy volunteers. *J Antimicrob Chemother* 33, 119-27.
- [Rabenau HF, Buxbaum S, Preiser W, et al (2002)] Seroprevalence of herpes simplex virus types 1 and type 2 in the Frankfurt am Main area, Germany. *Med Microbiol Immunol* 190(4), 153-60.
- [Reyes M, Shaik NS, Graber JM, et al (2003)] Aciclovir-resistant genital herpes among persons attending sexually transmitted disease and human immunodeficiency virus clinics. *Arch Intern Med* 163, 76-80.
- [Sáez-Llorens X, Yogev R, Arguedas A, et al (2009)] Pharmacokinetics and safety of famciclovir in children with herpes simplex or varicella-zoster virus infection. *Antimicrob Agents Chemother* 53, 1912-20.
- [Sande MA, Armstrong D, Corey L, et al 1998)] Perspectives on switching oral aciclovir from prescription to over-the-counter status: report of a consensus panel. *Clin Infect Dis* 26, 659- 63.
- [Sarisky RT, Bacon TH, Boon RJ, et al (2003)] Profiling penciclovir susceptibility and prevalence of resistance of herpes simplex virus isolates across eleven clinical trials. *Arch Virol* 148, 1757-69.

- [Schmitt DL, Johnson DW, Henderson FW (1991)] Herpes simplex type 1 infections in group day care. *Pediatr Infect Dis J* 10, 729-34.
- [Seward JF, Watson BM, Peterson CL, et al (2002)] Varicella disease after introduction of varicella vaccine in the United States. 1995-2000. *JAMA* 287(5), 606-11.
- [Simpson D, Lyseng-Williamson KA (2006)] Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs* 66, 2397-416.
- [Smith CG, Glaser DA (1996)] Herpes zoster in childhood: case report and review of the literature. *Pediatr Dermatol* 13(3), 226-9.
- [Smith, JS, Robinson, NJ (2002)] Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. *J Infect Dis*, 186 Suppl 1, S3-28.
- [Stone KM, Brooks CA, Guinan ME, et al (1989)] National surveillance for neonatal herpes simplex virus infections. *Sex Transm Dis* 16(3), 152-6.
- [Tayama, Y, Miyake, K, Sugihara, K, et al (2007)] Developmental changes of aldehyde oxidase activity in young Japanese children. *Clin Pharmacol Ther* 81, 567-72.
- [Volpi A, Gross G, Hercogova J, et al (2005)] Current management of herpes zoster: the European view. *Am J Clin Dermatol* 6, 317-25.
- [Vyse AJ, Gay NJ, Slomka MJ, et al (2000)] The burden of infection with HSV-1 and HSV-2 in England and Wales: implications for the changing epidemiology of genital herpes. *Sex Transm Infect* 76(3), 183-7.
- [Whitley RJ, Levin M, Barton N, et al (1984)] Infections caused by herpes simplex virus in the immunocompromised host: natural history and topical aciclovir therapy. *J Infect Dis* 150(3), 323-9.
- [Wutzler P, Doerr HW, Färber I, et al (2000)] Seroprevalence of herpes simplex virus type 1 and type 2 in selected German populations-relevance for the incidence of genital herpes. *J Med Virol* 61(2), 201-7.
- [Xu F, Lee FK, Morrow RA, et al (2007)] Seroprevalence of herpes simplex virus type 1 in children in the United States. *J Pediatr* 151, 374-7.
- [Yih WK, Brooks DR, Lett SM, et al (2005)] The incidence of varicella and herpes zoster in Massachusetts as measured by the Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing varicella vaccine coverage. 1998-2003. *BMC Public Health* 5, 68.