

**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/002

**Marketing Authorisation Holder:
Novartis Pharma GmbH**

Rapporteur:	Germany
Finalisation procedure (day 120):	08.06.2011
Date of finalisation of PAR	08.06.2011

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">- Herpes zoster- primary and recurrent genital herpes
Pharmaco-therapeutic group (ATC Code):	J05A B09
Pharmaceutical form(s) and strength(s):	Film-coated tablets, 25 mg and 100 mg

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 additional information about paediatric studies. The first Article 46 procedure of this product has been finalized on May 26, 2010.

Now, one study has been submitted in adolescents from 12 to <18 years of age with recurrent herpes labialis.

This study investigated primarily the safety and the pharmacokinetics of the commercially available dosage form, i.e. the 500 mg tablet. Since the study was small and uncontrolled, efficacy was assessed exploratory only.

The study results indicated no major differences in pharmacokinetic characteristics in adolescents as compared with adults. No new safety concerns arose. Symptoms of disease improved and were resolved in most cases by the end of the study.

II. RECOMMENDATION

The data from the submitted studies are considered of interest, however of minor regulatory relevance, as the MAH is not planning to pursue this indication in Europe – neither in adults nor in adolescents.

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. The last cluster of member states received renewal documentations in March 2007.

Beside the first Article 46 procedure also an Article 30 procedure as well as an Article 45 procedure for Famciclovir have been concluded in 2010.

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.

The MAH states that he does not pursue the indication “recurrent Herpes labialis” in adolescents based on the submitted study data, as the scientific support is considered insufficient. Also, the MAH sees no medical need for this, as the indication/population is already addressed by valaciclovir. Moreover, they state that the submitted paediatric study does not influence the benefit risk for Famvir and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Since adolescents can swallow tablets whole, no specific paediatric formulation has been used in this study. The commercially available famciclovir 500 mg tablet was used.

IV.2 Clinical aspects

1. Introduction

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, however not for herpes labialis.

Famciclovir 1500 mg single-dose treatment of recurrent herpes labialis (cold sores) in immunocompetent adults was first approved in the USA in 2006. In a multicenter, randomized, double-blind, placebo-controlled study, single-dose famciclovir significantly reduced the time to healing of vesicular lesions by approximately 2 days vs. placebo (4.4 vs. 6.2 days). This regimen also improved the time to return to normal skin (4.5 days vs. 7.0 days) and reduced the time to resolution of pain and tenderness (1.7 days vs. 2.9 days) vs. placebo.

The current study was required by the United States Food and Drug Administration (FDA) as part of a Pediatric Research Equity Act (PREA) requirement to obtain safety and pharmacokinetic (PK) data in adolescents with recurrent herpes labialis treated with a single 1500 mg dose of famciclovir.

By adolescence, more than 40% of Americans have been infected with HSV-1, and globally, as many as 60% to 90% of adults are seropositive for HSV-1.

Recurrent herpes labialis is a result of reactivation of latent virus in sensory ganglia and its spread to the perioral epithelium. Approximately 20% to 40% of the population experience recurrent herpes labialis. Recurrent outbreaks can have a negative impact on patient quality of life, particularly in young patients with frequent or severe recurrences

The development of herpes labialis lesions progresses rapidly after the onset of symptoms, with HSV titers, lesion size and pain being greatest in the first 24 hours following lesion onset. Most herpes labialis lesions progress from the vesicle stage to the ulcer/soft crust stage within 48 hours, with a hard crust forming by day 2 or 3. Given the early and brief period of viral replication and the rapid evolution of lesions, optimal treatment with antiviral therapy would be within the first 24 hours after the onset of symptoms/lesions, when viral replication is maximal.

Patient-initiated episodic therapy for recurrent herpes labialis is the ideal treatment option and was the strategy followed in recent adult studies in which randomized subjects would self-administer study medication at the onset of their next recurrence (symptoms or lesions).

However, in the current study with the main purpose being the collection of safety and PK data in adolescents with recurrent herpes labialis treated with a single 1500 mg of famciclovir, directly observed therapy within 24 hours of symptoms/lesions onset (i.e. within the therapeutic window) was administered by site personnel.

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 study to evaluate the safety and pharmacokinetics of famciclovir single 1500 mg dose in adolescents with recurrent herpes labialis (CFAM810B2305).

Study centers: USA (10 centers)

Study period: First patient enrolled: 25-Mar-2009

Last patient completed: 02-Jun-2010

Objectives:

The primary objective was to assess the safety and tolerability of a single 1500 mg dose of famciclovir in adolescents with recurrent herpes labialis.

The secondary objective was to evaluate the PK of a single 1500 mg dose of famciclovir in a subgroup of adolescents with recurrent herpes labialis.

The exploratory objectives were to:

- evaluate the time to healing of non-aborted herpes and all herpes labialis lesions (i.e. non-aborted and aborted).
- assess the response to treatment in adolescents with recurrent herpes labialis after administration of a single 1500 mg dose of famciclovir

The study was completed as planned.

Methodology:

This was a multicenter, open-label, single-arm study using a single 1500 mg dose of famciclovir. Approximately 50 eligible adolescents (12 to <18 years of age) with recurrent herpes labialis were treated. At least 8 of these patients were to be asked to participate in the pharmacokinetics (PK) assessment of the famciclovir 1500 mg single-dose treatment. Patient recruitment for both PK patients and the non-PK patients was to be approximately evenly distributed across the age range studied. Adolescents participating in the PK assessment may or may not have had an active recurrent herpes labialis episode at Visit 1, but must have had a documented history of recurrent herpes labialis.

Number of patients:

It was planned to enroll approximately 50 patients, of whom at least 8 were to be included in the PK assessment. A total of 53 patients were enrolled: 10 PK patients (including 1 with active recurrent herpes labialis) and 43 non-PK patients (all with active recurrent herpes labialis). All patients received study medication.

Indication and main criteria for inclusion:

The study population consisted of patients from 12 to <18 years of age and with prodromal symptoms or active lesions suggestive of a recurrent episode of herpes labialis (i.e. having had herpes labialis or cold sores in the past), with onset not exceeding 24 hours until the time of study drug administration.

Adolescents considered for the PK assessment part of the study could be enrolled with onset of signs/symptoms of a recurrent herpes labialis episode longer than 24 hours before study drug administration, or without an active herpes labialis outbreak at the time of enrollment as long as there was a documented history of recurrent herpes labialis. All adolescents participating in the PK part of the study fasted for at

least 8 hours prior to Visit 1 and were willing to fast for an additional 2 hours after study drug administration.

Patients with a history of malabsorption, with severe renal or hepatic deficiency, significant skin disease that would interfere with the oral labial assessment of lesions or with known immunosuppression were excluded from the trial. Use of any immuno-modifying treatment or probenecid, any other antiviral, of steroid products or topical products on the herpes lesions were not allowed after enrollment into the study.

Investigational drug:

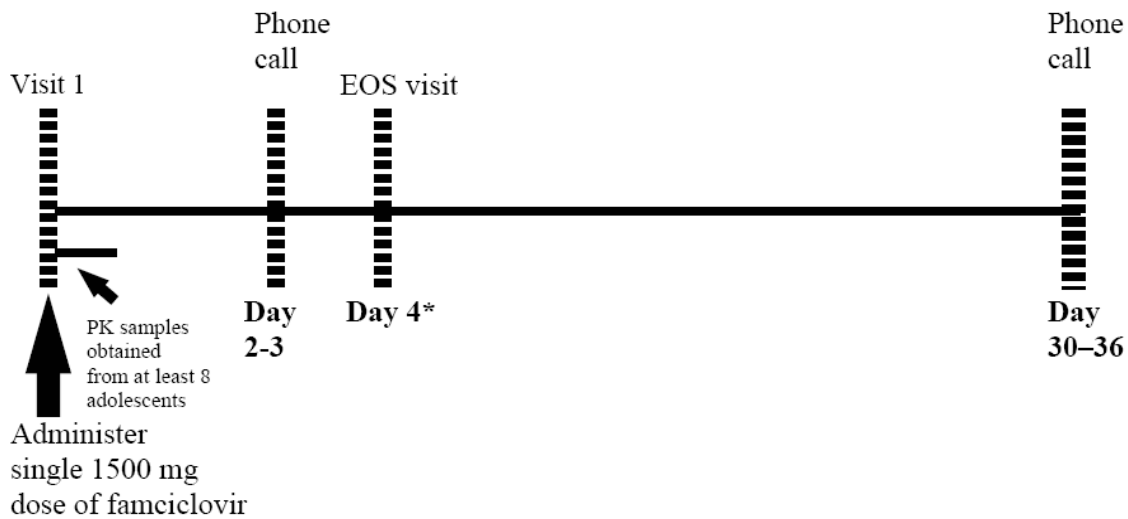
Famciclovir 1500 mg (3 x 500 mg tablets) p.o. The batch and formulation numbers of the famciclovir 500 mg tablets were 09-0006US and 10-0063US, and F0299 and F0302, respectively.

Reference therapy:

No reference therapy was used in this study.

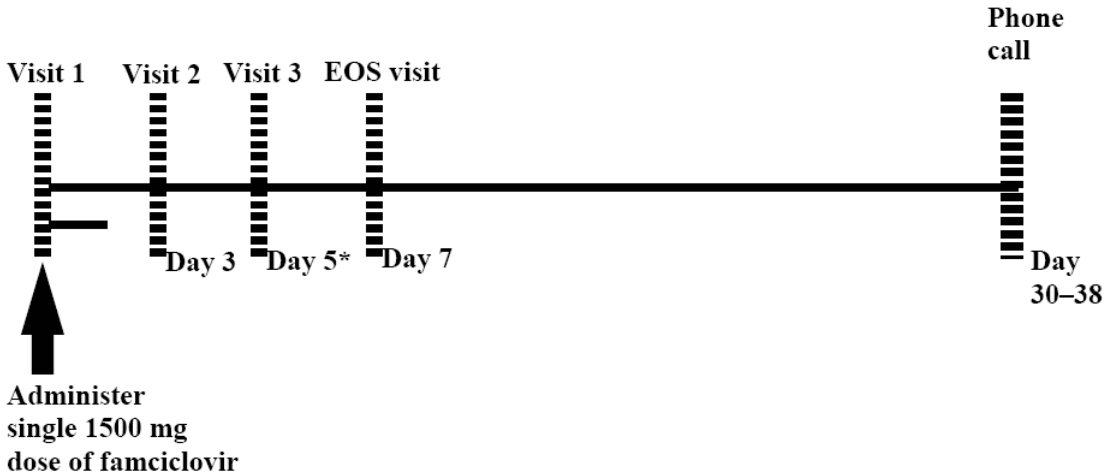
Study design

Figure 01: for PK patients



*Day 4 was targeted, but EOS visit could be conducted on Day 5 or 6 to accommodate the patient's/parent's schedule.

Figure 02: for non-PK patients



*EOS visit could be conducted at Visit 3 if patient was deemed to have confirmed healed lesions. Patient with lesions at Visit 3 continued to complete diary and return on Day 7 for EOS visit.
Window for each scheduled visit was to be within ± 1 day.

Duration of treatment:

1 day treatment with study medication. Patients were then followed at the site up to 7 days. They were contacted approximately 30 days following study drug administration to review safety.

Table 01: Analysis Populations

Analysis population	Famciclovir 1500 mg		
	12 to <15 years N=28 n (%)	15 to <18 years N=25 n (%)	Total N=53 n (%)
Intent-to-treat population (ITT)	28 (100.0)	25 (100.0)	53 (100.0)
Safety population	28 (100.0)	25 (100.0)	53 (100.0)
PK population	4 (14.3)	4 (16.0)	8 (15.1)

Criteria for evaluation

Efficacy (exploratory only): The time to healing of nonaborted herpes and all herpes labialis lesions (i.e. non-aborted and aborted) was evaluated. The response to treatment was also assessed.

Safety: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included assessments of vital signs and monitoring of haematology, clinical chemistry, and urinalyses in non-PK patients.

Pharmacokinetics: Blood samples were collected (1.0 ml) pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6 and 10 hours after dosing. Penciclovir and 6-deoxypenciclovir plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. The limit of quantification for both compounds was 0.15 µg/ml. Plasma concentration-time data were used to calculate the following pharmacokinetic parameters of penciclovir: C_{max} (maximum concentration), t_{max} (time to C_{max}), AUC_{0-tlast} (area under the plasma concentration time curve from 0 up to the last quantifiable concentration), AUC_{0-∞} (AUC up to infinity), t_{1/2} (apparent terminal elimination half-life) and Cl/F (apparent oral clearance).

Statistical methods: The primary objective of the study was to assess the safety and tolerability of a single 1500 mg dose of famciclovir in adolescents with recurrent herpes labialis. The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fell outside of the normal range or/and worsened.

Efficacy results were summarized for the intent-to-treat (ITT) population, which included all patients enrolled into the study. Disease symptoms and lesion stages were summarized using shift tables based on the absence or presence of symptoms and lesions for categories specified in the CRF. For non-PK ITT patients, time-to-healing of non-aborted lesions and all lesions (aborted and non-aborted) was estimated using Kaplan-Meier methods. There was no inferential analysis for efficacy and safety data.

Safety population: All patients who received study drug and had at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. The Safety population was used to summarize the safety data.

Pharmacokinetics (PK) population: All patients who participated in the PK assessment part and who did not miss more than one PK blood sampling. The PK population was used to summarize PK assessments. An interim analysis that covered PK and safety was performed on 10 patients, of whom 8 provided PK data.

Results

Patient disposition and baseline characteristics:

A total of 53 patients were enrolled into the study (Table 02); 43 non-PK patients and 10 PK patients. Two PK patients did not complete the study as they withdrew consent and were replaced in order to have the minimum requirement of number of PK patients. The two withdrawn patients were included in the Safety and ITT populations but were excluded from the PK population.

Table 02: Patient disposition (Safety population)

Disposition Reason	12 to <15 years N=28 n (%)	15 to <18 years N=25 n (%)	Total N=53 n (%)
Completed			
No	2 (7.1)	0	2 (3.8)
Yes	26 (92.9)	25 (100.0)	51 (96.2)
Discontinued			
Subject withdrew consent	2 (7.1)	0	2 (3.8)

Protocol variations were mostly minor and were not regarded as impacting the pk and safety analyses.

Sixty-two percent of the non-PK population was female; in the PK populations 50% were female. More than 80% were Caucasians.

Baseline disease characteristics for the safety, ITT and PK populations are summarized in Table 03. The mean duration of recurrent herpes labialis was 6.55 years.

Table 03: Baseline disease characteristics

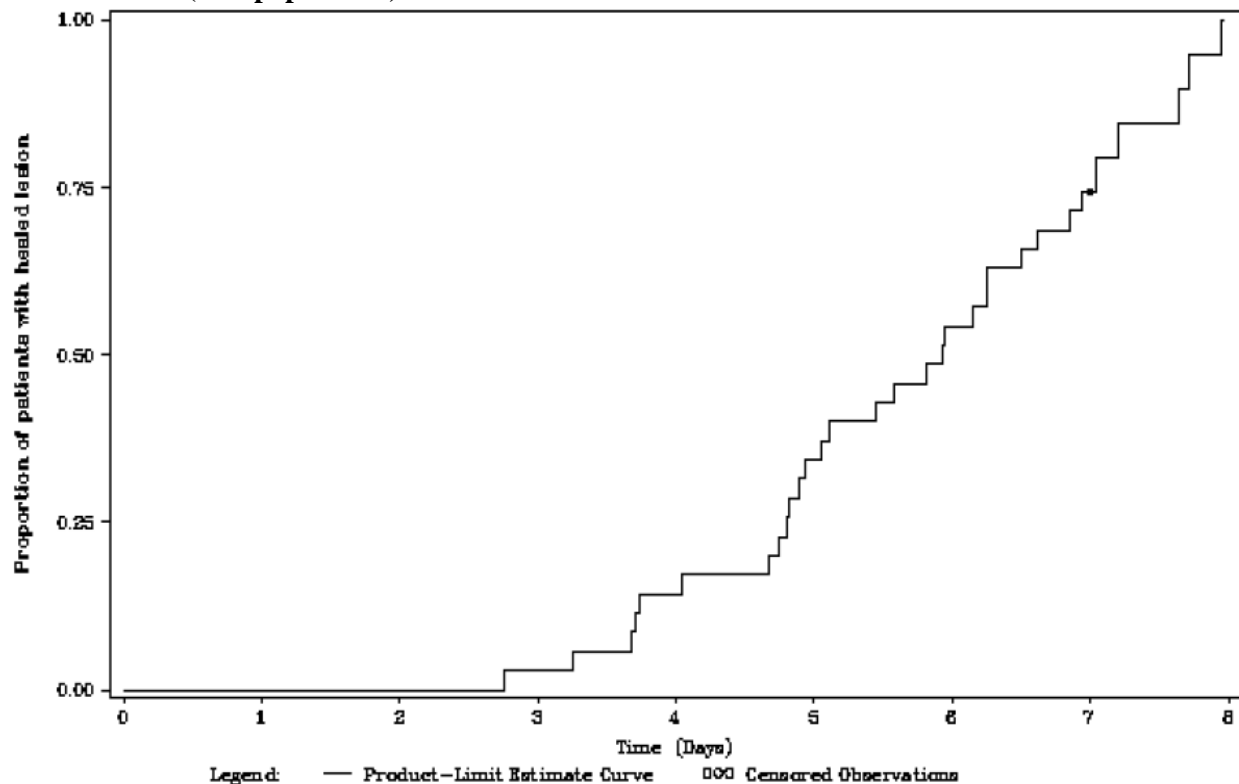
Characteristic Category/Statistic	Famciclovir 1500 mg		
	Safety population N=53	ITT population N=53	PK population N=8
HSV serology - n (%)			
HSV-1	40 (75.5)	40 (75.5)	4 (50.0)
HSV-2	1 (1.9)	1 (1.9)	0
Active herpes labialis - n (%)			
Yes	44 (83.0)	44 (83.0)	1 (12.5)
No	9 (17.0)	9 (17.0)	7 (87.5)
Duration of recurrent herpes labialis (years)			
n	53	53	8
Mean	6.55	6.55	6.04
SD	3.366	3.366	3.068
Median	6.00	6.00	6.00
Q1	4.00	4.00	4.00
Q3	10.00	10.00	8.65
Minimum	1.0	1.0	1.0
Maximum	13.0	13.0	10.0
Number of herpes labialis episodes during the last 12 months			
n	53	53	8
Mean	5.8	5.8	1.5
SD	7.57	7.57	1.31
Median	4.0	4.0	1.0
Q1	2.0	2.0	1.0
Q3	7.0	7.0	2.0
Minimum	0	0	0
Maximum	50	50	4
Previous oral antiherpes therapy - n (%)			
Yes	11 (20.8)	11 (20.8)	0
No	42 (79.2)	42 (79.2)	8 (100.0)

A relevant medical history or current medical condition was reported for 54.7% of patients, the most common (>10.0% of patients) being drug hypersensitivity (17.0% of patients), attention deficit/hyperactivity disorder (15.1% of patients), acne (15.1% of patients) and seasonal allergy (11.3% of patients).

Efficacy (exploratory): The majority of patients in the ITT population with active disease at baseline had symptoms (93.2%), of whom only 4 patients (9.1%) had symptoms at the end of the study. Of the 44 patients with active recurrent herpes labialis at baseline, 43 (97.7%) had an improved disease status compared to baseline, while one patient, a 15-year-old male, had a worsening of disease status.

There were 43 non-PK patients with active recurrent herpes labialis episodes at baseline that were eligible for the Kaplan-Meier time to healing analysis, of whom 8 (18.6%) had aborted lesions. The median time to healing of non-aborted lesions was 5.9 days. For patients with both aborted and nonaborted lesions the median time to healing was 5.1 days.

Figure 03: Kaplan-Meier plot of investigator assessed time to healing of all nonaborted herpes labialis lesions (ITT population)



Kaplan-Meier estimation performed for non-PK ITT patients who had herpes labialis onset within 24 hours before study drug administration.

The investigator assessed time to healing of all non-aborted herpes labialis lesions was estimated using Kaplan-Meier method for non-PK patients having non-aborted lesions.

If a patient dropped out before healing or before being determined as a case with aborted lesions, the time to healing of non-aborted lesions was censored at the last study visit or 7 days, whichever occurred earlier.

Safety: There were no deaths, SAEs, or discontinuations due to AEs during the study. Overall 4 patients (7.5%) had AEs requiring significant additional therapy: headache, upper abdominal pain, dysmenorrhoea, and anaemia. These AEs were mild, not suspected to be study drug related with the exception of headache, and of 1 day duration with the exception of anaemia that was a continuing event.

AEs were reported by 12 patients overall (22.6%) and by a similar proportion of patients in each age group. The most frequent AEs were dizziness (3 patients overall, [5.7%]) and headache (2 patients overall [3.8%]). All dizziness AEs were reported for patients in the 15 to <18 years age group. All other AEs were reported for 1 patient each. AEs were either mild (10 patients overall [18.9%]) or moderate (2 patients overall [3.8%]).

AEs suspected to be related to study medication were reported for 5 patients overall (9.4%). In the 12 to <15 years age group, AEs suspected to be study drug related were headache, pollakisuria, and diarrhoea and were reported by 1 patient each. In the 15 to <18 years age group, suspected AEs were headache and dizziness reported for 1 patient and dizziness reported for another patient. Suspected AEs were mild and no action was taken except for concomitant medication taken by one patient with headache in the 15 to <18 years age group.

There were no unexpected changes in haematology or clinical chemistry parameters. For patients who had normal haematology or clinical chemistry values at baseline, only one patient shifted after the initiation of study drug to a Grade 1 toxicity for serum creatinine. A low proportion of patients had abnormal values for urinalysis after treatment, with no patient shifting to a Grade 3 or 4 toxicity for blood or protein. There were no meaningful changes from baseline in vital signs at the end of the study.

Table 04: Number (%) of patients with AEs by preferred term (Safety population)

	Famciclovir 1500 mg		
	12 to <15 years N=28 n (%)	15 to <18 years N=25 n (%)	Total N=53 n (%)
Patients with at least one AE	6 (21.4)	6 (24.0)	12 (22.6)
Preferred term			
Dizziness	0	3 (12.0)	3 (5.7)
Headache	1 (3.6)	1 (4.0)	2 (3.8)
Abdominal pain upper	1 (3.6)	0	1 (1.9)
Anaemia	0	1 (4.0)	1 (1.9)
Diarrhoea	1 (3.6)	0	1 (1.9)
Dysmenorrhoea	1 (3.6)	0	1 (1.9)
Fatigue	1 (3.6)	0	1 (1.9)
Lymphadenopathy	0	1 (4.0)	1 (1.9)
Nausea	1 (3.6)	0	1 (1.9)
Pollakiuria	1 (3.6)	0	1 (1.9)
Pyuria	0	1 (4.0)	1 (1.9)
Vomiting	1 (3.6)	0	1 (1.9)

Preferred terms are sorted by descending frequency of the total column.

A patient with multiple occurrences of an AE is counted only once in the corresponding AE category.

Pharmacokinetic results: Ten patients were enrolled into the PK part of the study of whom 2 withdrew consent. Therefore PK samples were assessed from 8 patients: 2 in the 12 to <14 years age group, 4 in the 14 to <16 years age group and 2 in the 16 to <18 years age group.

The key PK parameters for penciclovir and 6-deoxypenciclovir in adolescents (12 to <18 years) are presented below. Mean C_{max} for penciclovir was 9.37 µg/ml and mean AUC_{0-∞} was 31.8 (µg/ml)h.

The mean clearance (CL/F) of penciclovir was 38.2 l/h.

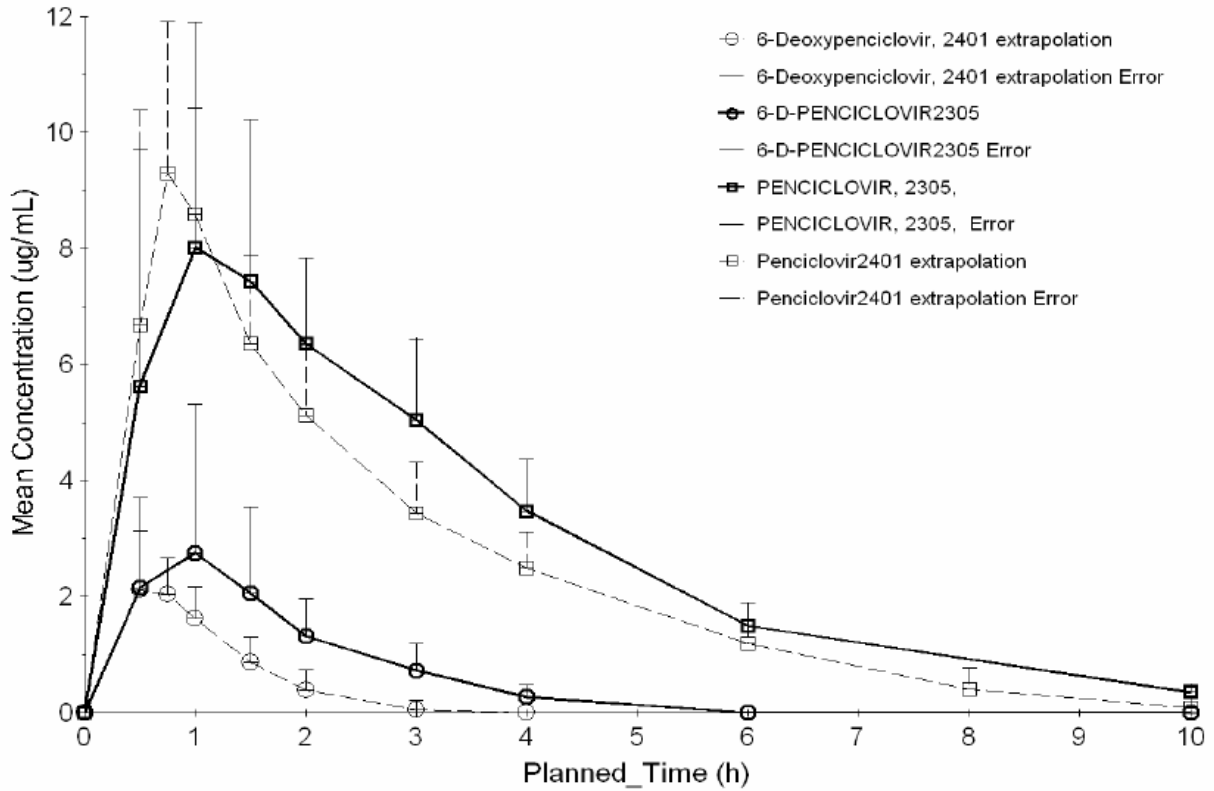
Table 05: Penciclovir PK parameters

Analyte		t _{max} [h]	C _{max} [µg/mL]	AUC _{0-∞} [(µg/mL)h]	t _{1/2} [h]	CL/F [L/h]	CL/F/BW [L/h/kg]
Penciclovir	N	8	8	8	8	8	8
	Mean ¹	1	9.37	31.76	1.81	38.2	0.60
	SD		2.68	5.53	0.22	6.1	0.14
6-Deoxypenciclovir	N	8	8	6	6		
	Mean ¹	1	3.32	6.61	0.78		
	SD		2.36	3.89	0.21		

¹ median for t_{max}

The results for adolescents were compared to those obtained in adult healthy volunteers after a single oral famciclovir dose of 500 mg (Study FAM810A2401). According to the MAH the C_{max} and AUC_{0-∞} values observed for penciclovir in adolescents were within the range of values extrapolated from adults in Study FAM810A2401.

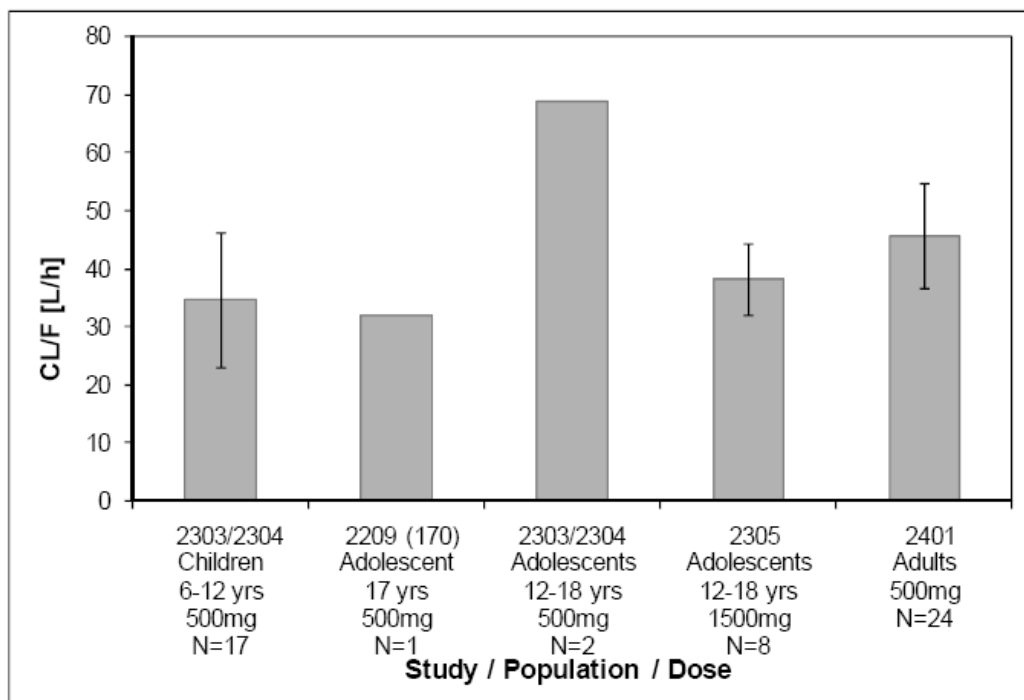
Figure 04: Mean (+/- SD) plasma concentration-time profiles of penciclovir and 6-deoxypenciclovir (BRL42359) in adolescents (12 to <18 years) and comparison to concentration-time profiles extrapolated from Study FAM810A2401 (adults, 500 mg) to a 1500 mg dose



The clearance of penciclovir observed in adolescents (38.2 l/h) was similar to and within the range of values previously measured in adolescents (32.1 l/h [n=1], Study FAM810A2209; 68.8 l/h [mean, n=2], Study FAM810B2303/2304), in adults (45.7 l/h [mean, SD=9 l/h, n=24], Study FAM810A2401) and in children (34.7 l/h [mean, SD=11.6 l/h, n=17], Study FAM810B2303/B2304).

The plasma concentrations of the intermediate metabolite 6-deoxypenciclovir in adolescents were somewhat higher than the extrapolation from Study FAM810A2401 in adults: the mean C_{max} and AUC_{0-∞} values were 1.3- and 2.2-fold higher, respectively, than the extrapolated values. However, exposure to this intermediate metabolite is still much lower than exposure to penciclovir.

Figure 05: Comparison of penciclovir clearance (mean +/- SD) across studies and populations



Conclusions

- A single 1500 mg dose of famciclovir was well-tolerated in adolescent patients 12 to <18 years of age with recurrent herpes labialis. There were no unexpected or new safety findings, with no safety signals indicative of clinically important toxicity of any major organ system. The safety profile in adolescents was similar to that previously described in adults.
- The MAH considered the systemic exposure of adolescents to penciclovir after a single oral 1500 mg dose of famciclovir to be in the range extrapolated from the data for a 500 mg dose in adults. The results suggest that pharmacokinetics of penciclovir in adults and adolescents are dose-linear up to a famciclovir dose of 1500 mg. However, mean values differ between adults and adolescents at almost each timepoint and variability in PK characteristics is high, especially in adolescents. Moreover, the methodology, i.e. the historical comparison of dose normalized data in different patient populations bears considerable limitations, so that the MAH's conclusion that the data in adolescents were in the range of those in adults cannot be fully endorsed. Also, concluding on dose linearity based on these data is considered questionable.

Moreover, the comparison of the penciclovir clearance values encompasses a very limited number of patients for some studies, not permitting a robust comparison in the different populations.

- For patients with active disease, the majority with symptoms at baseline had no symptoms at the end of the study.
- All patients with active recurrent herpes labialis had an improved disease status compared to baseline, except for one with a worsening of disease.
- A total of 8 patients (18.6%) with active recurrent herpes labialis at baseline had aborted lesions. The median time to healing for non-aborted lesions was 5.9 days. No comparisons can be made to historical data for adults due to differences in study design.

Overall conclusion

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

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

As the MAH currently does not intend to apply for a marketing authorisation for herpes labialis in adolescents – and as also the Rapporteur presently does not see a medical need for this product in this indication, no further regulatory action is regarded as necessary.

➤ Recommendation

N/A.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

N/A