

**Rapporteur's
Public Paediatric Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended**

**Famvir
(Famciclovir)**

DE/W/008/pdWS/001

Rapporteur:	Germany
Start of the procedure (day 0):	22.02.2010
Date of this report:	14.05.2010
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):	17.05.2010
Deadline for CMS's comments (day 85):	01.06.2010
Date re-start procedure (day 90):	N/A
Deadline for CMS's comments (day 115):	N/A
End of procedure:	20.07.2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	FAMVIR
INN (or common name) of the active substance(s):	Famciclovir
MAH (s):	Novartis Pharma GmbH
Pharmaco-therapeutic group (ATC Code):	J05A B09
Pharmaceutical form(s) and strength(s):	Film-coated tablets, 125, 250 and 500 mg
Rapporteur's contact person:	Name Durkhani Mangal Tel: +49 228 207 3605 Fax: +49 228 207 3534 Email: paediatric@bfarm.de
Name of the assessor(s):	Pre-Cinical Name: Dr. Angelika Seelbach Tel: +49 228 207 3288 Email: a.seelbach@bfarm.de Clinical Name: Regine Lehnert Tel: +49 228 207 3412 Fax: +49 228 207 3392 Email: rlehnert@bfarm.de

INDEX

I. Executive Summary

II. Recommendation

III. Introduction

IV. Scientific Discussion

IV.1 Information on the pharmaceutical formulation used in the clinical studies

IV.2 Non-clinical aspects

IV.3 Clinical aspects

V. Rapporteur's Overall Conclusion and Recommendation

VI. Request for supplementary information

VII. List of medicinal products and marketing authorisation holders involved

Annex 1

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.2, 5.1 and 5.2.

II. RECOMMENDATION

The SmPC and PL changes resulting from this procedure are detailed in Annex 1. Novartis agreed to include these by a variation to be submitted within three months after the finalization of this Article 45 procedure.

III. INTRODUCTION

One MAH, Novartis, submitted two completed paediatric studies for famciclovir, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for FAMVIR and that there is no consequential regulatory action.

In addition, no further documentation as per the procedural guidance, i.e. a line listing or an annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product has been included:

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

The film-coated tablets containing 125 mg, 250 mg or 500 mg famciclovir as available on the market as well as penciclovir vials for injection 250 mg (developed only for study purposes) were used.

According to the study protocols the tablets were to be taken whole or crushed (the latter only in part 2 of study BRL 42810).

Of note, data on a specific paediatric formulation are assessed in an ongoing Article 46 procedure (“sprinkle gelatine hard capsules”).

IV.2 Non-clinical aspects

1. Introduction

Three non-clinical studies in neonatal or juvenile animals conducted by SmithKline Beecham generally showed no increased sensitivity in juvenile animals compared to adults. While malformations were observed in one study, the same change was not observed in either a study of longer duration nor in a similar study where the active moiety, penciclovir, was administered. The following sub-sections provide an overview of these neonatal and juvenile animal studies and the results.

2. Non clinical studies

1) A study to determine the effects of oral administration on the peri- and post-natal development of the rat (famciclovir);

Study: T89515/4281/R/PO/PPN

➤ Description

Study [T89515/4281/R/PO/PPN] investigated the effects of oral famciclovir administration to pregnant or nursing rats (CrI:CD BR) beginning on Day 15 *post-coitum* and continuing daily until the day before necropsy at weaning on late gestation, parturition, and lactation of the rat and on post-natal development of offspring up to weaning. This study was conducted in compliance with the regulations of Good Laboratory Practice (GLP) at Beecham Pharmaceuticals, Stock, Essex, UK.

➤ Methods

Famciclovir (batch GBD32) was administered to groups of 22 female rats per group at doses of 0, 60, 250, or 1000 mg/kg/day at volume of 10 mL/. Control animals received the vehicle, distilled water. Dams were dosed from Day 15 *post-coitum* until the day before necropsy at weaning. Physical signs and body weights were recorded throughout with food and water consumption measurements during gestation. Females were allowed to deliver their litters and rear their pups to weaning (day 25 *post-partum*) for assessment of offspring growth, survival, and development. Spontaneous activity was measured in offspring at approximately day 27 of age. Macroscopic abnormalities were recorded during *post-mortum* examinations on all females and their offspring.

➤ Results

There were no treatment-related physical signs or mortalities.

Dams: At the high dose, lactation weight gain was significantly lower than in the control group from Day 3 – 21 *post-partum*. The mid dose group showed a modest decrease during days 6 –25 *post-partum*, which was sometimes statistically significant. Water intake was slightly increased from the start of treatment achieving statistical significance between days 15 and 18 *post-coitum* in the mid dose group and through day 20 *post-coitum* in the high dose group. Food intake and gestation length were unaffected by treatment.

Litters: At 1000 mg/kg/day, there was a slight increase in the number of cold, weak, unfed offspring during the first week *post partum*. Post-implant survival and live birth indices were unaffected by treatment. At the high dose, viability was slightly, but statistically significantly, reduced up to day 4 *post-partum* (89.5% compared to 99.3% in control), with only slight reductions thereafter. Offspring body weight gain was slightly reduced at the high dose (statistically significant on majority of occasions) from day 4 *post-partum* up to termination. Sex ratios and the timing of pre-weaning physical and reflexological developments showed no treatment-related trends. There was a treatment-related increase in the incidence of hydrocephaly. The incidence of this abnormality was 2/261, 1/247, and 2/255 at the low, mid, and high doses, respectively. Although the level of this abnormality appears to be low, it was outside the background incidence of a maximum of 1 in a control group and 2 per study, including treatment groups. In addition, other head abnormalities were seen in single or low incidences in all treatment groups. There were no other findings considered to be related to treatment.

➤ Conclusion

Treatment with famciclovir produced maternal toxicity at ≥ 250 mg/kg/day as evidenced by an increase in water intake during gestation and a reduced rate of body weight gain during lactation. In the litters, at 1000 mg/kg/day, there was a slight increase in the number of cold, weak, and unfed offspring during the first week post partum and a reduction in offspring body weight gain; the former correlating with a slight reduction in litter viability.

The slightly increased incidence of adverse physical signs within the litters is suggestive of an effect on the interactions between the dam and offspring, however, these were not sufficiently marked to cause total litter loss at the high dose. Furthermore, in the female fertility and general reproductive performance study with famciclovir (study T89503/42810/R/PO/F+GRP FEMALE) although there was a reduced rate of offspring body weight gain at the high dose (1000 mg/kg) there were no similar effects on the physical signs of the offspring or viability.

At *post mortem* examination head abnormalities, including hydrocephaly, were seen in the offspring at \geq 60 mg/kg. Although there were only single or low incidences an association with treatment cannot be precluded based on these results alone. However, head abnormalities were not seen among F0-F1 offspring in the female fertility and general reproductive performance study (T89503) where females were treated at the same dose levels for a period encompassing and greater than that used in the present study. This difference could be due to pharmacokinetic changes following more prolonged treatment. However, pharmacokinetic investigations (D87033/42810/35) showed no significant changes in plasma concentrations or urinary excretion of famciclovir and its known metabolites following repeated treatment in female rats for a period of time similar to that used in the fertility and general reproductive performance study. Therefore, the absence of malformations in study (T89503), despite longer exposure compared with the present study, suggests that the observations in the present study are more likely to be a chance occurrence than due to treatment.

2) Oral (gavage) investigative neonatal repeat dose study in the rat (famciclovir);

Study: TF-1017/BRL-042810/1

➤ Description

Study [TF-1017/BRL-042810/1] investigated if famciclovir administration to neonatal rats (CrI:CD BR) beginning on Day 4 *post-partum* and continuing daily for 10 weeks showed increased toxicity as compared to adult rats. This study was conducted in compliance with the regulations of Good Laboratory Practice (GLP) at Hazelton Corning Research, under the direction of SmithKline Beecham Pharmaceuticals, Hertfordshire, UK.

➤ Methods

Famciclovir (batch WPK9733) was administered to 16 male and 16 female rats per group at doses of 0, 40, 125, or 400 mg/kg/day. Control animals received the vehicle, distilled water. Treatment was administered on a "split litter" basis, i.e. one pup per sex per litter was allocated to each dose group. An additional 27 litters were dosed at the same dose levels to provide plasma samples on Day 10 *post-partum* for toxicokinetic analysis. Clinical signs, body weights, physical development, number of estrous cycles, haematology, clinical chemistry, urine, and pharmacokinetic parameters were assessed and selected organs were weighed. All study animals were examined at necropsy and selected tissues were either retained in fixative or subjected to histopathologic examination by a pathologist.

➤ Results

There were no treatment-related deaths and no treatment-related clinical observations. Body weight gain was comparable in all groups and there were no toxicologically significant effects on physical development (as assessed by vaginal opening or balano-preputial separation), estrous cycles, ophthalmoscopy, haematology, clinical chemistry, or urine parameters. High dose males had reduced testicular weights which were not accompanied by histopathologic findings. A summary of the toxicokinetic parameters for BRL 39123 (penciclovir, the active moiety) and BRL 42359 (6-deoxy penciclovir, the precursor of penciclovir, formed by deacetylation of famciclovir), derived from composite profiles are listed in Table 2-1.

Table 2-1 Toxicokinetic parameters in neonatal rats

BRL 39123 (penciclovir)						
Dose (mg/kg/day)	C _{max} (µg/mL)			AUC _{0-tlast} (µg.h/mL)		
	Day 10	Day 28	Week 10	Day 10	Day 28	Week 10
40	5.47	4.76	5.37	23.6	4.65	5.97
125	12.4	12.4	11.1	46.2	13.2	18.5
400	26.2	17.8	16.4	125	32.4	49.3
BRL 42359 (6-deoxy penciclovir)						
Dose (mg/kg/day)	C _{max} (µg/mL)			AUC _{0-tlast} (µg.h/mL)		
	Day 10	Day 28	Week 10	Day 10	Day 28	Week 10
40	5.77	2.49	6.32	13.3	1.44	4.34
125	29.2	10.8	23.8	50.9	8.39	21.6
400	77.6	31.6	51.3	238	38.7	81.1

On Days 10 and 28 *post-partum* and in Week 10, famciclovir was absorbed and converted to 6-deoxy penciclovir and penciclovir following oral gavage famciclovir administration of 40, 125, or 400 mg/kg/day to male and female rats. In general, plasma concentrations of the deacetylated metabolite, 6-deoxy penciclovir were higher than those of the (active) moiety, penciclovir, with the exception of those of the 40 and 125 mg/kg/day groups on Day 28. For both C_{max} and AUC, the ratio of 6-deoxy penciclovir to penciclovir increased with dose on all three sampling days. Plasma concentrations of both moieties increased with dose at each sampling time. As dose increased 10-fold from 40 to 400 mg/kg/day, C_{max} and AUC estimates for penciclovir increased between 3- and 5-fold and between 5- and 8-fold, respectively; for 6-deoxy penciclovir, C_{max} values increased between 8- and 13-fold and AUC values increased between 18- and 27-fold. Within each dose level there appeared to be no trend in C_{max} estimates between study days (day 10, Day 28 and Week 10). In general, AUC_{0-tlast} estimates for penciclovir and 6-deoxy penciclovir appeared to decrease substantially between Day 10 and Day 28 *post-partum*, following gavage administration of famciclovir at 40, 125, and 400 mg/kg/day. Subsequently, there was a slight increase in systemic exposure to both compounds between Day 28 *post-partum* and Week 10 of the study.

➤ Conclusion

Famciclovir administered by oral gavage at 40, 125, or 400 mg/kg/day was well tolerated by neonatal rats treated from Day 4 *post-partum* for 10 weeks. Famciclovir was absorbed and converted to 6-deoxy penciclovir and subsequently to penciclovir, the active moiety, when measured on Days 10 and 28 *post-partum* and in Week 10. Plasma concentrations of both moieties and the ratio of 6-deoxy penciclovir to penciclovir increased with dose on each of the three sampling days. Apart from a reduction in testicular weights in high dose males, in the absence of histopathologic changes, there were no toxicologically significant findings. The toxicity of famciclovir was therefore not enhanced in neonatal rats compared to that in adults.

3) A study to determine the effects of intravenous administration on the peri- and post-natal development of the rat (penciclovir);

Study: TF-1006/BRL-039123/2

➤ Description

Study [TF-1006/BRL-039123/2] investigated the effects of intravenous penciclovir administration to pregnant or nursing rats (CrI:CD BR) beginning on Day 15 *post-coitum* and continuing daily until the day before necropsy at weaning on late gestation, parturition, and lactation of the rat and on post-natal development of offspring up to weaning. This study was conducted in compliance with the regulations of Good Laboratory Practice (GLP) SmithKline Beecham Pharmaceuticals, Hertfordshire, UK.

➤ Methods

Penciclovir (BRL 39123A, batch WPB 2001) was administered to groups of 24 female rats per group at doses of 0, 30, 50, or 80 mg (free acid)/kg/day at volume of 10 mL/kg administered at a rate of 3 mL/min. Control animals received the vehicle, 0.9% w/v saline. Dams were dosed from Day 15 *post-coitum* until the day before necropsy at weaning.

Physical signs and body weights were recorded throughout with food and water consumption measurements during gestation. Females were allowed to deliver their litters and rear their pups to weaning (day 25 post partum) for assessment of offspring growth, survival, and development. Spontaneous activity was measured in offspring at approximately day 27 of age. Macroscopic abnormalities were recorded during *post-mortum* examinations on all females and their offspring. Kidney weights were recorded for the dams.

➤ **Results**

There were no treatment-related physical signs or mortalities. At the high dose, gestation weight gain was slightly, but statistically significantly lower than control from the third day of treatment whilst water intake was slightly increased from the start of treatment achieving statistical significance between days 15 and 18 *post-coitum*. Food intake, gestation length, lactation weight change, and terminal kidney weights were unaffected. There were no effects on the offspring.

➤ **Conclusion**

In the rat, penciclovir administered intravenously had no effect on post-natal growth, survival, and development of offspring at maternally toxic doses of up to 80 mg/kg/day administered from day 15 *post-coitum* until weaning.

3. Discussion on non clinical aspects

Three non-clinical studies in neonatal or juvenile animals showed no increased sensitivity in juvenile animals compared to adults. While malformations were observed in one study, the same change was not observed in either a study of longer duration or in a similar study where the active moiety, penciclovir, was administered.

IV.3 Clinical aspects

1. Introduction

The MAH submitted extended synopses and reports for:

- BRL-42810/170: An open, uncontrolled study to assess the safety, pharmacokinetics and preliminary efficacy of penciclovir and famciclovir in immunocompromised paediatric patients. 08th June 1998 to 12th Apr 1999;
- BRL-42810/212: A study to investigate the pharmacokinetics of penciclovir following oral administration of famciclovir to hepatitis B infected children; 13th Oct 1997 to 20th Aug 1999.

2. Clinical studies

BRL-42810/170: An open, uncontrolled study to assess the safety, pharmacokinetics and preliminary efficacy of penciclovir and famciclovir in immunocompromised paediatric patients.

➤ **Description**

Study BRL-042810/170 [Study A2209] was conducted in immunocompromised paediatric patients (aged 2 to 12 years) to investigate the PK of penciclovir following repeat dosing with i.v. penciclovir and/or oral famciclovir, administered as whole tablets, and to evaluate the clinical tolerability to intravenous penciclovir and oral famciclovir. The secondary study objective was to evaluate the preliminary clinical efficacy of i.v. penciclovir and oral famciclovir in immunocompromised paediatric patients with a confirmed or suspected herpes virus infection.

➤ **Methods**

- Objectives

The primary objectives of the study were:

1. To investigate the pharmacokinetics of penciclovir in immunocompromised paediatric patients (aged 2 to 12 years) following repeat dosing with i.v. penciclovir and/or oral famciclovir, administered as whole tablets;
2. To evaluate the clinical tolerability to intravenous penciclovir and oral famciclovir in immunocompromised paediatric patients.

The secondary objective of the study was to evaluate the preliminary clinical efficacy of i.v. penciclovir and oral famciclovir in immunocompromised paediatric patients with a suspected or confirmed herpes virus infection.

- Study design

An open, uncontrolled, repeat dose study at two centres in UK.

- Study population /Sample size

It was planned to recruit 16-24 immunocompromised paediatric patients (oncology or post-bone marrow transplant) from 2 to 12 years of age. Eight to 12 patients were to be enrolled into each of the two age groups: 2-6 y and 7-12 y with the aim to have 6 to 8 evaluable children per age group in each, the i.v. and the p.o. famciclovir group.

- Treatments

Penciclovir (BRL-39123) was supplied in the form of 25 mL clear glass vials, each containing 250 mg of penciclovir as a white to off-white lyophilised plug, which formed a colourless to pale yellow solution when reconstituted.

Famciclovir (BRL-42810) was supplied in the form of 125, 250 or 500 mg white film-coated tablets. Patients were dosed according to body weight. Patients received 5 mg/kg i.v. penciclovir t.i.d.; all doses of penciclovir were infused at a constant rate over a period of 1 hour. The dose of oral famciclovir was 10 mg/kg t.i.d., rounded to the nearest 125 mg. The maximum dose was 15 mg/kg t.i.d. Tablets were administered whole with a minimum of 30 mL of water. Both doses corresponded to recommended doses for treatment of herpes zoster in immunocompromised adults.

Patients were initially treated with penciclovir (5 mg/kg i.v.) three times a day for 5 days or until 48 hours after new lesion formation has ceased, whichever was longer. If, in the opinion of the investigator, there was no satisfactory response to the study medication, an alternative antiviral medication was to be used and the patient was to be withdrawn from the study. Patients changed from i.v. penciclovir to oral treatment with famciclovir when they had responded with a cessation of new lesion formation. Also if, in the opinion of the investigator, patients would have benefitted from oral famciclovir therapy without prior i.v. penciclovir therapy, oral famciclovir was administered. Patients were treated until, in the opinion of the investigator, treatment was no longer necessary, but not before 5 days of oral treatment had been completed.

- Outcomes/endpoints

Pharmacokinetic assessments: Following at least 60 hours of treatment, pharmacokinetic (PK) blood samples were collected pre-dose and at 8 more sampling time points up to 8 h after the first daily dose of each regimen (i.v. penciclovir or oral famciclovir). Plasma concentrations of penciclovir and 6-deoxy penciclovir (BRL 42359, precursor of penciclovir, following oral famciclovir only) were determined by liquid chromatography/tandem mass spectrometry (LC-

MS/MS). The lower limit of quantitation for both compounds was 0.150 µg/mL. Pharmacokinetic parameters were determined using non-compartmental methods.

Safety assessments: Blood and urine samples for haematology, urinalysis and clinical chemistry were collected before any dosing with study medication (Enrolment/Day 1), at predose and each PK assessment day, and at follow-up. Adverse events (AEs) were collected by direct, non-specific questioning/observation before any dosing with study medication, on each PK assessment day (pre-dose, 1, 8 and 24 hours post-dose), and at follow-up. In addition, spontaneous reporting of AEs was encouraged throughout the study.

Efficacy assessments: Time to cessation of acute pain, time to full crusting of all lesions, and time to complete healing were evaluated.

- Statistical Methods

Target sample size: The sample size of 6-8 evaluable children per age group (2-6 y and 7-12y) per treatment regimen (i.v. /p.o.) was based on feasibility.

Pharmacokinetic analysis: PK parameters were to be listed and summarised descriptively by treatment regimen (i.v. penciclovir or whole tablet of famciclovir).

Safety analysis: All patients who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Clinical monitoring and laboratory data were reviewed by the investigator to assess safety, but were not formally analysed. AEs were summarized by i.v. and oral regimen.

Efficacy analysis: The following parameters were to be summarized descriptively:
- time to cessation of acute pain,
- time to full crusting of all lesions,
- time to complete healing.

➤ **Results**

- Recruitment/ Number analysed

The penciclovir 250 mg injection supplies expired and could not be replaced during the study. Recruitment was therefore stopped and the study was closed after a total of 15 patients had been screened and 12 patients (11 patients in the age group 2 to 12 years, one 17-year-old patient) had been enrolled in the study.

Ten patients received i.v. penciclovir 5 mg t.i.d and four patients received oral famciclovir 10 mg/kg t.i.d. Only two subjects received both treatment regimens. A total of eight patients completed the study as planned.

- Baseline data

Key demographic data of these 12 patients are shown in Table 01 below.

A total of six patients were between 2-6 years of age, five patients were between 7 to 12 years of age, and one patient was above the upper age limit in the protocol.

Four subjects were immunocompromised because of bone marrow transplant; three of whom had a previous history acute lymphoblastic leukaemia: Eight subjects were immunocompromised because they were receiving chemotherapy for cancer (five for solid cancers, three for leukaemia).

Table 01: Demographic characteristics of patients enrolled in study BRL-042810/170

Subject Group	Parameter	Age (years)	Weight (kg)	Height (cm)	Sex/Race
2-12 years	N	11	11	1	Male: 3 (27.3%)
	Mean	6	24.7	129	Female: 8 (72.7%)
	SD	3.0	11.83	n/a	White: 11 (100%)
	Range	2-12	12.1-46.2	129-129	
> 12 years	N	1	1	n/d	Male: 1 (100%)
	Mean	17	56.9		Female: 0 (0%)
	SD	n/a	n/a		White: 1 (100%)
	Range	17-17	56.9-56.9		

n/a = not applicable; n/d = not done

- **Pharmacokinetic results**

PK data were available from 9/10 subjects who received i.v. penciclovir and from 2/4 subjects who received oral famciclovir. One of the subjects with evaluable PK data after both treatments was above the upper age limit (12 years); his data are therefore not included in PK summary statistics. Steady-state penciclovir PK parameters following either i.v. infusion of penciclovir or oral administration of famciclovir to immunocompromised children in the protocol defined age range of 2 to 12 years are summarized in table 02.

Table 02: Penciclovir pharmacokinetic parameters following repeat (t.i.d.) i.v. infusion of penciclovir (5 mg/kg) or oral administration of famciclovir (approximately 10 mg/kg t.i.d.) in immunocompromised pediatric patients

Parameter	I.V. penciclovir (N=8)		Oral famciclovir (N=1)
	mean ± SD	(range)	Individual value
C _{max} (µg/mL)	4.55 ± 1.79	(2.55 - 7.41)	2.22
AUC _{0-τ} (µg•h/mL)	10.0 ± 5.7	(3.5 - 19.2)	3.54
t _{1/2} (h)	1.53 ± 0.52	(0.86 - 2.11)	1.30
CL (L/h)	14.4 ± 6.8	(4.3 - 24.5)	35.3 ^a
(L/h/kg)	0.678 ± 0.416	(0.268 - 1.476)	2.02 ^a
V _{ss} (L)	26.9 ± 10.7	(14.0 - 41.3)	ND
(L/kg)	1.17 ± 0.31	(0.87 - 1.79)	

C_{max}: maximum plasma concentration; AUC_{0-τ}: area under the plasma concentration time curve in the dosing interval τ; t_{1/2}: terminal elimination half-life; CL: systemic clearance, V_{ss}: volume of distribution at steady-state; CL and V_{ss} are also listed normalized to body weight; ^a oral clearance = CL/F

Penciclovir PK parameters, following its i.v. infusion, appeared to fall into two distinct subgroups, those individuals with low exposure, and high CL (Group 1) and a second group with higher exposure and lower penciclovir CL estimates (Group 2). Summary (arithmetic mean ± SD (range)) of AUC_{0-τ}, CL and t_{1/2} estimates for the two groups are presented in table 03.

Table 03: Penciclovir pharmacokinetic parameters for the two subgroups of children following repeat (t.i.d.) i.v. infusion of penciclovir (5 mg/kg)

Parameter	Group 1 (N=4)		Group 2 (N=4)	
	mean ± SD	(range)	mean ± SD	(range)
AUC _{0-τ} (µg•h/mL)	5.14 ± 1.13	(3.47 - 5.98)	14.9 ± 3.4	(11.5 - 19.2)
t _{1/2} (h)	1.00 ± 0.14	(0.86 - 1.14)	1.92 ± 0.24	(1.60 - 2.11)
CL (L/h/kg)	1.01 ± 0.32	(0.75 - 1.48)	0.344 ± 0.070	(0.268 - 0.434)

There was a good correlation between CL (and thereby AUC) of penciclovir and creatinine clearance (CL_{cr}) in the majority (7/8) of the children, and this most likely explains the apparent group differences. The group differences were not attributable either to indication [oncology versus bone marrow transplant (BMT)] or age of the child.

Penciclovir volume of distribution (1.2l/kg) exceeded values of total body water. This observation indicated that in children as in adults, penciclovir distributes out of plasma into tissues.

Penciclovir oral bioavailability was estimated to be 88% in the single child who received i.v. penciclovir and oral famciclovir. 6-deoxy penciclovir was quantifiable at three time points in the plasma of this individual following oral famciclovir.

- Safety results:

A total of 19 AEs (20 episodes; one subject experienced two episodes of epistaxis in the same dosing session) were reported by eight subjects within 30 days after dosing with i.v. penciclovir or oral famciclovir and were therefore classified as treatment-emergent AEs (TEAEs). There was one death and one serious non-fatal AE (grand mal convulsion). Neither of these were considered by the investigator to be related to study medication, but were considered by the investigator to be a consequence of the underlying disease.

Apart from the subject who died, there were no subjects withdrawn because of an AE. Almost all AEs were considered by the investigator to be related to the subjects' underlying disease and not to study medication. There was no obvious trend in the type, frequency, relationship or intensity of TEAEs within or between treatment regimens.

Five of the 10 subjects who received i.v. penciclovir 5 mg/kg t.i.d. reported a total of 13 TEAEs. There was one severe TEAE (pulmonary haemorrhage, which resulted in death), four moderate TEAEs and eight mild TEAEs; most were considered to be not related to study medication; the remaining 4/13 TEAEs were considered unlikely to be related to study medication. Three of the four subjects who received oral famciclovir 10 mg/kg t.i.d. reported a total of six TEAEs. Four TEAEs were moderate and two TEAEs were mild in severity; there were no severe TEAEs. The majority of TEAEs were not related to study medication (tables 04 and 05).

Table 04: Treatment emergent Adverse Experiences

Adverse Experience (Preferred Term)	Number of TEAEs	
	I.V. Penciclovir	Oral Famciclovir
Abdominal Pain	1	0
Anaemia	2	0
Constipation	0	1
Convulsions Grand Mal	0	1
Epistaxis	1*	0
Oesophagitis	1	0
Fever	0	2
Hypomagnesaemia	1	0
Melaena	1	0
Pneumonia	1	0
Pulmonary haemorrhage	1	0
Rash maculo-papular	2	0
Renal function abnormal	1	0
SGPT increased	0	1
Vomiting	1	1
Number of Patients with TEAEs	5	3
Number of Patients Exposed	10	4
Total number of TEAEs	13	6

Source: Table DS6

*Although subject 012 experienced epistaxis twice in the same dosing session, this is counted as only one TEAE in this table.

Table 05: Summary of adverse experiences by intensity and relationship to study medication

Relationship & Intensity	Number of Episodes	
	I.V. Penciclovir	Oral Famciclovir
Probable	0	0
Suspected	0	1
Unlikely	4	1
Not related	10*	4
Mild	9*	2
Moderate	4	4
Severe	1	0
Total number of episodes	14*	6
Number of Patients with TEAEs	5	3
Number of Patients Exposed	10	4

Source: Tables DS6 and DS9.

*Table includes one AE (mild epistaxis, not related to study medication) that occurred twice in the same subject (012) in the same dosing session.

There were very few clinically relevant changes in clinical laboratory values during the study. Apart from the increased SGPT in one subject, none were considered to be related to study medication (table 06).

Table 06: Summary of subjects with haematology values of potential clinical concern (PCC)

Parameter	Number of Subjects with Potential Clinical Concern Values				
		Enrolment/ Repeat at enrolment	PK Day Pre-dose Penciclovir 5mg/kg i.v.	Famciclovir 10mg/kg p.o.	Follow-up
Haematology					
Platelets	High	0	0	0	1
	Low	11*	8	2	4
WBC	High	0	1		1
	Low	12*	7	1	7
Haematocrit	Low	5*	4	2	3
Haemoglobin	Low	2	3	1	1
RBC	Low	3	2	1	1
Number of subjects with PCC values		12	9	2	9
Number of subjects with clinical laboratory data		12	10	3	10

Data Source: Table DS16

* Subject 003 had low platelets, low WBC and low haematocrit of potential clinical concern at enrolment and at repeat enrolment, but is only counted once in this table.

Table 07: Subjects who had clinically significant clinical chemistry laboratory values

Subject	Treatment	Parameter	Laboratory Reference Range and Units	Screening	PK Pre-dose	Follow-Up
007	Famciclovir p.o.	ALT	0-39 IU/L	85	672*	108*
010	Penciclovir i.v.	Magnesium	0.65-1.05 mmol/L	0.56	0.45	0.52

Data Source: Tables DS17 and DS18.

* Flagged as being of potential clinical concern.

• Efficacy results:

All 12 patients had clinically diagnosed herpes simplex virus infection and treatment with study medication was started within two days after start of infection. Most lesions were completely healed within 35 days of the first dose of i.v. penciclovir or oral famciclovir (n=10). Limited data (n=3) showed that full crusting of lesions occurred within 11 days of the start of i.v. penciclovir or oral famciclovir treatment and that acute pain from lesions stopped within 6 days of the start of study medication. Pain assessment was hampered by concomitant administration of opioids for pain relief. Also the assessment of crusting was hampered – by the fact that mucous membranes were affected in most subjects.

Conclusions:

- Following i.v. infusion to immunocompromised children (2-12 years), penciclovir was rapidly cleared from plasma with an apparent terminal elimination half-life of about 1-2 hours. Penciclovir volume of distribution was in excess of total body water, indicating significant tissue distribution.
- Overall, penciclovir plasma AUC_{0-τ} was slightly lower in immunocompromised children compared to an historical healthy adult population.
- Intravenous penciclovir and oral famciclovir were generally well tolerated in immunocompromised children with suspected herpes virus infection.
- The limited data do not allow conclusions regarding the clinical efficacy of i.v. penciclovir and oral famciclovir in immunocompromised paediatric patients with a suspected or confirmed herpes virus infection.

Assessor's comments:

Overall, the study design is of – at best - moderate quality, specifying only a few conditions in the protocol and leaving many, relevant, decisions up to the investigator (e.g. type of treatment, i.v./p.o. or its duration). Also, it must be considered dissatisfying and even unethical that the study could not be conducted and completed as planned due to a shortness of study medication. Whereas the limited pk data add at least a little bit of knowledge of the products' use in paediatric patients, the safety assessment is clearly hampered by the uncontrolled, open-label design, especially questioning the validity of the assessment of the "relation to study medication". Least informative, however, is the efficacy assessment, as also acknowledged by the MAH. Indeed, most of the MAH's conclusions can be endorsed. However, data supporting the statement that "Overall, penciclovir plasma AUC_{0-τ} was slightly lower in immunocompromised children compared to an historical healthy adult population" could neither be found in the critical expert overview nor in the study report.

In summary, due to major deficiencies in the study design and conduct, this study adds little knowledge to the use of famciclovir in (immunocompromised) paediatric patients. Some pieces of information on the pk data are proposed to be included in section 5.2 of the SmPC as detailed below.

BRL-42810/212: A study to investigate the pharmacokinetics of penciclovir following oral administration of famciclovir to hepatitis B infected children**➤ Description**

Study BRL-42810/212 [Study A2210] was conducted in hepatitis B infected children to estimate the accumulation of penciclovir following single and repeat dosing of famciclovir, to determine the safety of famciclovir in these patients, and to estimate the effect of crushing famciclovir tablets on the PK of penciclovir.

➤ Methods**Objectives****• Study design**

This study was intended to be comprised of three parts.

Part 1 was an open, safety and tolerability study with a pharmacokinetic profile of penciclovir on day 1 after single dose of famciclovir and day 8 after repeat dosing of famciclovir for 7 days.

Part 2 was an open, randomised, 2-way crossover single dose pharmacokinetic study to compare the bioavailability of penciclovir from crushed tablets with intact famciclovir tablets.

Part 3 was an extension of treatment phases for all patients for one year, and a 5-month follow-up.

• Study population /Sample size

Subjects included male or female children aged 2 to 12 years with chronic hepatitis B who had a hepatitis B surface antigen (HBsAg) positive test within the previous 6 months and a detectable serum HBV DNA at pre-study visit, as determined by conventional hybridisation. Subjects were excluded if they had a history or clinical suspicion of renal dysfunction or were receiving or likely to receive diuretics or were immunocompromised. For Part 1 of the study it was planned that the study population should be comprised of 6 patients aged 2 to 4 years, 6 patients aged 5 to 6 years and 12 patients aged 7 to 12 years (at least 6 patients in this group should have weighed >33.3 kg). For part 3 all patients enrolled into Parts 1 and 2 were eligible for entry into the study.

However, patients who participated in Part 1 were not allowed to participate in Part 2 of the study and vice-versa.

- Treatments

Patients received an oral dose of study medication according to age for 2 to 6 year olds and weight for 7 to 12 year olds according to the following dosing schedule: 2 to 4 years: 125 mg famciclovir (crushed or intact tablet); 5 to 6 years: 250 mg famciclovir (tablet); 7 to 12 years: 250 or 500 mg famciclovir (tablets).

These doses were chosen in order to correspond to the adult dose of 500 mg t.i.d. on a mg/kg basis. In the 7 to 12 year old age group, patients weighing ≤ 33.3 kg received 250 mg doses and those weighing > 33.3 kg received 500 mg.

In part 1, patients received their dose of medication three times daily for eight days.

In part 2 of the study, patients were protocolled to receive a single dose of medication on days one and eight. In part 3 of the study patients received medication three times daily for 12 months. Patients were then followed up for 6 months following the end of treatment.

Outcomes/endpoints

- Primary

1. Estimation of the accumulation of penciclovir following single and repeat dosing of famciclovir in HBV infected paediatric patients and determination of the safety of famciclovir in HBV infected paediatric patients.
2. Estimation of the effect of crushing famciclovir tablets on the pharmacokinetics of penciclovir in HBV infected paediatric patients.
3. Safety.

- Secondary

1. Efficacy by HBV-DNA and other hepatitis markers.

Pharmacokinetic assessments: During part 1 of the study a series of blood samples was collected from each patient up to 8 hours after oral dosing with famciclovir on days 1 (single dose) and 8 (repeat dose). Plasma concentrations of penciclovir and 6-deoxy penciclovir (BRL 42359, precursor of penciclovir) were determined by LC-MS/MS. The lower limit of quantitation for both compounds was 0.150 $\mu\text{g/mL}$. Pharmacokinetic parameters of penciclovir were determined using non-compartmental methods.

Safety assessments: Haematology, clinical chemistry & urinalysis, ECG and blood pressure measurements were done at screening, pre-dose Days 1 and 8 and within 14 days of Day 8 in part 1, and on several occasions (at least monthly) in part 3. Adverse experiences were recorded.

- Statistical Methods

It was protocolled for a statistical evaluation to be performed on the pharmacokinetic data. However, as only 14 patients were recruited to part 1 before the study was closed, instead of the proposed 24 patients, it was decided not to perform a formal statistical evaluation.

➤ **Results**

- Recruitment/ Number analysed

Due to difficulties in recruiting subjects this study was closed before the planned number of patients was enrolled. No subjects were recruited for part 2 of the study. Hence the results presented are from Parts 1 and 3 of the study only.

A total of fourteen patients (5 female and 9 male) completed part 1 of this study and progressed into Part 3. Three children were recruited in the 5-6 year age group and were administered 250 mg t.i.d. famciclovir. Of those over the age of 7 years (n=11), six received 250 mg t.i.d. famciclovir, with the remaining five receiving 500 mg t.i.d. famciclovir. Key demographic data are shown in table 8.

- Baseline data

Table 8: Demographic characteristics of patients in study BRL-42810/212

Parameter	Age (years)	Weight (kg)	Height (cm)	Sex/Race
N	14	14	14	Male: 9 (64%)
Mean	9	30.4	135	Female: 5 (36%)
SD	2.1	10.2	14.6	White: 8 (57%)
Range	6-11	16.0-55.7	116-163	Black: 5 (36%)
				Oriental: 1 (7%)

- Pharmacokinetic results

In general, penciclovir pharmacokinetic parameters estimates were similar following single and repeat (t.i.d.) dosing of famciclovir (250 or 500 mg t.i.d.) to paediatric patients infected with hepatitis B. There was no accumulation of penciclovir after repeated t.i.d. dosing. Pharmacokinetic parameters of penciclovir following single and repeat dose administration of famciclovir are summarised in table 9.

Table 9: Penciclovir pharmacokinetic parameters following administration of famciclovir 250 mg t.i.d. or 500 mg t.i.d. to children with hepatitis B

Parameter	Dose (mg)	Single dose Day 1	Repeat dose Day 8
C_{max} ($\mu\text{g/mL}$)	250 t.i.d.	4.99 ± 1.43^a	4.63 ± 1.51^c
	500 t.i.d.	5.61 ± 2.69^b	5.54 ± 1.72^b
AUC ($\mu\text{g}\cdot\text{h/mL}$)	250 t.i.d.	8.92 ± 1.35^a	8.46 ± 1.32^c
	500 t.i.d.	12.4 ± 2.71^b	11.8 ± 2.24^b
t_{max} (h)	250 t.i.d.	$0.67 (0.25 - 2.00)^a$	$0.75 (0.50 - 1.03)^c$
	500 t.i.d.	$1.08 (0.50 - 1.50)^b$	$0.50 (0.50 - 1.02)^b$
$t_{1/2}$ (h)	250 t.i.d.	1.36 ± 0.32^a	1.57 ± 0.32^c
	500 t.i.d.	1.48 ± 0.18^b	1.66 ± 0.24^d

Mean \pm SD for C_{max} , AUC and $t_{1/2}$, median (range) for t_{max}

C_{max} : maximum plasma concentration; AUC: area under the plasma concentration time curve, i.e. $AUC_{0-\infty}$ (up to infinity) for single dose and $AUC_{0-\tau}$ (in the dosing interval τ) for repeat dose; t_{max} : time to reach C_{max} ; $t_{1/2}$: terminal elimination half-life

^a N=8; ^b N=5; ^c N=9; ^d N=4

Plasma concentrations of 6-deoxy penciclovir were consistently lower than those of penciclovir.

- Safety results

There were no deaths or withdrawals due to adverse events reported during this study. One serious adverse experience was reported pre-study (torsion of the spermatic cord) and two further serious adverse experiences were reported during the study (part 3, 250 mg and 500 mg (Nissens operation and a fall). It was the opinion of the principal investigator that these SAEs were unrelated to the study treatment. A total of forty one adverse events were reported throughout the study which were generally mild or moderate. The most common treatment emergent adverse experiences are summarised in table 10. Ten patients were withdrawn from the study due to insufficient therapeutic effect. No consistent trends, changes or differences between treatment groups were noted for vitals, blood pressure, urinalysis and haematology. Some changes in laboratory data were reported by the investigator as adverse events.

Table 10 Frequently occurring adverse experiences in study BRL-42810/212

Adverse Experience	Part 1 250 mg (n=9 patients)	Part 1 500 mg (n=5 patients)	Part 3 250 mg (n=9 patients)	Part 3 500 mg (n=5 patients)
Elevated ALP	0	0	2	2
Elevated SGPT (ALT)	0	0	2	1
Elevated SGOT (AST)	0	0	2	0
Elevated Hepatic Enzymes	0	0	0	2
Headache	1	1	0	1
Abdominal pain	2	0	1	1
Pharyngitis	0	0	1	1
Pneumonia	0	0	2	0
Upper RTI	0	0	2	0
Albuminuria	0	0	2	0

- Efficacy results

Ten subjects were withdrawn from the study prior to completion due to insufficient therapeutic effect. Efficacy results for the remaining four patients were not reported.

- Conclusions

- Repeated oral dosing of famciclovir (250 or 500 mg t.i.d.) to paediatric patients infected with hepatitis B did not have a notable effect on the pharmacokinetics of penciclovir compared to single dose data. There was no accumulation of penciclovir.
- With the dosing regimens used in this study (250 mg t.i.d. for children aged 5 to 12 years weighing ≤ 33.3 kg or 500 mg t.i.d. for children aged 7 to 12 years weighing > 33.3 kg) penciclovir systemic exposure (AUC) was generally consistent with values reported in adults following 500 mg oral famciclovir.
- Single and repeated oral administration of famciclovir to hepatitis B infected children were generally well tolerated. However 10 subjects were withdrawn from the study prior to completion due to insufficient therapeutic effect. The most commonly observed AEs were alterations in levels of hepatic enzymes. There were three SAEs throughout the study, one of which occurred prior to dosing. The two remaining SAEs were considered unrelated to the study drug.
- Due to difficulties in recruiting subjects this study was closed before the target number of patients was reached. No subjects were recruited for part 2 of the study and therefore the effect of crushing famciclovir tablets was not examined.

Assessor's comments:

Unfortunately, neither in the study report nor in the expert summary a rationale is provided for investigating penciclovir in HBV-infected children. A Medline search undertaken by the assessor, revealed, however, several references (search terms "penciclovir and HBV") for studies in the mid to late 1990s, investigating penciclovir's efficacy in this indication. In vitro data had pointed at an anti-HBV activity of penciclovir. The Medline search indicated that this indication has not been further pursued in the past five years.

Also, this study is of a rather poor quality, especially as major deficiencies in the conduct and analysis of the data have been noted.

Indeed, the most relevant information for the further investigation of famciclovir in children would have been the comparison of the pk parameters of crushed and uncrushed tablets. This comparison, however, has not been performed due to recruitment problems.

Whereas some of the MAH's conclusions can be endorsed, some others are disputable: Data supporting the statement that "With the dosing regimens used in this study (250 mg t.i.d. for children aged 5 to 12 years weighing ≤ 33.3 kg or 500 mg t.i.d. for children aged 7 to 12 years weighing > 33.3 kg) penciclovir systemic exposure (AUC) was generally consistent with values reported in adults following 500 mg oral

famciclovir” could neither be found in the critical expert overview nor in the study report. Also, the assessment of the safety as “generally well tolerated” must be questioned in view of the very limited data and the lack of a control group. Overall, the safety assessment is hampered by the lack of information on the duration of famciclovir treatment, i.e. it is not clear how many doses were administered. No information on the efficacy of famciclovir in HBV infected children is provided. In summary, due to major deficiencies in the study conduct and analysis, this study adds very little knowledge to the use of famciclovir in (HBV-infected) paediatric patients. Some pieces of information on the pk data are proposed to be included in section 5.2 of the SmPC as detailed below.

V. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The submitted study data are of poor quality and do not add relevant information to the use of famciclovir (tablets) in the paediatric population.

Taken together with the data submitted and assessed within the Article 46 procedure, some changes/additions to the SmPC are proposed as detailed in Annex 1 (separate document).

➤ Recommendation

A variation - to be requested from the MAH within three months after finalisation of this procedure.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable.

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form
Austria	Novartis Pharma GmbH Brunner Strasse 59 1235 Wien	Famvir 125 mg – Filmtabletten	125 mg	Film-coated tablets for oral use
Austria	Novartis Pharma GmbH Brunner Strasse 59 1235 Wien	Famvir 250 mg – Filmtabletten	250 mg	Film-coated tablets for oral use
Austria	Novartis Pharma GmbH Brunner Strasse 59 1235 Wien	Famvir 500 mg – Filmtabletten	500 mg	Film-coated tablets for oral use
Cyprus	Demetriades & Papaellinas Ltd 21 Kasou P.O. Box 23490 Nicosia	Famvir	125 mg	Film-coated tablets for oral use
Cyprus	Demetriades & Papaellinas Ltd 21 Kasou P.O. Box 23490 Nicosia	Famvir	250 mg	Film-coated tablets for oral use
Denmark	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø	Famvir	125 mg	Film-coated tablets for oral use
Denmark	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø	Famvir	500 mg	Film-coated tablets for oral use
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo	Famvir	125 mg	Film-coated tablets for oral use
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo	Famvir	250 mg	Film-coated tablets for oral use
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo	Famvir	500 mg	Film-coated tablets for oral use
France	Novartis Pharma S.A.S. 2 - 4, rue Lionel Terray 92500 RUEIL-MALMAISON	Oravir	125 mg	Film-coated tablets for oral use

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form
France	Novartis Pharma S.A.S. 2 - 4, rue Lionel Terray 92500 RUEIL-MALMAISON	Oravir	500 mg	Film-coated tablets for oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg	Famvir 125 mg Filmtabletten	125 mg	Film-coated tablets for oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg	Famvir 250 mg Filmtabletten	250 mg	Film-coated tablets for oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg	Famvir Zoster 250 mg Filmtabletten	250 mg	Film-coated tablets for oral use
Germany	Grünwalder Gesundheitsprodukte GmbH Ruhlandstr. 5 83646 Bad Tölz	Famciclovir- Sandoz 250 mg Filmtabletten	250 mg	Film-coated tablets for oral use
Germany	Grünwalder Gesundheitsprodukte GmbH Ruhlandstr. 5 83646 Bad Tölz	Famciclovir- Sandoz 500 mg Filmtabletten	500 mg	Film-coated tablets for oral use
Germany	Grünwalder Gesundheitsprodukte GmbH Ruhlandstr. 5 83646 Bad Tölz	Famciclovir-SB 250 mg Filmtabletten	250 mg	Film-coated tablets for oral use
Germany	Grünwalder Gesundheitsprodukte GmbH Ruhlandstr. 5 83646 Bad Tölz	Famciclovir-SB Zoster 250 mg Filmtabletten	250 mg	Film-coated tablets for oral use
Greece	Novartis (Hellas) S.A.C.I. 12th Km National Road No. 1 GR-144 51 Metamorphosis	Famvir	125 mg	Film-coated tablets for oral use
Greece	Novartis (Hellas) S.A.C.I. 12th Km National Road No. 1 GR-144 51 Metamorphosis	Famvir	250 mg	Film-coated tablets for oral use
Greece	Novartis (Hellas) S.A.C.I. 12th Km National Road No. 1 GR-144 51 Metamorphosis	Famvir	500 mg	Film-coated tablets for oral use
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Famvir	125 mg	Film-coated tablets for oral use
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Famvir	250 mg	Film-coated tablets for oral use
Iceland	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø Denmark	Famvir	125 mg	Film-coated tablets for oral use

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form
Iceland	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø Denmark	Famvir	500 mg	Film-coated tablets for oral use
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	125 mg	Film-coated tablets for oral use
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	250 mg	Film-coated tablets for oral use
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	750 mg	Film-coated tablets for oral use
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Famvir	125 mg	Film-coated tablets for oral use
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Famvir	250 mg	Film-coated tablets for oral use
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Famvir	500 mg	Film-coated tablets for oral use
Italy	Sandoz S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Famciclovir Sandoz	125 mg	Film-coated tablets for oral use
Italy	Sandoz S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Famciclovir Sandoz	250 mg	Film-coated tablets for oral use
Italy	Sandoz S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Famciclovir Sandoz	500 mg	Film-coated tablets for oral use
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg Germany	Famvir 125 mg Filmtabletten	125 mg	Film-coated tablets for oral use
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg Germany	Famvir 250 mg Filmtabletten	250 mg	Film-coated tablets for oral use

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	Famvir	125 mg	Film-coated tablets for oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley	Famvir	250 mg	Film-coated tablets for oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	Famvir	500 mg	Film-coated tablets for oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	Famvir	750 mg	Film-coated tablets for oral use

Annex 1

SmPC/Labelling/PIL

see separate document (based on the CHMP adopted version, resulting from the Article 30 procedure, April 2010)