OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDA: 20-363 (S-036)
TYPE: Efficacy Supplement (sNDA)
DRUG: Famvir® (Famciclovir)
APPLICANT: Novartis
OCP Division: DCP 4
OND Division: Division of Antiviral Products
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Famvir® (famciclovir) is an orally administered pro-drug of penciclovir. Famvir is indicated for the treatment of acute herpes zoster (shingles), for the treatment or suppression of recurrent episodes of genital herpes in immunocompetent adults, and for the treatment of recurrent episodes of herpes simplex infection in HIV-infected patients. Famvir is available as a tablet formulation in 3 strengths (125 mg, 250 mg, and 500 mg).

In this supplement, the applicant proposed changes to the Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, and Clinical Studies of the package insert to include pediatric information. Further, the approved package insert was converted to the Physicians Labeling Rule (PLR) format. The labeling changes were proposed based on the results of the following three studies:

FAM810B2301:

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 infection.

FAM810B2303:

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.

FAM810B2304:

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.

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in this efficacy supplement. Although the pharmacokinetics of penciclovir in patients in some of the age groups was similar to the pharmacokinetics of penciclovir in adults after

administration of 500 mg, Famvir will not be approved for any indication in patients < 18 years of age because of the following reasons:

HSV

- The efficacy and safety of famciclovir have not been established as suppressive therapy in infants following neonatal HSV infections. In addition, the efficacy cannot be extrapolated from adults to infants because there is no similar disease in adults.
- *Genital herpes:* Clinical information on genital herpes in children is limited. Therefore, efficacy data from adults cannot be extrapolated to children. Further, famciclovir has not been studied in children 1 to < 12 years of age with recurrent genital herpes; none of the children in Study FAM810B2303 had genital herpes.
- *Herpes labialis:* There are no pharmacokinetic and safety data in children to support a famciclovir dose that provides penciclovir systemic exposures comparable to the penciclovir systemic exposures in adults after a single dose administration of 1500 mg.

VZV

- The efficacy and safety of famciclovir for the treatment of chickenpox has not been established in either pediatric or adult patients.
- Famciclovir is approved for treatment of herpes zoster in immunocompetent adult patients. However, extrapolation of efficacy data from adults with herpes zoster to children with chicken pox would not be appropriate. Although chicken pox and herpes zoster are caused by the same virus, the diseases are different.

SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

FAM810B2301

Title

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 infection.

Study Design

The primary objectives of this study were to evaluate the pharmacokinetics of a single dose of famciclovir in infants 1 month to < 1 year of age who are at risk of, or who have herpes simplex virus infection. Eligible patients were assigned to one of the three cohorts according to their age as follows:

Cohort 1: 1 month to < 3 months; approximately 6 patients
Cohort 2: 3 months to < 6 months; approximately 6 patients
Cohort 3: 6 months to < 12 months; approximately 6 patients

Famciclovir sprinkle capsules of 25 mg and 100 mg, were to be opened and the contents were mixed with OraSweet syrup to form a suspension. This suspension was then administered to the patient using the dosing algorithm shown in table 1.

Table 1: Dosing Algorithm in Study FAM810B2301

Weight (kg) (range of weights)	**Dose (mg)**
< 5 (≤4.5)	25
5 (4.6 to 5.4)	25
6 (5.5 to 6.4)	50
7 (6.5 to 7.4)	75
8 (7.5 to 8.4)	100
9 (8.5 to 9.4)	125
10 (9.5 to 10.4)	150
11 (10.5 to 11.4)	175
12-137 (11.5 to 13.4)	200

Famciclovir dose(s) were selected to provide systemic exposure of penciclovir similar to the systemic exposure of penciclovir observed in adults after administration of famciclovir 500 mg.

Results

The applicant enrolled the following patients between the ages of 1 month to < 1 year.

1 month to < 3 months: 8 subjects (pharmacokinetic data from 7)
3 months to < 6 months: 5 subjects (pharmacokinetic data from 5)
6 months to < 1 year: 5 subjects (pharmacokinetic data from 5)

Table 2 shows the pharmacokinetic parameters of penciclovir by pediatric age group.

Table 2: Pharmacokinetic parameters of penciclovir by pediatric 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)
$AUC_{0\text{-}tlast}$ ((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)
$AUC_{0\text{-}6h}$ ((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)

Source: Appendix 16.2.5 – Pharmacokinetics data report, Table 8, 9 and 10

The systemic exposures of penciclovir in patients < 6 months of age were lower as compared to the systemic exposures (C_{max} and AUC) of penciclovir in adults after administration of 500 mg famciclovir (mean C_{max} = 3.3 µg/mL and mean $AUC_{0\text{-}\infty}$ = 8.95 µg*hr/mL). In patients 6-12 months old, the systemic exposures of penciclovir were in the range of systemic exposures of penciclovir previously observed in adults after administration of 500 mg famciclovir.

Conclusion

The efficacy and safety of famciclovir have not been established as suppressive therapy in infants following neonatal HSV infections. In addition, the efficacy cannot be extrapolated from adults to infants because there is no similar disease in adults. Therefore, famciclovir is not recommended for use in infants.

FAM810B2303

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.

Objectives

The primary objectives of the study were to evaluate the safety and tolerability, and pharmacokinetics (PK) of a single dose of famciclovir oral pediatric formulation in children 1 to 12 years of age with herpes simplex virus (HSV) infection. The secondary objectives were to assess patient acceptability of the pediatric formulation.

Study Design

Open label, multiple-dose, single arm study with a two-step design (Part A and Part B). Patients were stratified by age (1to < 2 years, 2 to < 6 years, and 6 to 12 years). In part A, each patient received 12.5 mg/kg single dose of famciclovir with a maximum dose of 500 mg. Patients weighing ≥ 40 kg received a famciclovir dose of 500 mg. In part B, the sponsor revised the doses and developed an 8 step dosing algorithm Table 3 shows the dosing algorithm used in part B of the trial.

Table 3: Dosing Algorithm used in Part B of Trial FAM810B2303

Weight (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

Famciclovir sprinkle capsules of 25 mg and 100 mg, were to be opened and the contents were mixed with OraSweet syrup to form a suspension. This suspension was then administered to the patient. The daily doses ranged from 150 mg b.i.d to 500 mg b.i.d depending on the patient's body weight and were administered for 7 days.

Famciclovir dose(s) were selected to provide systemic exposure of penciclovir similar to the systemic exposure of penciclovir observed in adults after administration of famciclovir 500 mg.

Results

The applicant enrolled the following patients between the ages of 1 year to <18 years.

1 year to < 2 years: 4 patients
2 years to < 6 years: 13 patients
6 years to < 12 years: 8 patients
12 years to < 18 years: 2 patients

The pharmacokinetic data were available from all patients in part A of the trial. Of note, the applicant did not collect the pharmacokinetic data in part B of the trial.

Table 4 shows the mean pharmacokinetic parameters of penciclovir after administration of famciclovir (in Part A of the study) by pediatric age group.

Table 4: Mean pharmacokinetic parameters of penciclovir after administration of Famciclovir (in Part A of the study) by pediatric 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	1.21	1.07	1.00	1.47	0.75
(Range)	(1.00 - 1.50)	(1.00 - 4.03)	(1.00 - 2.07)	(0.97 – 1.97)	(0.5 - 1.50)
C_{max} (µg/mL)					
Mean ± SD	2.84 ± 1.25	2.44 ± 0.94	2.82 ± 0.65	1.89 [a]	3.45 ± 0.82
(Range)	(1.42 - 4.47)	(0.42 - 3.81)	(1.52 - 3.79)	(1.06 - 2.72)	(1.88 - 5.82)
$AUC_{0\text{-tlast}}$ ((µg/mL)•h)					
Mean ± SD	5.73 ± 2.34	5.71 ± 1.75	6.98 ± 1.14	4.81 [a]	8.54 ± 1.70
(Range)	(3.02 - 8.45)	(1.63 - 8.17)	(4.72 - 8.66)	(3.57 - 6.06)	(5.80 - 11.40)
$AUC_{0\text{-}\infty}$ ((µg/mL)•h)					
Mean ± SD	6.17 ± 2.42	6.85 ± 1.55 [b]	8.15 ± 1.01	5.93 [a]	8.94 ± 1.69
(Range)	(3.43 - 8.99)	(3.19 - 9.12) [b]	(6.49 - 9.71)	(4.84 - 7.01)	(6.31 - 11.84)
$t_{1/2}$ (h)					
Mean ± SD	1.09 ± 0.08	1.36 ± 0.20 [b]	1.60 ± 0.25	1.86 [a]	1.89 ± 0.28
(Range)	(1.01 - 1.18)	(1.10 - 1.70) [b]	(1.30 - 2.11)	(1.60 - 2.12)	(1.27 - 2.39)
CL/F (L/h)					
Mean ± SD	20.8 ± 8.5	25.1 ± 4.3 [b]	43.7 ± 9.6	68.8 [a]	45.7 ± 9.0
(Range)	(11.0 - 28.8)	(18.1 - 33.3) [b]	(32.4 - 60.8)	(56.2 - 81.5)	(33.3 - 62.5)
Body weight adjusted dose (mg/kg) [c]					
Mean ± SD	12.7 ± 0.4	12.8 ± 1.7	11.7 ± 1.7	6.6 [a]	6.7 ± 0.8
(Range)	(12.3 - 13.3)	(7.3 - 13.7)	(8.1 - 12.9)	(6.2 - 7.1)	(5.8 - 8.7)

[a] SD not reported since N=2; [b] N=12; [c] Body weight adjusted dose was calculated using the baseline body weights (as summarized in Table 7-4)

Sources: CFAM810B2303: Appendix 8.2, Pharmacokinetics data report, Table 10, Table 11, Table 12 and Table 13.

Healthy adults: Data from study [FAM810A2401] in healthy fasted volunteers (age: 34 ± 7 years) following a single oral dose of famciclovir 500 mg

The results suggest that the mean systemic exposures of penciclovir up to 6 years of age was lower as compared to the systemic exposures (C_{max} and AUC) of penciclovir in adults after administration of 500 mg famciclovir (mean C_{max} = 3.45 μg/mL and mean $AUC_{0-\infty}$ = 8.95 μg*hr/mL). The mean systemic exposures of penciclovir in the 6 to ≤12 years of age cohort was in the range of penciclovir systemic exposures previously observed in adults after administration of 500 mg famciclovir.

Conclusion

There is insufficient data to support the use of famciclovir in children for the treatment of infections due to HSV for the following reasons:

Genital herpes: Clinical information on genital herpes in children is limited. Therefore, efficacy data from adults cannot be extrapolated to children. Further, famciclovir has not been studied in children 1 to <12 years of age with recurrent genital herpes. None of the children in Study CFAM810B2303 had genital herpes.

Herpes labialis: There are no pharmacokinetic and safety data in children to support a famciclovir dose that provides penciclovir systemic exposures comparable to the penciclovir systemic exposures in adults after a single dose administration of 1500 mg.

FAM810B2304

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.

Objectives

The primary objectives of the study were to evaluate the safety and tolerability, and pharmacokinetics (PK) of a single dose of famciclovir oral pediatric formulation in children 1 to 12 years of age with varicella zoster virus (VZV) infection. The secondary objectives were to assess patient acceptability of the pediatric formulation.

Study Design

Open label, multiple-dose, single arm study with a two-step design (Part A and Part B). Patients were stratified by age (1to < 2 years, 2 to < 6 years, and 6 to 12 years). In part A, each patient received 12.5 mg/kg single dose of famciclovir with a maximum dose of 500 mg. Patients weighing ≥ 40 kg received a famciclovir dose of 500 mg. The 12.5 mg/kg dose was selected to provide comparable systemic exposures to the adult dose of 500 mg. In part B, the sponsor revised the doses and developed an 8 step dosing algorithm Table 5 shows the dosing algorithm used in part B of the trial.

Table 5: Dosing Algorithm used in Part B of Trial FAM810B2304

Weight (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

Famciclovir sprinkle capsules of 25 mg and 100 mg, were to be opened and the contents were mixed with OraSweet to form a suspension. This suspension was then administered to the patient. The daily doses ranged from 150 mg t.i.d to 500 mg t.i.d depending on the patient's body weight and were administered for 7 days.

Famciclovir dose(s) were selected to provide systemic exposure of penciclovir similar to the systemic exposure of penciclovir observed in adults after administration of famciclovir 500 mg.

Results

The applicant enrolled the following patients between the ages of 1 year to <12 years:

1 year to < 2 years: 6 patients
2 years to < 6 years: 11 patients
6 years to < 12 years: 9 patients

The pharmacokinetic data were available from all patients in part A of the trial. Of note, the applicant did not collect the pharmacokinetic data in part B of the trial.

Table 6 shows the mean pharmacokinetic parameters of penciclovir after administration of famciclovir (in Part A of the study) by pediatric age group.

Table 6: Mean pharmacokinetic parameters of penciclovir after administration of Famciclovir (in Part A of the study) by pediatric age group.

	Study B2304			Study A2107	Study A2401
	Pediatric age group			Adults	Adults
Parameter	**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)
$AUC_{0\text{-tlast}}$ ((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)
$AUC_{0\text{-}\infty}$ ((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)
Body weight adjusted dose (mg/kg)					
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

The mean penciclovir systemic exposures following 12.5 mg/kg famciclovir in children 1 to < 6 years of age were lower (AUC: ↓18%) than the mean penciclovir exposures in adults after administration of a single 500 mg dose. The mean penciclovir systemic exposures following 12.5 mg/kg famciclovir oral formulation in children 6 to 12 years of age were similar to the mean penciclovir exposures in adults after administration of a single 500 mg dose.

Conclusion

The results of study CFAM810B2304 are not adequate to support the use of famciclovir in patients 1 to < 12 years of age with VZV infection because of the following reasons:

- The efficacy and safety of famciclovir for the treatment of chickenpox has not been established in either pediatric or adult patients.
- Famciclovir is approved for treatment of herpes zoster in immunocompetent adult patients. However, extrapolation of efficacy data from adults with herpes zoster to children with chicken pox would not be appropriate. Although chicken pox and herpes zoster are caused by the same virus, the diseases are different.

Labeling Recommendations

The major labeling revision was the inclusion of the information in the Use in Specific Populations: pediatric use section as follows:

The efficacy and safety of FAMVIR tablets have not been established in pediatric patients. The pharmacokinetic profile and safety of famciclovir experimental granules mixed with OraSweet® were studied in two open-label studies.

Study 1 was a single-dose pharmacokinetic and safety study in infants 1 month to <1 year of age who had an active herpes simplex virus (HSV) infection or who were at risk for HSV infection. Eighteen subjects were enrolled and received a single dose of famciclovir experimental granules mixed with OraSweet® based on the patient's body weight (doses ranged from 25 mg to 175 mg). These doses were selected to provide penciclovir systemic exposures similar to the penciclovir systemic exposures observed in adults after administration of 500 mg famciclovir. The efficacy and safety of famciclovir have not been established as suppressive therapy in infants following neonatal HSV infections. In addition, the efficacy cannot be extrapolated from adults to infants because there is no similar disease in adults. Therefore, famciclovir is not recommended in infants.

Study 2 was an open-label, single-dose pharmacokinetic, multiple-dose safety study of famciclovir experimental granules mixed with OraSweet® in children 1 to <12 years of age with clinically suspected HSV or varicella zoster virus (VZV) infection. Fifty-one subjects were enrolled in the pharmacokinetic part of the study and received a single body weight adjusted dose of famciclovir (doses ranged from 125 mg to 500 mg). These doses were selected to provide penciclovir systemic exposures similar to the penciclovir systemic exposures 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 part of the study. Pharmacokinetic data were not obtained with the revised weight-based dosing algorithm.

A total of 100 patients were enrolled in the multiple-dose safety part of the study; 47 subjects with active or latent HSV infection and 53 subjects with chickenpox. Patients with active or latent HSV infection received famciclovir twice a day for seven days. The daily dose of famciclovir ranged from 150 mg to 500 mg twice daily depending on the patient's body weight. Patients with chickenpox received famciclovir three times daily for seven days. The daily dose of famciclovir ranged from 150 mg to 500 mg three times daily depending on the patient's body weight. The clinical adverse events and laboratory test abnormalities observed in this study were similar to these seen in adults. The available data are insufficient to support the use of famciclovir for the treatment of children with chickenpox or infections due to HSV for the following reasons:

Chickenpox: The efficacy of famciclovir for the treatment of chickenpox has not been established in either pediatric 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 chickenpox would not be appropriate. Although chickenpox and herpes zoster are caused by the same virus, the diseases are different.

Genital herpes: Clinical information on genital herpes in children is limited. Therefore, efficacy data from adults cannot be extrapolated to this population. Further, famciclovir has not been studied in children 1 to <12 years of age with recurrent genital herpes. None of the children in Study 2 had genital herpes.

Herpes labialis: There are no pharmacokinetic and safety data in children to support a famciclovir dose that provides penciclovir systemic exposures comparable to the penciclovir systemic exposures in adults after a single dose administration of 1500 mg.

In addition, the label was converted from the "traditional" format to the PLR format. Therefore, there were several minor editorial changes to the various sections with clinical pharmacology information to avoid redundancy and ensure compliance with the PLR format.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20363	SUPPL-36	NOVARTIS PHARMACEUTICALS CORP	FAMVIR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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12/16/2009

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12/17/2009