CLINICAL REVIEW

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Reviewer Name	Andreas Pikis, M.D.
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Established Name	Famciclovir
Trade Name	FAMVIR
Therapeutic Class	Antiviral
Applicant	Novartis Pharmaceutical Corporation
Priority Designation	P
Formulation	Tablets
Dosing Regimen	Varies with indication
Indication	Treatment of infections caused by HSV-1, HSV-2 or VZV
Intended Population	Children 1 month to < 12 years of age

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This supplemental NDA (sNDA) includes pharmacokinetic and safety data from two pediatric studies conducted in response to the Pediatric Written Request for the use of famciclovir in children < 12 years of age with herpes simplex virus (HSV) or varicella zoster virus (VZV) infections. After a thorough review, the Division of Antiviral Products (DAVP) concluded the submitted data do not support approval of famciclovir for any indication in children < 12 years of age. The Applicant agreed with DAVP's decision not to approve famciclovir for the treatment of HSV or VZV infections in children < 12 years of age. Although famciclovir was not approved for any indication in children < 12 years of age, the "Use in Specific Populations", Pediatric Use subsection of the package insert was modified to include the results of the pediatric studies conducted in response to the Pediatric Written Request. Modifications of the proposed label have been discussed with and agreed upon by the Applicant.

Study 1 was a single-dose pharmacokinetic and safety study in infants 1 month to < 1 year of age who had an active 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. (b) (4) 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 children 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 VZV infection. Fifty-one subjects were enrolled in the pharmacokinetic part of the study and received a single (b) (4) Based on these pharmacokinetic data, 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 patient's body weight. The clinical adverse events and laboratory test abnormalities observed in this study were similar to those seen in adults. The available data are insufficient to support the use of famciclovir for the treatment of chickenpox or infections due to 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.

1.2 Recommendations for Postmarketing Risk Management Activities

No specific Risk Management Activities were requested from the Applicant.

1.3 Recommendations for other Post Marketing Study Commitments

No Phase 4 commitments were requested from the Applicant.

2 Introduction and Regulatory Background

2.1 Product Information

Description: Famciclovir is the orally administered prodrug of the antiviral agent penciclovir. After oral administration, famciclovir is rapidly and extensively converted into the active antiviral compound penciclovir. Penciclovir, as with acyclovir, must be phosphorylated to the triphosphate form in viral infected cells to exercise antiviral activity.

Established name and Trade name: Famciclovir (Famvir®)

Pharmacological class: A nucleoside analogue DNA polymerase inhibitor with antiviral activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and VZV.

Indications, dosing regimens, age groups: Currently, famciclovir is approved for the following indications:

Immunocompetent Adult Patients

- Herpes labialis (cold sores): 1500 mg as a single dose
- Genital herpes
  - Treatment of recurrent episodes: 1 gram twice daily for 1 day
  - Suppressive therapy of recurrent episodes: 250 mg twice daily
- Herpes zoster (shingles): 500 mg every eight hours for 7 days

HIV-Infected Adult Patients (1.2)

- Treatment of recurrent episodes of orolabial or genital herpes: 500 mg twice daily for 7 days

2.2 Currently Available Treatments for Proposed Indications

At present, only three antiviral drugs for the systemic treatment of infections caused by HSV-1, HSV-2, and VZV are approved in the United States. These three drugs are: acyclovir, valacyclovir, and famciclovir. The treatment indications for these drugs are summarized in Table 1.

Table 1. Antiviral drugs for systemic treatment against herpes simplex and varicella-zoster virus infections.[a]

Adult Dosage			
	Drug		
Clinical indication	**Acyclovir**	**Valacyclovir**	**Famciclovir**
Cold sores			
Immunocompetent patients		2 g PO twice a day for 1 day	Single dose of 1.5 g PO
HIV-infected patients			500 mg PO twice daily x 7 days
HSV encephalitis	10 mg/kg i.v. every 8 hours x 10 days[b]		
Mucosal and cutaneous herpes simplex infections in immunocompromised patients	5 mg/kg i.v. every 8 hours x 7 days		
Genital herpes			
Initial episode	200 mg PO five times daily x 7-10 days	1 g PO twice daily x 10 days	
Severe initial episodes	5 mg/kg i.v. every 8 hours x 5days		
Recurrent episodes			
Immunocompetent patients	200 mg five times daily x 5 days	500 mg twice daily x 3 days	1 g PO twice daily x 1 day
HIV-infected patients			500 mg PO twice daily x 7 days
Suppressive therapy			
Immunocompetent patients	400 mg PO twice a day Alternate regimens: 200 mg three times daily or 200 mg five times daily	1 g PO once daily Alternate dose in patients with ≤9 recurrences/yr: 500 mg PO once daily	250 mg PO twice daily
HIV-infected patients (CD4 cell count ≥100 cells/mm^3)		500 mg twice daily	
Reduction of transmission		500 mg once daily	
Herpes zoster			
Immunocompetent patients	800 mg PO five times daily x 7-10 days		500 mg PO three times daily x 7 days
Immunocompromised Patients	10 mg/kg i.v. every 8 hours x 7 days		
Chickenpox			
Immunocompetent patients	800 mg PO four times daily x 5 days		

Pediatric Dosage			
	Drug		
Clinical indication	**Acyclovir**	**Valacyclovir**	**Famciclovir**
Cold sores (≥12 years of age) Immunocompetent patients		2 g PO twice a day for 1 day	
Herpes simplex encephalitis			
≥ 12 years of age	10 mg/kg i.v. every 8 hours x 10 days[c]		
3 months to < 12 years of age	20 mg/kg i.v. every 8 hours x 10 days[d]		
Birth to < 3 months	10 mg/kg i.v. every 8 hours x 10 days[e]		
Mucosal and cutaneous herpes simplex infections in immunocompromised patients			
< 12 years of age	10 mg/kg i.v. every 8 hours x 7 days		
≥ 12 years of age	5 mg/kg i.v. every 8 hours x 7 days		
Genital herpes Severe initial episodes (≥ 12 years of age)	5 mg/kg i.v. every 8 hours x 5 days		
Herpes zoster Immunocompromised patients			
< 12 years of age	20 mg/kg i.v. every 8 hours x 7 days		
≥ 12 years of age	10 mg/kg i.v. every 8 hours x 7 days		
Chickenpox Immunocompetent patients ≥ 2 years of age		20 mg/kg PO three times daily x 5 days (not to exceed 1 gram three times daily)	
and weight ≤40 kg	20 mg/kg per dose PO four times daily x 5 days		
> 40 kg	800 mg PO four times daily x 5 days		

[a]Foscarnet is approved for the treatment of mucocutaneous acyclovir-resistant HSV-infections in immunocompromised patients; [b]In clinical practice patients are treated 14-21 days; [c, d]In clinical practice patients are treated 14-21 days; [e]In clinical practice patients are treated with 20 mg/kg i.v. every 8 hours x 14-21 days

Acyclovir:

Acyclovir is a deoxyguanosine analogue with an acyclic side chain that lacks the 3'-hydroxyl group of natural nucleosides. Acyclovir must be phosphorylated to the triphosphate form in viral infected cells to exercise antiviral activity by inhibiting viral DNA replication. In cells infected with HSV-1, HSV-2, or VZV, acyclovir is initially phosphorylated to acyclovir monophosphate by a virus-specific thymidine kinase. Host cell thymidine kinase is approximately 1 million fold less capable of converting acyclovir to its monophosphate form. Further phosphorylation to the triphosphate form occurs by cellular kinases.

Acyclovir is used for the treatment of HSV- and VZV-infections. Acyclovir is approximately 10 times more potent against HSV-1 and HSV-2 than against VZV. Activity against CMV is limited because CMV does not code for thymidine kinase. Oral acyclovir is effective in the treatment of initial and recurrent episodes of genital herpes and to suppress the frequency of genital HSV recurrences in immunocompetent adults. Oral acyclovir can also be used to treat chickenpox and herpes zoster in immunocompetent patients. Intravenous acyclovir is the drug of choice for treatment of invasive or disseminated HSV infections and HSV- or VZV-infections in immunocompromised patients.

Acyclovir HSV- and VZV-resistance occurs mainly in immunocompromised patients treated with the drug. Despite its widespread use, the development of resistance in immunocompetent patients is not common (<1%). Acyclovir resistance should be suspected if antiviral response is less than anticipated.

Acyclovir is generally well tolerated. Gastrointestinal symptoms, including nausea, abdominal pain, diarrhea, and headache are the most common adverse events. When given intravenously, acyclovir may cause phlebitis and inflammation at sites of infusion or extravasation. Intravenous or oral acyclovir may cause renal failure in elderly patients (with or without reduced renal function), patients with underlying renal disease who receive higher than recommended doses for their level of renal function, patients receiving concomitant nephrotoxic drugs, or inadequately hydrated patients. Intravenous or oral acyclovir may also cause central nervous system adverse events particularly in elderly people and patients with renal impairment. Other adverse events include neutropenia and other signs of bone marrow toxicity and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

Valacyclovir:

As previously stated, valacyclovir is the L-valyl ester of acyclovir. Valacyclovir's mechanism of action, anitiviral spectrum, resistance pattern, and safety profile are the same as those of the parent drug acyclovir. Valacylcovir has some advantages over oral acyclovir because of the better pharmacokinetic profile and more convenient dosing schedule.

Valacyclovir's approved indications for pediatric patients are for herpes labialis (immunocompetent children ≥ 12 years of age) and chickenpox (immunocompetent children ≥ 2 years of age).

Famciclovir:

Famciclovir is the orally administered prodrug of the antiviral agent penciclovir. After oral administration, famciclovir is rapidly converted to penciclovir. Penciclovir, as with acyclovir, must be phosphorylated to the triphosphate form in viral infected cells to exercise antiviral activity.

Famciclovir is currently approved for the treatment or suppression of recurrent episodes of genital herpes in immunocompetent adults. Famciclovir is also used for the treatment of herpes zoster and herpes labialis in immunocompetent adults and for the treatment of orolabial or genital herpes in HIV-infected patients. HSV and VZV strains resistant to acyclovir are generally resistant to famciclovir. Famciclovir is not approved for any use in children.

Famciclovir is generally well tolerated. The most common adverse events are headache, nausea, and diarrhea.

2.3 Availability of Proposed Active Ingredient in the United States

Famciclovir is available in the United States as film-coated tablets as follows: 125 mg in bottles of 30; 250 mg in bottles of 30; 500 mg in bottles of 30 and single unit packages of 50 (intended for institutional use only).

2.4 Presubmission Regulatory Activity

June 1994: Famciclovir was approved by FDA for the treatment of herpes zoster in immunocompetent adult patients.

September 1995: (b) (4)

December 1995: Famciclovir was approved by FDA for the treatment of recurrent genital herpes in immunocompetent adult patients (125 mg twice daily for 5 days).

September 1997: Famciclovir was approved by FDA for suppression of recurrent genital herpes in immunocompetent adults.

June 1998: Famciclovir was approved by FDA for treatment of recurrent mucocutaneous (orolabial or anogenital) herpes simplex infections in HIV-infected adult patients.

(b) (4)

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November 1999: (b) (4) .

September 2001: To obtain needed pediatric information on famciclovir, the FDA issued a formal Written Request, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to submit information from the following three pediatric studies. The reports of the studies were to be submitted to the Agency on or before December 31, 2003.

Study 1: A single-dose pharmacokinetic study in infants and children age one month to five years of age who are receiving suppressive therapy for recurrent episodes of central nervous system (CNS) or skin-eye-mouth disease due to neonatal herpes simplex virus infection.

Study 2: A single-dose pharmacokinetic study of famciclovir in immunocompetent and/or immunocompromised infants and children age 1 to 12 years of age who have HSV infections.

Study 3: A single-dose pharmacokinetic study of famciclovir in immunocompetent and/or immunocompromised infants and children age 1 to 12 years who have varicella-zoster virus (VZV) infections.

December 2003: The Pediatric Written Request was amended to broaden enrollment in Study 1, to convert Study 2 and Study 3 to single-dose pharmacokinetic, multiple-dose safety trials, and to extend the timeframe of submission to December 31, 2006. The modified studies read as follows:

Study 1: A single-dose pharmacokinetic and safety study in infants and children ages one month to less than one year who have a current herpes simplex virus infection or who may have a potential recurrence, or immunocompromised infants who are at risk for development of a herpes simplex virus infection.

Study 2: A multiple-dose safety study with a pharmacokinetic substudy in infants and children ages 1 to 12 years who have HSV infection.

Study 3: A multiple-dose safety study with a pharmacokinetic substudy in infants and children ages 1 to 12 years who have VZV infection.

July 2006: Famciclovir was approved by FDA for a shorter treatment course of recurrent genital herpes in immunocompetent adult patients (specifically, a reduction in course of therapy from famciclovir 125 mg bid for 5 days to 1000 mg bid for 1 day).

Famciclovir was also approved by FDA for the treatment of recurrent herpes labialis in immunocompetent adult patients (a single dose of famciclovir 1500 mg).

August 2006: The Pediatric Written Request was amended to extend the timeframe for submitting study reports to June 30, 2009, to modify the sections "Types of studies" and "Age groups in which studies will be performed and the number of patients to be studied." The modified studies read as follows:

Study 1: A single-dose pharmacokinetic and safety study in infants ages 1 month to < 1 year who have: a current HSV infection, or who may have a potential recurrence, or immunocompromised patients who are at risk for development of a HSV infection.

Study 2: A multiple-dose safety study with a pharmacokinetic substudy in pediatric patients ages 1 to 18 years who have HSVor VZV infection.

April 2007: The Pediatric Written Request was amended to modify the sections "Types of studies" and "Age groups in which studies will be performed and the number of patients to be studied" by eliminating the adolescent cohort from Study 2. The Pediatric Written Request was also amended to modify the pharmacokinetic study endpoints sections and clarify the section "Indication to be studied." The modified studies read as follows:

Study 1: A single-dose pharmacokinetic and safety study in infants ages 1 month to < 1 year who have: a current HSV infection, or who may have a potential recurrence of HSV infection, or immunocompromised patients at risk for development of a HSV infection.

Study 2: A multiple-dose safety study with a single-dose pharmacokinetic substudy in pediatric patients ages 1 to 12 years who have HSV or VZV infection.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Audits by the Division of Scientific Investigations were not requested for this application.

3.2 Compliance with Good Clinical Practices

The Applicant states the studies were conducted according to accepted ethical standards based on the precepts established by the declaration of Helsinki. All studies were conducted with the

approval of Ethics Committees or Institutional Review Boards and Informed Consent was obtained from all subjects.

3.3 Financial Disclosures

In compliance with the rule of Financial Disclosure by Clinical Investigators the Applicant provided financial interest information for all clinical investigators participated in studies FAM810B2301, FAM810B2303, and FAM810B2304. According to the Applicant, the $25,000 threshold for "payments of other sorts" and the $50,000 threshold for equity interest was not exceeded by any investigator.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

(b) (4)

4.2 Preclinical Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with this sNDA. Please refer to the original NDA reviews for background information.

5 Review of Clinical Study Results

5.1 Review Methods

The clinical review is focused on the pharmacokinetic and safety data from the pediatric studies conducted in response to the Pediatric Written Request. The Applicant's conclusions regarding safety (and efficacy when indicated) were confirmed by independent analyses of data. The Medical Officer reviewed study design, patient demographics, adverse events and laboratory abnormalities, pharmacokinetic data and efficacy data when indicated. The safety data were evaluated either with the use of JMP Statistical Discovery software or manually. In this review, tables derived from the Applicant's presentation of the data are cited as to source in the table footnotes, while tables derived from review-generated results are not referenced.

Overview of materials consulted in review: The safety and pharmacokinetic data from all studies were submitted electronically following the common technical document format.

Please also refer to Dr. Vikram Arya's review for more detailed information on the pharmacokinetic data submitted with this sNDA.

5.2 Study Design, Pharmacokinetics, Efficacy, and Safety Results, and Conclusions

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

This is an open-label, single-arm, single-dose, multicenter, pharmacokinetic and safety study of famciclovir oral pediatric formulation in infants. Subjects 1 month to < 1 year of age who had an active herpes simplex virus (HSV) infection or who were at risk for HSV infection were eligible for enrollment. All subjects received a single dose of famciclovir experimental granules mixed with OraSweet® based on the patient's body weight (Table 2). Plasma samples for pharmacokinetic analysis were obtained at 0.5, 1, 2, 4, and 6 hours after dosing. Laboratory samples for safety assessment were obtained at screening and 24 hours after study drug administration.

Table 2. Famciclovir dose.

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
12-13 (11.5 to 13.4)	200

Source: Clinical study report (Study CFAM810B2301) – p. 36

Dose rationale: Famciclovir dose(s) were selected to provide comparable systemic exposure to the adult dose of 500 mg.

A total of 18 infants between 1 month to < 1 year of age who met the inclusion criteria were enrolled in this study. The age distribution of the enrolled subjects was as follows:

Cohort 1: 1 month to < 3 months; 8 subjects (pharmacokinetic data available from 7)
Cohort 2: 3 months to < 6 months; 5 subjects (pharmacokinetic data available from 5)
Cohort 3: 6 months to < 1 year; 5 subjects (pharmacokinetic data available from 5)

Of note, an interim analysis of pharmacokinetic and safety data was performed when 9 subjects were enrolled in the study (1 subject in Cohort 1, 4 subjects in Cohort 2; and 4 subjects in Cohort 3).

Complete pharmacokinetic data are available from 17 of the 18 enrolled subjects and single-dose safety data from all enrolled subjects.

Baseline characteristics and disposition of subjects:
Of the 18 subjects enrolled in this study, 11 (61%) were male. Eight (44%) subjects were white, 5 (28%) were black, 3 (17%) were Native Americans, and 2 (11%) of other race. The ethnicity breakdown was 4 (22%) Hispanic/Latino, 1 (6%) mixed ethnicity, and 13 (72%) of other ethnicity.

Twelve of the 18 (66.7%) subjects had confirmed HSV infection at baseline (most commonly by PCR).Two of the 18 subjects were immunocompromised, 15 subjects were immunocompetent, and 1 subject was of unknown immune status.

Pharmacokinetic results:
Penciclovir exposures after a single body weight adjusted dose (Table 2) of famciclovir experimental granules mixed with OraSweet® as well as the adult historical data after a single 500 mg dose of famciclovir are shown in Table 3. Famciclovir 500 mg twice daily for 7 days is approved for treatment of recurrent episodes of orolabial or genital herpes in HIV-infected adult

patients and famciclovir 500 mg three times daily for 7 days is approved for the treatment of herpes zoster in immunocompetent adult patients.

Table 3. Penciclovir pharmacokinetic parameters following a single body weight adjusted dose of famciclovir oral suspension in infants and after a single 500 mg dose in adults.

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**	**Healthy adults (Study A2401) N=24**
T_{max} (h) Median (range)	1.00 (1.00 – 5.17)	4.00 (1.00 – 4.17	1.02 (0.58 – 1.10)	0.75 (0.5 – 1.50)
C_{max} (µg/mL) Mean ± SD (range)	0.69 ± 0.41 (0.25 – 1.52)	0.74 ± 0.17 (0.51 – 0.98)	3.24 ± 1.01 (1.83 – 4.47)	3.45 ± 0.82 (1.88 – 5.82)
$AUC_{0\text{-}tlast}$ ([µg/mL]•h) Mean ± SD (range)	2.09 ± 1.38 (0.28 – 4.30)	3.16 ± 0.68 (2.36 – 4.12)	8.68 ± 2.09 (5.42 – 11.15)	8.54 ± 1.70 (5.80 – 11.40)
$AUC_{0\text{-}6h}$ ([µg/mL]•h) Mean ± SD (range)	2.22 ± 1.23 (0.71 – 4.30)	3.16 ± 0.68 (2.36 – 4.12)	8.77 ± 2.14 (5.42 – 11.15)	N/A
Body weight adjusted dose (mg/kg) Mean ± SD (range)	6.6 ± 1.4 (4.8 – 8.3)	9.4 ± 2.2 (7.8 – 13.0)	13.5 ± 2.0 (10.9 – 15.8)	6.7 ± 0.8 (5.8 – 8.7)

Source: Clinical study report (Study CFAM810B2301) – p. 58 (modified)

Comments: The pharmacokinetic results in infants 6 months to 12 months of age revealed that the weight-based dose provides comparable systemic exposures to the adult dose of 500 mg famciclovir. However, in infants < 6 months of age penciclovir systemic exposures resulting from the weight-based famciclovir dose were significantly lower (1 to < 3 months, C_{max}: ↓80%, AUC: ↓76% ; 3 to < 6 months, C_{max}: ↓79%, AUC: ↓63%) than penciclovir exposures following the 500 mg dose of famciclovir in adults.

Efficacy results:
Not applicable.

Safety results:
Sixteen of the 18 subjects enrolled in the study received the full dose of study medication. One patient received a dose of 175 mg instead of 200 mg that he was supposed to receive according to the body weight adjusted dose. One patient in the 1 to < 3 month cohort had a significant

emesis after administration of study drug and at the request of patient's mother re-dosing did not occur.

Adverse events: Eight of the 18 (44%) subjects reported at least one adverse event during the study. All but one subject had adverse events mild or moderate in intensity. The most frequently reported adverse events were vomiting (3 subjects, 17%), diarrhea (2 subjects, 11%), pyrexia (2 subjects, 11%), and dehydration (2 subjects, 11%). All other adverse events were experienced by a single subject only.

Only one subject experienced adverse event considered by the investigator to be possibly related to study drug. This was a 1-month old female who had vomiting on Day 1 of the study after receiving the study drug. The event was considered moderate in severity and resolved the same day.

No deaths were reported during the study. One subject experienced serious adverse events. This was a 4-month-old male who had two serious adverse events (dehydration and aggravated condition) reported on Day 2 after receiving a single dose of famciclovir oral suspension for eczema herpeticum. Patient's medical history was significant for atopic dermatitis, macrognathia, impetigo, eczema herpeticum, intermittent fever, flatulence, food allergy, and cardiac arrhythmia. The patient was hospitalized one day after drug administration due to aggravated condition following dehydration. He was treated with intravenous acyclovir. The serious adverse events were resolved after 16 days. These adverse events were considered by the investigator as not related to study drug but due to progression of the underlying disease.

Laboratory abnormalities: Most of the clinical laboratory changes were small and not clinically significant. There was only one patient who exhibited a worsening of 3 grades (abnormal Hgb level) and one patient who exhibited a worsening of 2 grades (abnormal Na^+ level). All other patients who had abnormal laboratory values exhibited a worsening of 1 grade.

Comments: The overall safety profile of oral famciclovir was consistent with that obtained in adults and there were no unexpected safety findings.

Conclusions:

This study was undertaken to provide pharmacokinetic and safety data to support a potential use of famciclovir as suppressive therapy in infants following neonatal HSV infection of the central nervous system or HSV infection limited to the skin, eye, and mouth. 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 children because there is no similar disease in adults. Therefore, famciclovir is not recommended for approval in infants.

Study 2 (Protocols CFAM810B2303 and CFAM810B2304): A multiple-dose safety study with a single-dose pharmacokinetic substudy in pediatric patients ages 1 to 12 years of age who have HSV or VZV infection.

Study 2 of the Pediatric Written Request is a multiple-dose safety study with a single-dose pharmacokinetic substudy in pediatric patients 1 to 12 years of age who have HSV or VZV infection. Of note, the initial Pediatric Written Request was asking for two studies in children 1 to 12 years of age; one in pediatric patients who have HSV infection and the other in pediatric patients who have VZV infection. Because no significant differences were observed in the pharmacokinetic substudy between patients with HSV and VZV infections, the Applicant asked to integrate these two studies into one and the DAVP agreed. For practical purposes, the two protocols will be described separately in this section.

Protocol CFAM810B2303: 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

This is an open-label, single-arm, single-dose pharmacokinetic, multiple-dose safety study of famciclovir oral formulation in children 1 to 12 years of age with active or latent HSV infection. The study consisted of two steps; the pharmacokinetic substudy (Step 1) and the multiple-dose safety study (Step 2):

Step 1: Twenty-five subjects 1 to < 12 years of age were enrolled in the pharmacokinetic section of the study. Each subject received a single oral dose of 12.5 mg/kg of famvir experimental granules mixed with OraSweet® (maximum dose was 500 mg). Plasma samples for pharmacokinetic analysis were obtained at pre-dose and at 1, 2, 3, 4, and 5 hours after dosing. Laboratory samples for safety assessment were not obtained after study drug administration.

Dose rationale: The 12.5 mg/kg dose was selected to provide comparable systemic exposure to the adult dose of 500 mg (famciclovir 500 mg twice daily for 7 days is approved for treatment of recurrent episodes of orolabial or genital herpes in HIV-infected adult patients and famciclovir 500 mg three times daily for 7 days is approved for the treatment of herpes zoster in immunocompetent adult patients).

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A total of 25 subjects 1 to < 12 years of age who met the inclusion criteria were enrolled in the pharmacokinetic section of the study. The age distribution of the enrolled subjects was as follows:
Cohort 1: 1 year to < 2 years, 4 subjects
Cohort 2: 2 years to < 6 years, 13 patients
Cohort 3: 6 years to < 12 years, 8 patients

Pharmacokinetic and safety data are available for all subjects.

Baseline characteristics and disposition of subjects enrolled in Step 1 of the study:
Of the 25 subjects enrolled in this study, 16 (64%) were female. Nine (36%) subjects were white, 13 (52%) were black, and 3 (12%) of other race. The ethnicity breakdown was 7 (28%) Hispanic/Latino, 1 (4%) mixed ethnicity, and 15 (60%) other ethnicity. In two subjects ethnicity was not recorded.

Twelve subjects had a confirmed HSV serology test. The remaining patients were enrolled based on clinical criteria. Twenty-two of the 25 subjects were immunocompetent and the remaining 3 were immunocompromised.

Pharmacokinetic results:
Penciclovir exposures after a single 12.5 mg/kg dose of famciclovir experimental granules mixed with OraSweet® as well as the adult historical data after a single 500 mg dose of famciclovir are shown in Table 4.

Table 4. Penciclovir pharmacokinetic parameters following a single 12.5 mg/kg dose of famciclovir in pediatric patients and after a single 500 mg dose in healthy adults.

Parameter	**Cohort 1 1 to < 2 years N=4**	**Cohort 2 2 to < 6 years N=13**	**Cohort 3 6 to ≤ 12 years N=8**	**Healthy adults (Study A2401) N=24**
T_{max} (h) Median (range)	1.21 (1.00 – 1.50)	1.07 (1.00 – 4.03)	1.00 (1.00 – 2.07)	0.75 (0.5 – 1.50)
C_{max} (µg/mL) Mean ± SD (range)	2.84 ± 1.25 (1.42 – 4.47)	2.44 ± 0.94 (0.42 – 3.81)	2.82 ± 0.65 (1.52 – 3.79)	3.45 ± 0.82 (1.88 – 5.82)
$AUC_{0\text{-}tlast}$ ([µg/mL]•h) Mean ± SD (range)	5.73 ± 2.34 (3.02 – 8.45)	5.71 ± 1.75 (1.63 – 8.17)	6.98 ± 1.14 (4.72 – 8.66)	8.54 ± 1.70 (5.80 – 11.40)
$AUC_{0\text{-}\infty}$ ([µg/mL]•h) Mean ± SD (range)	6.17 ± 2.42 (3.43 – 8.99)	6.85 ± 1.55 (3.19 – 9.12)	8.15 ± 1.01 (6.49 – 9.71)	8.94 ± 1.69 (6.31 – 11.84)
$t_{½}$ (h) Mean ± SD (range)	1.09 ± 0.08 (1.01 – 1.18)	1.36 ± 0.20 (1.10 – 1.70)	1.60 ± 0.25 (1.30 – 2.11)	1.89 ± 0.28 (1.27 – 2.39)
CL/F (L/h) Mean ± SD (range)	20.8 ± 8.5 (11.0 – 28.8)	25.1 ± 4.3 (18.1 – 33.3)	43.7 ± 9.6 (32.4 – 60.8)	45.7 ± 9.0 (33.3 – 62.5)
Body weight adjusted dose (mg/kg) Mean ± SD (range)	12.7 ± 0.4 (12.3 – 13.3)	12.8 ± 1.7 (7.3 – 13.7)	11.7 ± 1.7 (8.1 – 12.9)	6.7 ± 0.8 (5.8 – 8.7)

Source: Clinical study report (study CFAM810B2303) – p. 55 (modified)

Comments: Average penciclovir systemic exposures following 12.5 mg/kg famciclovir oral formulation in children 1 to 12 years of age were lower (C_{max}: ↓18 to 29%, AUC: ↓18 to 33%) than the targeted historical adult exposures resulting from a single 500 mg dose.

Efficacy results:
Not applicable.

Safety results:
A total of 3 (12%) patients had adverse events in the single-dose pharmacokinetic part of the study. All adverse events were mild in severity and resolved the same day (abdominal pain 1, headache 1, and furuncle, rash 1).

Laboratory abnormalities: Blood samples for laboratory safety assessment were not obtained after study drug administration.

Based on the pharmacokinetic results, the Applicant designed a new weight-based dosing algorithm for the Step 2 of the study (multiple-dose safety). The new dosing algorithm is shown in Table 5.

Table 5. Dosing scheme for Step 2.

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

Source: Clinical study report (Study CFAM810B2303) – p. 30)

Step 2: Forty-seven subjects 1 to < 12 years of age with active or latent HSV infection were enrolled in the multiple-dose safety part of the study. Each subject received famciclovir experimental granules mixed with OraSweet® twice daily for seven days. The daily dose of famciclovir ranged from 150 mg to 500 mg twice daily depending on the patient's body weight (Table 5).

Dose rationale: Famciclovir dose(s) were selected based on the single-dose pharmacokinetic data obtained during the first step of the study and were targeting the famciclovir systemic exposure in adults after a single dose administration of 500 mg.

Baseline characteristics and disposition of subjects enrolled in Step 1 of the study:
Of the 47 subjects enrolled in the multiple-dose safety part of the study, 24 (51%) were female. Twenty-one (45%) subjects were white, 10 (21%) were black, 2 (4%) were Asians, and the remaining 14 (30%) of other race. The ethnicity breakdown was 16 (34%) Hispanic/Latino, 2 (4%) mixed ethnicity, 29 (62%) other ethnicity

Only 21 (45%) of the 47 subjects had active HSV disease. Forty-four of the 47 subjects were immunocompetent, 2 were immunocompromised, and 1 of unknown immune status.

Pharmacokinetic results: Pharmacokinetic data were not obtained with the revised weight-based dosing algorithm.

Efficacy results: Efficacy was not the primary objective of this study and was carried out for exploratory purposes. In 19 of the 21 subjects who had active HSV disease at enrollment, symptoms were resolved at the end of the study. For the remaining two patients, the disease was not changed from baseline.

Of note, the Applicant did not provide the specific HSV disease investigated and therefore no comparison could be made with the approved indications in adult patients. This deficiency, coupled with the small number of patients with active HSV disease, does not allow for any conclusion on the efficacy of famciclovir on diseases caused by HSV in children 1 to 12 years of age.

Safety results:

Adverse events: A total of 26 patients (55%) experienced at least one adverse event. The most common adverse events were vomiting (5 patients), diarrhea and headache (4 patients each), nausea and cough (3 patients each) and abdominal pain and pyrexia (2 patients each). All other adverse events occurred in only one patient. All adverse events were mild or moderate in severity.

No deaths or serious adverse events were reported during the study and no subject experienced adverse event leading to premature discontinuation of study drug.

Laboratory abnormalities: No clinically important changes in hematology or chemistry values were observed during the study. Of note, no patient experienced a worsening of 2 or more grades.

Conclusions: There are 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 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 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.

Protocol CFAM810B2304: 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

This is an open-label, single-arm, single-dose pharmacokinetic, multiple-dose safety study of famciclovir oral formulation in children 1 to 12 years of age with VZV infections. The study consisted of two steps; the pharmacokinetic substudy (Step 1) and the multiple-dose safety study (Step 2):

Step 1: Twenty-six subjects 1 to < 12 years of age were enrolled in the pharmacokinetic section of the study. Each subject received a single oral dose of 12.5 mg/kg of famvir experimental granules mixed with OraSweet® (maximum dose was 500 mg). Plasma samples for pharmacokinetic analysis were obtained at pre-dose and at 1, 2, 3, 4, and 5 hours after dosing. Laboratory samples for safety assessment were not obtained after study drug administration.

Dose rationale: The 12.5 mg/kg dose of famciclovir was selected to provide comparable systemic exposure to the adult dose of 500 mg.

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A total of 26 subjects 1 to < 12 years of age who met the inclusion criteria were enrolled in the pharmacokinetic section of the study. The age distribution of the enrolled subjects was as follows:
Cohort 1: 1 year to < 2 years, 6 subjects
Cohort 2: 2 years to < 6 years, 11 patients
Cohort 3: 6 years to < 12 years, 9 patients

Pharmacokinetic and safety data are available for all subjects.

Baseline characteristics and disposition of subjects enrolled in Step 1 of the study:
Of the 26 subjects enrolled in this study, 15 (58%) were male. Four (15%) subjects were white, 2 (8%) were black, 1 (4%) was Asian, and 19 (73%) of other race. The ethnicity breakdown was 16 (61%) Hispanic/Latino, 1 (4%) Chinese, and 9 (35%) other ethnicity.

Five of the enrolled patients had a confirmed VZV test and a clinical picture of chickenpox. The remaining 21 patients were enrolled based only on clinical evidence. All subjects in the pharmacokinetic study were immunocompetent.

Pharmacokinetic results: Penciclovir exposures after a single 12.5 mg/kg dose of famciclovir experimental granules mixed with OraSweet® as well as the adult historical data after a single 500 mg dose of famciclovir are shown in Table 6.

Table 6. Penciclovir pharmacokinetic parameters following a single 12.5 mg/kg dose of famciclovir in pediatric patients with chickenpox and after a single 500 mg dose in healthy adults and adults with herpes zoster.

	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)
$AUC_{0\text{-last}}$ ((µg/mL) h)					
Mean ± SD	7.05 ± 2.48	7.01 ± 1.77	8.88 ± 1.51	8.95 ± 2.03	8.54 ± 1.70
(Range)	(5.24 - 11.97)	(5.53 - 11.85)	(6.66 - 11.41)	(6.50 - 12.27)	(5.80 - 11.40)
$AUC_{0-\infty}$ ((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)

Source: Clinical study report (Study CFAM810B2304) – p. 51

Comments: Penciclovir systemic exposures following 12.5 mg/kg famciclovir oral formulation in children 1 to < 6 years of age were lower (AUC: ↓18%) than the targeted historical adult exposures resulting from a single 500 mg dose.

Penciclovir systemic exposures following 12.5 mg/kg famciclovir oral formulation in children 6 to 12 years of age were similar to the targeted historical adult exposures resulting from a single 500 mg dose.

Efficacy results:
Not applicable.

Safety results:
Adverse events: There were no adverse events reported following the single-dose drug administration of Step 1 of the study.

Laboratory abnormalities: Blood samples for laboratory safety assessment were not obtained.

Based on the pharmacokinetic results, the Applicant designed a new weight-based dosing algorithm for the Step 2 of the study (multiple-dose safety). The new dosing algorithm is shown in Table 5.

Step 2: Fifty-three subjects 1 to < 12 years of age were enrolled in the multiple-dose safety part of the study. Each subject received famciclovir experimental granules mixed with OraSweet® 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 (Table 5).

Dose rationale: Famciclovir dose(s) were selected based on the single-dose pharmacokinetic data obtained during the first step of the study and were targeting the famciclovir systemic exposure in adults after a single dose administration of 500 mg.

Baseline characteristics and disposition of subjects enrolled in Step 1 of the study:
Of the 53 subjects in the multiple-dose safety part of the study, 27 (51%) were male. Thirty-two (60%) subjects were white, and 21 (40%) of other race. All subjects were Hispanic/Latino.

All 53 subjects enrolled in Step 2 of the study had a clinical diagnosis of active chickenpox. Fifty-two of the 53 subjects were immunocompetent and the remaining one of unknown immune status.

Pharmacokinetic results: Pharmacokinetic data were not obtained with the revised weight-based dosing algorithm.

Efficacy results: Efficacy was not the primary objective of this study and was carried out for exploratory purposes. In 49 of the 53 subjects enrolled in the multiples safety part of the study, symptoms were resolved at the end of the study. Disease status was improved in all but one patient. The patient without improvement from baseline did not show any signs of deterioration.

Safety results:
Adverse events: A total of 24 patients (45%) experienced at least one adverse event. The most common adverse events were diarrhea (6 patients, 11%), vomiting (65patients, 9%), pyrexia (4 patients, 8%), and abdominal pain, nausea, cellulitis, headache, pruritus (2 patients each). All other adverse events occurred in only one patient. Adverse events were mild or moderate in intensity.

No deaths or serious adverse events were reported during the study. Two patients experienced adverse events leading to premature discontinuation of study drug. Both patients had moderate abdominal pain lasted for 4 days. These events were considered by the investigators to be related to study medication.

Laboratory abnormalities: The laboratory changes observed in this study were not clinically significant. There was only one patient who experienced a worsening of 2 grades. This patient

had normal Na^+ levels at baseline and shifted to Grade 2 on Day 2. This patient had also abnormal transaminases at baseline.

Conclusions:
The pharmacokinetic and safety data obtained in Study CFAM810B2304 are not adequate to support the use of famciclovir in pediatric patients 1 to < 12 years of age with chickenpox for the following reasons.

- The efficacy and safety of famciclovir for the treatment of chickenpox have 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 chickenpox is not possible. Although chickenpox and herpes zoster are caused by the same virus, the diseases are different.

6 Overall Assessment

6.1 Conclusions

Pediatric use information for many of the approved drugs, including antiviral drugs against HSV and VZV, is needed. Children have fewer therapeutic options than adults due to lack of pediatric formulations and information to guide clinicians in dosing children.

This supplement includes pharmacokinetic and safety data from two pediatric studies conducted in response to the Pediatric Written Request for the use of famciclovir in children < 12 years of age with HSV or VZV infections. After a thorough review, the DAVP concluded the submitted data do not support approval of famciclovir for any indication in children < 12 years of age. The Applicant agreed with DAVP's decision not to approve famciclovir for the treatment of HSV or VZV infections in children < 12 years of age. Although famciclovir was not approved for any indication in children < 12 years of age, the "Use in Specific Populations", Pediatric Use subsection of the package insert was modified to include the results of the pediatric studies conducted in response to the Pediatric Written Request. Modifications of the proposed label have been discussed with and agreed upon by the Applicant.

Study 1 was a single-dose pharmacokinetic and safety study in infants 1 month to < 1 year of age who had an active 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. (b) (4)

(b) (4). 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 children 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 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. (b) (4) Based on these pharmacokinetic data, 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 patient's body weight. The clinical adverse events and laboratory test abnormalities observed in this study were similar to those seen in adults. The available data are insufficient to support the use of famciclovir for the treatment of chickenpox or infections due to 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.

6.2 Labeling Review

The proposed label submitted with this sNDA has been reviewed by all disciplines involved in the review. Modifications of the proposed label have been discussed with and agreed upon by the

Applicant. The major changes in the modified label involve the section of "Use in specific populations."

USE IN SPECIFIC POPULATIONS

The following was added under the subsection of Pediatric Use:

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.

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

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/s/

ANDREAS PIKIS
12/23/2009

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12/23/2009