

## CLINICAL REVIEW

Application Type 20-487  
Submission Number 014 (b) (4)  
Submission Code SE5

Letter Date December 10, 2007  
Stamp Date December 10, 2007  
PDUFA Goal Date September 10, 2008

Reviewer Name Andreas Pikis, M.D.  
Review Completion Date August 25, 2008

Established Name Valacyclovir  
Trade Name VALTREX  
Therapeutic Class Antiviral  
Applicant GlaxoSmithKline

Priority Designation P

Formulation Caplets: 500 mg, 1 g  
Dosing Regimen Varies with indication  
Indication Treatment of infections caused by  
(b) (4) VZV  
Intended Population Children 1 to <18 years of age

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

This supplemental NDA (sNDA) includes safety and pharmacokinetic data from three pediatric studies conducted in response to the Pediatric Written Request for use of Valtrex in children with HSV or VZV infections. Based on these studies, the Applicant seeks approval for Valtrex for (b) (4) chickenpox (NDA 20487/SE-014) in children (b) (4) to < 12 years of age. (b) (4)

(b) (4)

Although the projected mean daily acyclovir exposures following valacyclovir oral suspension 10 mg/kg every 12 hours in children did not meet the targeted adult historical exposures from valacyclovir 500 mg twice daily, the mean acyclovir exposures in children were comparable to historical data in adults receiving oral acyclovir 200 mg five times daily (an approved dose for the treatment of recurrent genital herpes in adults). However, clinical information on recurrent genital herpes in young children is limited; therefore, extrapolating efficacy data from adults to this population is not possible. Moreover, valacyclovir has not been studied in children 1 to < 12 years of age with recurrent genital herpes. None of the children enrolled in Study HS210915 had genital herpes.

(b) (4)

The pharmacokinetic and safety data submitted in NDA 20-487/SE014, together with the previous demonstration of efficacy in pediatric patients with chickenpox treated with acyclovir, support the approval of Valtrex for the treatment of chickenpox in immunocompetent children 2 to < 12 years of age. However, on May 2, 2008 the Applicant submitted for review pharmacokinetic data to support approval of valacyclovir for the treatment of chickenpox for children 12 to < 18 years of age. The Applicant and the Division agreed the May 2, 2008 submission is a major amendment and the Division decided to extend the review clock for three months for NDA 20-487/SE014 in order to review the submitted data. Therefore, no regulatory action was taken on June 10, 2008 for the use of valacyclovir in children for the treatment of chickenpox. In addition, it was agreed that the Applicant would submit safety information from

previously conducted clinical trials with acyclovir and valacyclovir to justify dosing in children 12 to < 18 years of age with chickenpox. The additional safety data were submitted on July 23, 2008.

The interpolated pharmacokinetic data from existing pharmacokinetic data from children < 12 years of age and pharmacokinetic data from adults, together with safety data from previously conducted trials with acyclovir and valacyclovir, support the approval of Valtrex for the treatment of chickenpox in immunocompetent children 12 to < 18 years of age. An addendum to this review was added summarizing the data submitted to justify valacyclovir dosing in children 12 to < 18 years of age for the treatment of chickenpox.

The submitted pharmacokinetic and safety data from the three pediatric studies fulfilled the intent and requirements of the Pediatric Written Request; therefore, exclusivity was granted by the Pediatric Exclusivity Board on February 26, 2008.

The overall safety profile of valacyclovir in children appears similar to that observed in adults. No new or unexpected safety findings were observed.

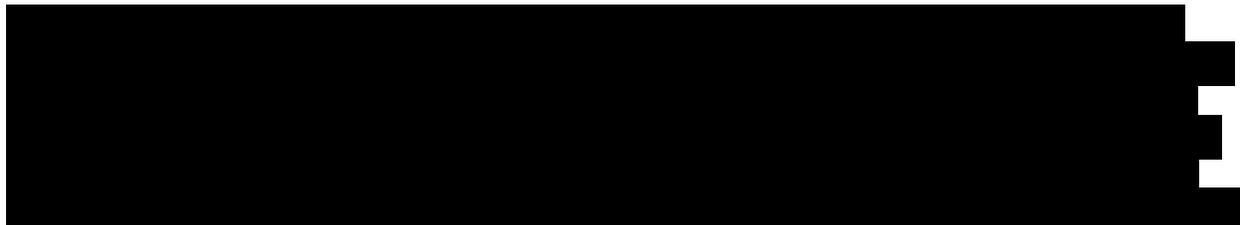
## **1.2 Recommendation on Postmarketing Actions**

### **1.2.1 Risk Management Activity**

No specific Risk Management Activities were requested from the Applicant.

### **1.2.2 Required Phase 4 Commitments**

(b) (4)



(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4) [Redacted]

[Redacted]

The Pediatric Review Committee agreed with Applicant's justification studies in children < 2 years of age with chickenpox are not feasible because the disease is rare in this age group. The Division will waive the pediatric study requirement for the treatment of chickenpox for this age group. (b) (4) [Redacted]

(b) (4)

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• (b) (4)

- The current sNDA triggers PREA for the indication of chickenpox.
- Approval of valacyclovir for the treatment of chickenpox in children 12 to < 18 years of age could be based on the interpolation of pharmacokinetic data from known pharmacokinetic data in adults and existing pediatric data with provided scientific justification for this approach. In addition, if the Applicant believes safety data for this indication are not needed, they must justify their decision on the totality of the safety experience in adults and children receiving valacyclovir and its parent drug acyclovir.

The above comments were conveyed to the Applicant during a teleconference held on June 6, 2008. The Applicant and the Division agreed the data included in the May 2, 2008 submission (NDA 200-487/SE5-014 (b) (4) ) summarizing the pharmacokinetic rationale for dosing children 12 to < 18 years of age is a major amendment and they decided to extend the review clock for three months for NDA 20-487/SE014 in order to review the submitted data. Therefore, no regulatory action will be taken at this time for the use of valacyclovir in children for the treatment of chickenpox. The Applicant also agreed to submit within a month safety data supporting the use of valacyclovir for children 12 to < 18 years of age with chickenpox.

(b) (4)

### 1.2.3 Other Phase 4 Requests

Aside from those listed in the previous section, no other Phase 4 commitments are requested from the Applicant.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Description: Valacyclovir is the L-valyl ester of acyclovir. After oral administration, valacyclovir is rapidly and extensively hydrolyzed by gastrointestinal and liver esterases into acyclovir and the essential amino acid valine. Its mechanism of action, antiviral spectrum, resistance pattern, and safety profile are the same as those of its parent drug acyclovir (see Section 2.2). The bioavailability of valacyclovir is three to five times greater than that of acyclovir. The concentration-time curve for valacyclovir administered orally as 1 gram 3 times daily is similar to that for acyclovir given as 5 mg/kg intravenously every 8 hours. In clinical practice, valacyclovir is preferable than oral acyclovir because of valacyclovir's better pharmacokinetics and more convenient schedule.

Established name and Trade name: Valacyclovir (Valtrex®)

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, valacyclovir is approved for the following indications:

#### Adults

- Cold Sores (Herpes labialis): 2 grams twice daily for 1 day
- Genital Herpes
  - Treatment in immunocompetent patients (initial or recurrent episode)
    - Initial episode: 1 gram twice daily for 10 days
    - Recurrent episodes: 500 mg twice daily for 3 days
  - Suppression in immunocompetent or HIV-infected patients
    - Immunocompetent patients: 1 gram once daily (alternate dose in immunocompetent adults with  $\leq 9$  recurrences/year: 500 mg once daily)
    - HIV-infected patients (CD4 count  $\geq 100$  cells/mm<sup>3</sup>): 500 mg twice daily
  - Reduction of transmission : 500 mg once daily
- Herpes Zoster: 1 gram three times daily for 7 days

#### Children

- Cold Sores (Herpes labialis) for children  $\geq 12$  years of age: 2 grams twice daily for 1 day

The proposed indications in this supplement are for treatment of chickenpox (b) (4)

(b) (4) in children 6 to < 12 years of age. The proposed dosing regimens are:

- Chickenpox: 20 mg/kg three times daily x 5 days
- (b) (4)

## 2.2 Currently Available Treatment for Indications

At present, only three antiviral drugs for the systemic treatment of infections caused by herpes simplex virus types 1 (HSV-1), 2 (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.

<b>Adult Dosage</b>			
<b>Clinical indication</b>	<b>Drug</b>		
	<b>Acyclovir</b>	<b>Valacyclovir</b>	<b>Famciclovir</b>
<b>Cold sores</b> Immunocompetent patients  HIV-infected patients		2 g PO twice a day for 1 day	Single dose of 1.5 g PO  500 mg PO twice daily x 7 days
<b>HSV encephalitis</b>	10 mg/kg i.v. every 8 hours x 10 days <sup>a</sup>		
<b>Mucosal and cutaneous herpes simplex infections in immunocompromised patients</b>	5 mg/kg i.v. every 8 hours x 7 days		
<b>Genital herpes</b>			
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 5 days		
Recurrent episodes Immunocompetent patients  HIV-infected patients	200 mg five times daily x 5 days	500 mg twice daily x 3 days	1 g PO twice daily x 1 day  500 mg PO twice daily x 7 days
Suppressive therapy Immunocompetent patients  HIV-infected patients (CD4 cell count $\geq 100$ cells/mm <sup>3</sup> )	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 $\leq 9$ recurrences/yr: 500 mg PO once daily  500 mg twice daily	250 mg PO twice daily
Reduction of transmission		500 mg once daily	
<b>Herpes zoster</b> Immunocompetent patients  Immunocompromised Patients	800 mg PO five times daily x 7-10 days  10 mg/kg i.v. every 8 hours x 7 days		500 mg PO three times daily x 7 days
<b>Chickenpox</b> Immunocompetent patients	800 mg PO four times daily x 5 days		

<b>Pediatric Dosage</b>			
<b>Clinical indication</b>	<b>Drug</b>		
	<b>Acyclovir</b>	<b>Valacyclovir</b>	<b>Famciclovir</b>
<b>Cold sores</b> (≥12 years of age) Immunocompetent patients		2 g PO twice a day for 1 day	
<b>Herpes simplex encephalitis</b>			
≥ 12 years of age	10 mg/kg i.v. every 8 hours x 10 days <sup>b</sup>		
3 months to < 12 years of age	20 mg/kg i.v. every 8 hours x 10 days <sup>c</sup>		
Birth to < 3 months	10 mg/kg i.v. every 8 hours x 10 days <sup>d</sup>		
<b>Mucosal and cutaneous herpes simplex infections in immunocompromised patients</b>			
< 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		
<b>Genital herpes</b> Severe initial episodes (≥ 12 years of age)	5 mg/kg i.v. every 8 hours x 5 days		
<b>Herpes zoster</b> 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		
<b>Chickenpox</b> Immunocompetent Patients ≥ 2 years of age 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		

<sup>a</sup>In clinical practice they treat 14-21 days

<sup>b</sup>In clinical practice they treat 14-21 days

<sup>c</sup>In clinical practice they treat 14-21 days

<sup>d</sup>In clinical practice they use 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 valacyclovir 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, antiviral spectrum, resistance pattern, and safety profile are the same as those of the parent drug acyclovir. Valacyclovir has some advantages over oral acyclovir because of the better pharmacokinetic profile and more convenient dosing schedule.

Valacyclovir's only approved indication for pediatric patients is herpes labialis ( $\geq 12$  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, herpes labialis 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**

Valacyclovir is available in the United States as 500 mg unscored caplet and as 1 gram scored caplet.

### **2.4 Presubmission Regulatory Activity**

- |                 |   |
|-----------------|---|
| June 1995:      | Valtrex was approved by FDA for treatment of herpes zoster in immunocompetent adults.   |
| December 1995:  | Valtrex was approved by FDA for treatment of recurrent episodes of genital herpes in immunocompetent adults   |
| October 1996:   | Valtrex was approved by FDA for treatment of initial episode of genital herpes in immunocompetent adults.   |
| September 1997: | Valtrex was approved by FDA as suppressive therapy for recurrent genital herpes in immunocompetent adults.  |
| June 2001:      | Valtrex was approved by FDA for a shorter treatment course (3 days) of recurrent episodes of genital herpes.  |
| August 2001:    | To obtain needed pediatric information on valacyclovir, 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 valacyclovir in immunocompetent and/or immunocompromised infants and children age 1 -12 years of age who have HSV infections.

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

September 2002: Valtrex was approved by FDA for treatment of cold sores in immunocompetent patients  $\geq$  12 years of age.

January 2003: The Pediatric Written Request was amended to broaden enrollment in Study 1, to convert Study 2 and Study 3 to multiple-dose trials, and to extend the timeframe of submission to December 31, 2005. The modified studies read as follows:

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

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

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

April 2003: Valtrex was approved by FDA for suppression of recurrent genital herpes in HIV-infected patients.

September 2003: Valtrex was approved by FDA for reduction of the risk of transmission of genital herpes during suppressive therapy of the source partner in a heterosexual couple.

January 2005: The Pediatric Written Request was amended to extend the timeframe for submitting all clinical study reports to December 31, 2006.

December 2006: The Pediatric Written Request was amended to extend the timeframe for submitting all clinical study reports to June 22, 2009.

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 Chemistry Manufacturing and Controls

As part of the Pediatric Written Request, the Sponsor is asked to develop a commercially-marketable age-appropriate formulation for children. However, if the Sponsor cannot develop a commercially marketable age-appropriate formulation, they are asked to provide the Agency with documentation of their attempts to develop such a formulation and the reasons why such attempts failed. In such cases, the Sponsor must submit instructions for compounding an age-appropriate formulation from commercially available ingredients acceptable to the Agency.

In this case, the Applicant tried to develop an age-appropriate formulation but such trials were unsuccessful due primarily to (b) (4)

[REDACTED]

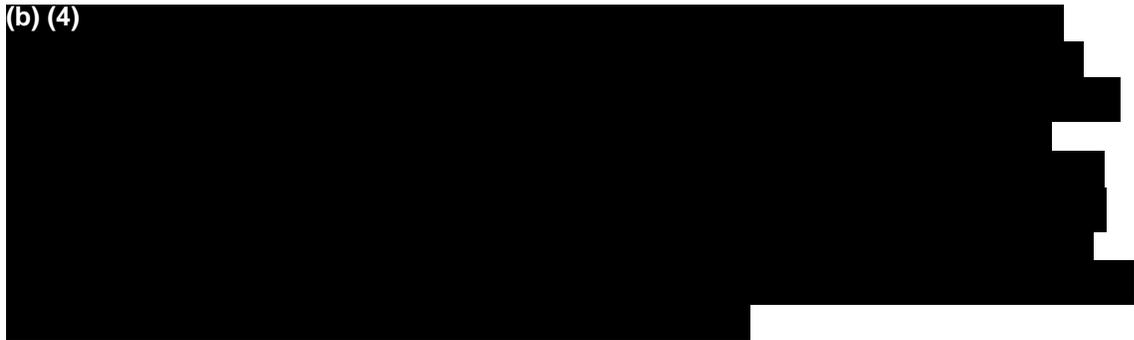
Finally, the Applicant provided instructions for the extemporaneous preparation of valacyclovir oral suspension.

(b) (4)  
[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)



(b) (4)



Development of an Extemporaneous formulation:

Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously by pharmacists from 500 mg Valtrex caplets for use in pediatric patients for whom a solid dosage form is not appropriate. The instruction for the extemporaneous preparation of valacyclovir oral suspension is included in the label and is as follows:

Ingredients and preparation per USP-NF: Valtrex Caplets 500 mg, cherry flavor, and Suspension Structured Vehicle USP-NF (SSV). Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) should be prepared in lots of 100 mL.

Prepare Suspension at Time of Dispensing as Follows:

- Prepare SSV according to the USP-NF.
- Using a pestle and mortar, grind the required number of VALTREX 500-mg Caplets until a fine powder is produced (5 VALTREX Caplets for 25-mg/mL suspension; 10 VALTREX Caplets for 50-mg/mL suspension).
- Gradually add approximately 5-mL aliquots of SSV to the mortar and triturate the powder until a paste has been produced. Ensure that the powder has been adequately wetted.
- Continue to add approximately 5-mL aliquots of SSV to the mortar, mixing thoroughly between additions, until a concentrated suspension is produced, to a minimum total quantity of 20 mL SSV and a maximum total quantity of 40 mL SSV for both the 25-mg/mL and 50-mg/mL suspensions.
- Transfer the mixture to a suitable 100-mL measuring flask.
- Transfer the cherry flavor\* to the mortar and dissolve in approximately 5 mL of SSV. Once dissolved, add to the measuring flask.
- Rinse the mortar at least 3 times with approximately 5 mL aliquots of SSV, transferring the rinsing to the measuring flask between additions.
- Make the suspension to volume (100 mL) with SSV and shake thoroughly to mix.
- Transfer the suspension to an amber glass medicine bottle with a child-resistant closure.
- The prepared suspension should be labeled with the following information “Shake well before using. Store suspension between 2° to 8°C (36° to 46°F) in a refrigerator. Discard after 28 days.”

\*The amount of cherry flavor added is as instructed by the suppliers of the cherry flavor.

The Applicant provided stability data justifying the recommended storage conditions and shelf-life for valacyclovir oral suspensions 25 mg/mL and 50 mg/mL.

Please also refer to Dr. Swapan De’s review for a detailed review of the new chemistry and manufacturing data submitted with this application.

### **3.2 Animal Pharmacology/Toxicology**

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

## **4 DATA SOURCES AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

This review is based on pharmacokinetic and safety data from three studies (HS210914, HS210915, and HS210916) conducted in response to the final amended Pediatric Written

Request to support the Pediatric Exclusivity claim and dosing recommendations in children (b) (4) to < 12 years of age with (b) (4) VZV infections.

## 4.2 Data Quality and Integrity

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

## 4.3 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.

## 4.4 Financial Disclosures

In compliance with the rule of Financial Disclosure by Clinical Investigators the Applicant provided financial interest information for clinical investigators participated in studies HS210914, HS210915, and HS210916.

(b) (6) was a clinical sub-investigator for protocols HS210914 and HS210915 when she was an employee at (b) (6) Medical Center. (b) (6) (b) (4) Medical Center and became a full-time employee of GlaxoSmithKline. Protocols HS210914 and HS210915 continued at (b) (4) Medical Center under the direction of other individuals. The sites at which (b) (6) participated in these studies enrolled 1 subject in study HS210914 and no subject in HS210915.

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.

# 5 REVIEW OF CLINICAL STUDY RESULTS

## 5.1 Review methods

The clinical review is focused on the pharmacokinetic and safety data from three pediatric studies conducted in response to the Pediatric Written Request. The Medical Officer reviewed study design, patient demographics, adverse events, and laboratory safety data monitoring, and pharmacokinetic data. The safety data were evaluated either with the use of JMP Statistical Discovery software or manually. No efficacy evaluations were conducted in any of the three studies.

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

Please also refer to Dr. Shirley Lu's review for a more detailed review of the pharmacokinetic data submitted with this supplemental NDA.

## **5.2 Study Design, Pharmacokinetic and Safety Results, and Conclusion**

### **Study HS210914:**

This is an open-label, single-dose, multicenter, pharmacokinetic, safety and tolerability study of valacyclovir oral suspension in infants and children. Subjects 1 month to < 6 years of age who had an active herpes virus infection or who were at risk for herpes virus infection were eligible for enrollment. All subjects received a single dose of 25 mg/kg of an extemporaneously prepared valacyclovir oral suspension. Plasma samples for pharmacokinetic analysis were obtained within 15 minutes before dosing and at 0.5, 1, 2, 4, and 6 hours after dosing. Laboratory samples for safety assessment were obtained before dosing and 2-4 days after study drug administration.

Dose rationale: The 25 mg/kg dose was selected to provide comparable systemic exposure to the adult dose of 1 gram of valacyclovir (suppressive therapy for recurrent genital herpes in immunocompetent adults). The 25 mg/kg dose is also expected to provide similar exposures to the daily oral acyclovir regimen (300 mg/m<sup>2</sup> three times daily) used in two NIH trials evaluating the effect of oral acyclovir as suppressive therapy following neonatal HSV infection.

A total of 57 infants and children between 1 month to < 6 years of age who met the inclusion criteria were enrolled in this study. The age distribution of the enrolled patients was as follows:

- 1 month to <3 months: 14 subjects (full pharmacokinetic data from 9)
- 3 months to < 6 months: 12 subjects (full pharmacokinetic data from 9)
- 6 months to < 1 year: 10 subjects (full pharmacokinetic data from 6)
- 1 year to < 2 years: 9 subjects (full pharmacokinetic data from 7)
- 2 years to < 6 years: 12 subjects (full pharmacokinetic data from 12)

Of note, pharmacokinetic and safety data from an interim analysis of 9 children  $\geq$  2 years of age who received valacyclovir oral suspension dosages in this study and Study HS210915 were reviewed before enrolling children < 2 years of age.

Complete pharmacokinetic data are available from 43 of the 57 enrolled subjects and single-dose safety data from all enrolled subjects.

### **Baseline characteristics and disposition of patients:**

Of the 57 subjects enrolled in this study, 32 (56%) were male. Twenty-four (42%) were black, 23 (40%) were white, 9 (16%) were Native Americans/Eskimo and 1 (2%) of other race. The ethnicity breakdown was 15 (26%) Hispanic or Latino and the remaining 42 (74%) not Hispanic or Latino.

Six subjects had active herpes virus infection (chickenpox 4, herpes labialis 1, neonatal herpes 1); fifty-one had no active infection but were considered at risk for development of herpes virus infection. Twenty-four of the 57 subjects were immunocompromised.

Pharmacokinetic results:

Acyclovir exposures after a single 25 mg/kg dose of valacyclovir oral suspension as well as the adult historical data after a single 1 gram dose of Valtrex are shown in Table 2. The data from the adult 1 gram dose were used as a target historical comparison. The adult historical data were obtained from intensive pharmacokinetic sampling. The Applicant has included estimates of pharmacokinetic parameters using the pediatric sampling for more appropriate comparison. Valtrex 1 gram once daily is approved for suppression of recurrent genital herpes in immunocompetent adults.

**Table 2.** Acyclovir pharmacokinetic parameter estimates following a single 25 mg/kg dose of valacyclovir oral suspension in pediatric patients and after a single 1 gram dose of Valtrex in adults.

Acyclovir PK Parameter	25 mg/kg Suspension in Pediatric Subjects						1 g Solid Dose in Adults <sup>a</sup> (N=15)	
	Cohort 1 2 to <6 yr (N=12)	Cohort 2 1 to <2 yr (N=9)	Cohort 3 6 mo to <1 yr (N=7)	Cohort 4 3 to <6 mo (N=9)	Cohort 5 1 to <3 mo (N=9)	Overall: 1 mo to <6 yrs (N=46)	Actual Adult PK Sampling Schedule	Estimates Using Peds PK Sampling Schedule
<b>AUC(0-∞) (µg•h/mL)</b>								
Mean (CV%)	19.9 (13)	15.3 <sup>1</sup> (34)	14.1 <sup>2</sup> (25)	17.7 (37)	27.6 (25)	19.5 <sup>3</sup> (35)	18.8 (24)	17.2 (18)
Geometric Mean (95% CI)	19.8 (18.2-21.5)	14.5 <sup>1</sup> (10.3-20.4)	13.7 <sup>2</sup> (10.6-17.7)	16.0 (10.5-24.5)	26.9 (22.2-32.5)	18.2 <sup>3</sup> (16.1-20.6)	N/A	N/A
<b>C<sub>max</sub> (µg/mL)</b>								
Mean (CV%)	6.52 (19)	4.67 (44)	4.94 (21)	5.17 (43)	7.02 (22)	5.75 (32)	5.20 (37)	4.72 (29)
Geometric Mean (95% CI)	6.40 (5.63-7.28)	4.14 (2.67-6.43)	4.86 (4.03-5.86)	4.67 (3.13-6.97)	6.88 (5.85-8.08)	5.38 (4.76-6.07)	N/A	N/A
<b>t<sub>1/2</sub> (h)</b>								
Mean (CV%)	1.45 (14)	1.33 <sup>1</sup> (7)	1.25 <sup>2</sup> (12)	1.79 (41)	2.03 (23)	1.60 <sup>3</sup> (31)	2.77 (13)	2.11 (21)
Geometric Mean (95% CI)	1.44 (1.32-1.57)	1.33 <sup>1</sup> (1.24-1.42)	1.24 <sup>2</sup> (1.09-1.41)	1.69 (1.31-2.19)	1.99 (1.69-2.34)	1.54 <sup>3</sup> (1.42-1.67)	N/A	N/A
<b>t<sub>max</sub> (h)</b>								
Median (Range)	1.00 (0.50-2.00)	2.00 (1.00-4.02)	2.00 (1.08-2.30)	2.00 (0.98-2.08)	2.03 (0.97-2.25)	2.00 (0.50-4.02)	2.0 (0.75-2.50)	2.0 (1.00-2.00)
Mean (CV%)	1.21 (41)	1.93 (48)	1.81 (27)	1.58 (34)	1.87 (22)	1.64 (39)	1.82 (32)	1.67 (29)
<b>CL/F/kg (mL/min/kg)</b>								
Mean (CV%)	14.9 (13)	21.2 <sup>1</sup> (38)	21.9 <sup>2</sup> (24)	21.6 (85)	11.0 (25)	17.5 <sup>3</sup> (57)	9.0 (21)	11.6 (31)
Geometric Mean (95% CI)	14.8 (13.6-16.0)	20.0 <sup>1</sup> (14.3-28.1)	21.3 <sup>2</sup> (16.4-27.7)	18.0 (11.8-27.5)	10.7 (8.84-13.0)	15.9 <sup>3</sup> (14.1-18.0)	N/A	N/A

Source Data: Table 11.5 and Table 11.6; <sup>a</sup>[Weller, 1993]  
<sup>1</sup>N=7; <sup>2</sup>N=6; <sup>3</sup>N=43

The pharmacokinetic results in infants and children 3 months to < 6 years of age revealed that the 25 mg/kg dose provides comparable systemic exposures to the adult dose of 1 g of valacyclovir. In infants 1 month to <3 months of age, acyclovir exposures resulting from the 25 mg/kg dose were higher (C<sub>max</sub>: ↑30%, AUC: ↑60%) than acyclovir exposures following the 1 gram dose of valacyclovir in adults. This difference in the 1 month to <3 months of age group is probably due to age-related under-developed renal function.

Safety results:

*Adverse events:* Twelve of the 57 (21%) subjects reported at least one adverse event during the study. All adverse events were mild or moderate in intensity. Only two adverse events were reported by two or more subjects: diarrhea 3 subjects and pyrexia 2 subjects. All other adverse events were experienced by a single subject only. Three of the 12 subjects had laboratory abnormalities reported as adverse events (occasional schistocytes and thrombocytosis in a 7-month-old girl, elevated basophils, monocytes, lymphocytes and LDH and decreased platelet count in a 1-year-old boy, and elevated BUN in another 1-year-old boy).

Four (7%) subjects experienced adverse events considered by the investigators as possibly related to study drug; 2 subjects had diarrhea, 1 subject had occasional schistocytes and thrombocytosis; and the fourth subject had elevated basophils, monocytes, lymphocytes and LDH and decreased platelet count.

No deaths were reported during the study. One subject experienced a serious adverse event. This was a 2-month-old male who developed fever and diarrhea eight days after receiving a single dose valacyclovir oral suspension. Sepsis work-up was done which showed enteroviral meningitis. This adverse event was considered by the investigator as not related to study drug.

*Laboratory abnormalities:* A single subject developed occasional schistocytes and thrombocytosis between the screening and the follow-up visit. The thrombotic microangiopathy tree (TMA) was performed and was ruled out. Otherwise, no important changes in mean laboratory values from screening to follow-up were observed.

Conclusion:

This study was undertaken to provide pharmacokinetic and safety data to support a potential use of valacyclovir as suppressive therapy in infants and children following neonatal herpes simplex virus infection of the central nervous system or herpes simplex virus infection limited to the skin, eye, and mouth. Study HS210914 was designed to provide similar exposures to the adult valacyclovir dose of 1 gram (suppressive therapy for recurrent genital herpes in adults) and to the acyclovir suppressive dose (300 mg/m<sup>2</sup> three times daily) used in two NIH trials evaluating the effect of acyclovir suppressive therapy following neonatal HSV infection. Although acyclovir systemic exposures in infants and children 3 months to < 6 years of age after a single 25 mg/kg dose were comparable to systemic exposures to the adult dose of 1 gram of valacyclovir, there are insufficient data to support valacyclovir suppressive therapy for HSV infection in infants and children. Acyclovir is not approved for suppressive therapy in infants and children following neonatal HSV infections. Therefore, valacyclovir is not recommended for this indication because efficacy cannot be extrapolated from acyclovir to support its approval. (b) (4)

(b) (4)

### **Study HS210915**

This is an open-label, single-dose pharmacokinetic, multiple-dose safety and tolerability study of valacyclovir oral suspension in infants and children with HSV infection. Twenty-eight subjects 1 to <12 years of age were enrolled in this study. Each subject received 10 mg/kg extemporaneously prepared valacyclovir oral suspension administered every 12 hours for 3-5 days. Plasma samples for pharmacokinetic analysis were obtained within 15 minutes before dosing and at 0.5, 1, 2, 4, and 6 hours after the first dose. Laboratory samples for safety assessment were obtained before dosing and 2-4 days after study drug discontinuation.

Dose rationale: This dose was selected to provide comparable systemic exposure to the adult dose of 500 mg twice daily (approved treatment for recurrent episodes of genital herpes in adults).

A total of 28 children 1 to < 12 years of age were enrolled in this study. The age distribution of the enrolled patients was as follows:

- 1 year to < 2 years: 7 subjects (pharmacokinetic data from 6)
- 2 years to < 6 years: 13 subjects (pharmacokinetic data from 12)
- 6 years to < 12 years: 8 subjects (pharmacokinetic data from 8)

Pharmacokinetic and safety data from an interim analysis of children  $\geq 2$  years of age were reviewed before enrolling children 1 to < 2 years of age.

Pharmacokinetic data are available from 26 of the 28 enrolled subjects. All subjects included in the safety analysis. Safety data are available for: 1 subject after 1 day valacyclovir; 1 subject after 2 days; 16 subjects after 3 days; 1 subject after 4 days; 8 subjects after 5 days; and 1 subject after 6 days valacyclovir treatment. In total, 26 subjects were treated for  $\geq 3$  days.

#### Baseline characteristics and disposition of patients:

Of the 28 subjects enrolled in this study, 11 (39%) were male and 17 (61%) were female. Six (21%) were black, 15 (54%) were white, and the remaining 7 (25%) of other race. The ethnicity breakdown was 27 (96%) not Hispanic/Latino and 1 (4%) Hispanic/Latino.

All subjects enrolled in the study had a clinical diagnosis of HSV infection. Seventeen subjects had herpes labialis, 12 herpetic gingivostomatitis, 1 ocular herpes, and 3 subjects had other herpetic infections (subjects could record more than one HSV infection). The exact clinical diagnosis is shown in Table 3.

**Table 3.** HSV disease in patients enrolled in study HS210915

	Valacyclovir oral suspension 10 mg/kg twice daily x 3-5 days			
	Total population N=28	Age 6 to < 12 years N=8	Age 2 to < 6 years N=13	Age 1 to < 2 years N=7
Documented HSV infection*	n (%)	n (%)	n (%)	n (%)
Herpes labialis	17 (61)	8 (100)	8 (62)	1 (14)
Herpetic gingivostomatitis	12 (43)	0	6 (46)	6 (86)
Ocular herpes	1 (4)	0	1 (8)	0
Other	3 (11)	0	3 (23)	0

\*Subjects could record more than one HSV infection  
 Source: Study HS210915, Table 9.10

Comment: Most of the patients had herpes labialis or herpetic gingivostomatitis. Although the proposed dose (10mg/kg twice daily) was selected to provide comparable systemic exposures to the adult dose for the treatment of recurrent episodes of genital herpes (500 mg twice daily), none of the enrolled subjects had recurrent genital herpes.

Twenty-seven of the 28 subjects enrolled in study HS210915 completed the study and only one subject withdrew from the study. This is a patient whose IV line became dislodged after the initial dose. The subject's family decided to withdraw the subject from the study after attempts to restore the IV line failed.

Pharmacokinetic results:

Mean (%CV) acyclovir pharmacokinetic parameter estimates after administration of a single 10 mg/kg dose of valacyclovir oral suspension in pediatric patients are shown in the following table. In the table are also shown the adult historical data after a single 500 mg dose of Valtrex. The adult historical data were obtained from intensive pharmacokinetic sampling. The Applicant also included analysis of the same data based on the reduced sampling schedule used for all pediatric subjects enrolled in this study.

**Table 4.** Study HS210915: Mean (%CV) acyclovir pharmacokinetic parameter estimates after a single 10 mg/kg dose of valacyclovir oral suspension in pediatric patients and after a single 500 mg dose of Valtrex in adults.

Acyclovir PK Parameter	10 mg/kg Valaciclovir Oral Suspension in Pediatric Subjects (N=26)				500 mg Solid Dose in Adults (N=15)	
	Cohort 1 6 to <12 yr (N=8)	Cohort 2 2 to <6 yr (N=12 <sup>a</sup> )	Cohort 3 1 to <2 yr (N=6)	Overall: 1 to <12 yr (N=26 <sup>b</sup> )	Actual Adult PK Sampling Schedule	Estimates Using Peds PK Sampling Schedule
<b>AUC(0-∞) (µg·h/mL)</b>						
Mean (CV%)	8.84 (17)	5.72 (30)	6.63 (27)	6.94 (31)	11.1 (16)	10.3 (18)
<b>C<sub>max</sub> (µg/mL)</b>						
Mean (CV%)	3.08 (15)	2.05 (23)	2.49 (37)	2.47 (30)	3.37 (28)	3.07 (29)
<b>t<sub>1/2</sub> (h)</b>						
Mean (CV%)	1.58 (19)	1.65 (45)	1.39 (22)	1.57 (34)	2.90 (13)	2.09 (29)
<b>t<sub>max</sub> (h)</b>						
Median (Range)	1.00 (0.50-2.00)	1.00 (0.50-2.00)	0.96 (0.58-2.07)	1.00 (0.50-2.07)	1.0 (0.75-2.5)	1.0 (0.5-2.0)
<b>CL/F/kg (mL/min/kg)</b>						
Mean (CV%)	13.5 (17)	21.9 (31)	18.8 (23)	18.5 (34)	7.33 (18)	9.52 (23)

Source data: m5.3.3.3, Study HS210915 Table 17.

a. N=12 for C<sub>max</sub> and t<sub>max</sub>; N=11 for AUC(0-∞), t<sub>1/2</sub> and CL/F/kg

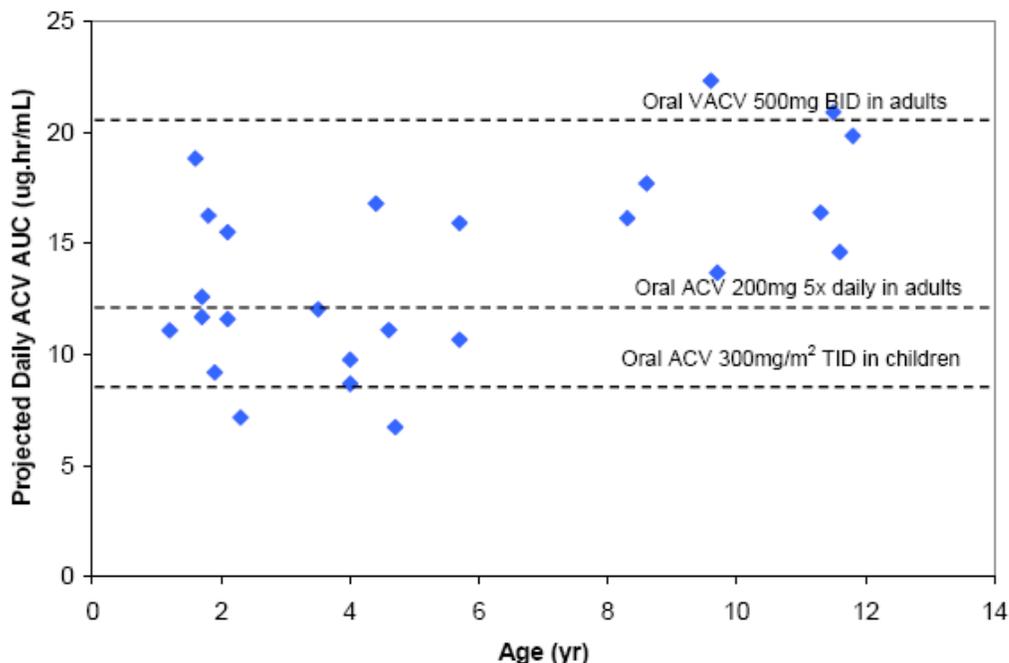
b. N=26 for C<sub>max</sub> and t<sub>max</sub>; N=25 for AUC(0-∞), t<sub>1/2</sub> and CL/F/kg

Comment: Average acyclovir systemic exposures following a single 10 mg/kg dose of valacyclovir oral suspension in children 1 to < 12 years of age were lower (AUC: ↓33%, C<sub>max</sub>: ↓20%) than the targeted historical adult exposures resulting from a single 500 mg dose of Valtrex.

The 6 to < 12 year group had higher AUC and C<sub>max</sub> exposures approaching the adult exposure levels.

In addition to comparing the pharmacokinetic results of this study with those from adults who received valacyclovir 500 mg, the Applicant compared the pediatric pharmacokinetic results from valacyclovir oral suspension with those from oral acyclovir since acyclovir 200 mg five times daily for 5 days is an approved treatment of episodic recurrent genital herpes. This comparison is shown in Figure 1.

**Figure 1.** Comparison of projected daily acyclovir AUC exposures following a single 10 mg/kg dose of valacyclovir oral suspension in children with historical average results in adults and children.



VACV=valacyclovir, ACV=acyclovir, BID=twice daily, TID=three times daily

Note: Oral valacyclovir 500 mg BID for 3 days is approved for the treatment of recurrent genital herpes in adults.

Oral acyclovir 200 mg 5 times daily for 7-10 days is approved for the treatment of initial episodes of genital herpes in adults. The same dose for 5 days is approved for the treatment of recurrent episodes of genital herpes in adults.

Oral ACV 300 mg/m<sup>2</sup> TID in children is not an approved dose. This dose is used in two NIH trials assessing the effect of acyclovir suppressive therapy following neonatal HSV infection. It has also been used off-label for treatment of HSV infections in children.

Comment: The comparison indicates the mean projected daily acyclovir systemic exposures in children are lower compared to the acyclovir systemic exposures in adults receiving valacyclovir 500 mg twice daily but higher than systemic exposures in adults receiving acyclovir 200 mg five times daily.

Based on the comparison with acyclovir systemic exposures in adults receiving 200 mg five times daily and the safety data obtained from study HS210915, (b) (4)

Safety results:

As previously stated, all subjects included in the safety analysis. A total of 26 subjects received study drug for three or more days.

*Adverse events:* Nine of the 28 subjects (32%) experienced at least one adverse event during the study. Only two adverse events were reported by more than one subject; diarrhea (2 subjects) and dehydration (2 subjects). All adverse events were mild or moderate in intensity. Four of the nine subjects had laboratory abnormalities reported as adverse events (glucosuria/ketonuria/hyperuricosuria and neutrophilia in a 4-year-old girl, eosinophilia in a 3-year-old girl, elevated bilirubin in a 4-year-old girl, and reticulocytosis in a 4-year-old boy).

Three subjects had adverse events considered by the investigators possibly related to study drug. The adverse events were eosinophilia, diarrhea, and glucosuria/ketonuria/hyperuricosuria in one subject each.

No deaths were reported during the study and no subject experienced adverse event leading to premature discontinuation of study drug. One subject experienced serious adverse events during the study. A 2-year-old girl whose medical history included gastroesophageal reflux, developed vomiting, diarrhea, and dehydration three days after the last dose of valacyclovir. The patient was hospitalized for three days and treated with intravenous fluids. She was discharged on Day 4 of hospitalization and a follow-up visit after two weeks revealed resolution of the events. These events were considered by the investigator as not related to study drug.

*Laboratory abnormalities:* There were four subjects with laboratory abnormalities considered by investigators as of potential clinical concern. These subjects were those with laboratory abnormalities reported as adverse events. The laboratory abnormalities in two of these subjects were considered by the investigators as possibly related to study drug (the subjects with eosinophilia and glycosuria/hyperuricosuria/ ketonuria).

The 4-year-old girl with eosinophilia had normal WBC count with differential at screening. She received valacyclovir for three days and at follow-up (three days after dosing) she was found to have moderate eosinophilia. Repeat WBC count with differential 10 days later was normal.

The 4-year-old girl with glucosuria/ketonuria/hyperuricosuria had normal laboratory tests at screening (including hematology, chemistry, and urinalysis). She received valacyclovir for 5 days for herpes labials. No laboratory assessments were conducted during the dosing period. Follow-up laboratory tests three days after the last dose of study drug revealed elevated WBC count, normal clinical chemistry and abnormal urinalysis with 4+ glucose and ketones and uric acid on microscopy. Repeat blood test and urinalysis 5 days later were normal. The Applicant was unable to provide additional information about this subject when asked by the review team.

Otherwise, no important changes in mean laboratory values from screening to follow-up were observed. No thrombotic microangiopathy related abnormalities were observed in any subject during the study.

**Conclusion:**

The mean projected daily acyclovir systemic exposures following a single 10 mg/kg dose of valacyclovir oral suspension in pediatric patients 1 to < 12 years of age were lower ( $C_{max}$ : ↓20%, AUC: ↓33%) compared with the acyclovir systemic exposures in adults receiving valacyclovir 500 mg twice daily, but were higher (daily AUC: ↑16%) than systemic exposures in adults receiving acyclovir 200 mg 5 times daily. However, there are insufficient data to support valacyclovir therapy for the treatment of recurrent episodes of genital herpes in this age group. Clinical information on recurrent genital herpes in young children is limited; therefore, extrapolating efficacy data from adults to this population is not possible. Of note, none of the enrolled subjects in Study HS20915 had genital herpes.

**Study HS210916:**

This is an open-label, single-dose pharmacokinetic, multiple-dose safety and tolerability study of valacyclovir oral suspension in infants and children with VZV infection. Twenty-seven subjects 1 to <12 years of age were enrolled in this study. Each subject received 20 mg/kg extemporaneously prepared valacyclovir oral suspension administered three times daily for 5 days. Plasma samples for pharmacokinetic analysis were obtained within 15 minutes before dosing and at 0.5, 1, 2, 4, and 6 hours after the first dose. Laboratory samples for safety assessment were obtained before dosing and 2-4 days after study drug discontinuation.

**Dose rationale:** This dose was selected to provide comparable systemic exposures to the adult dose of valacyclovir 1 gram three times daily (approved treatment for herpes zoster in adult patients).

A total of 27 children 1 to < 12 years of age were enrolled in this study. The age distribution of the enrolled subjects was:

- 1 year to < 2 years: 6 (pharmacokinetic data from 6)
- 2 years to < 6 years: 13 (pharmacokinetic data from 12)
- 6 years to < 12 years: 8 (pharmacokinetic data from 8)

Pharmacokinetic and safety data from an interim analysis of children  $\geq 2$  years of age were evaluated before enrolling children 1 to < 2 years of age.

Pharmacokinetic data are available from 26 of the 27 enrolled subjects. All subjects were included in the safety analysis. Safety data after 5 days of treatment are available from 19 subjects and after 6 days from 1 subject. The remaining 7 subjects had valacyclovir for less than five days: 1 subject had 1 day valacyclovir; 1 subject for 2 days; 1 subject for 3 days; and 4 subjects for 4 days.

**Baseline characteristics and disposition of patients:**

Of the 27 subjects enrolled in this study, 13 (48%) were male and 14 (52%) were female. Two (7%) were black, 19 (70%) were white, 1 (4%) was Asian and the remaining 5 (19%) of other race. All enrolled subjects were not Hispanic or Latino.

All subjects enrolled in the study had a clinical diagnosis of VZV infection. However, the data provided did not indicate whether the patients had chickenpox or herpes zoster infection. The Applicant believes all patients had chickenpox but is not able to confirm the diagnosis because it was not stated in the case report forms.

Of the 27 subjects enrolled in study HS210916, 26 subjects completed the study and only one subject withdrew consent after the first dose. This subject was excluded from the pharmacokinetic analysis but included in the safety analysis.

Pharmacokinetic results:

Mean (%CV) acyclovir pharmacokinetic parameter estimates after administration of a single 20 mg/kg dose of valacyclovir oral suspension in pediatric patients are shown in Table 5. The table also shows the adult historical data after a single 1 gram dose of Valtrex. The adult historical data were obtained from intensive pharmacokinetic sampling. For more appropriate comparison, the Applicant has included analysis of the same data based on the reduced sampling schedule used for the pediatric subjects enrolled in this study.

**Table 5.** Mean (% CV) acyclovir pharmacokinetic parameter estimates after a single 20 mg/kg dose of valacyclovir oral suspension in pediatric patients and after a single 1 gram dose of Valtrex in adults.

Acyclovir PK Parameter	20 mg/kg Suspension in Pediatric Subjects (N=26)				1 g Solid Dose in Adults <sup>a</sup> (N=15)	
	Age 6 to <12 yrs (N=8)	Age 2 to <6 yrs (N=12)	Age 1 to <2 yrs (N=6)	Overall: Age 1 to <12 yrs (N=26)	Actual Adult PK Sampling Schedule	Estimates Using Peds PK Sampling Schedule
<b>AUC(0-∞) (µg•h/mL)</b>						
Mean (CV%)	13.08 (26)	10.09 (33)	14.41 (43)	12.01 (37)	18.8 (24)	17.2 (18)
Geometric Mean (95% CI)	12.75 (10.50-15.48)	9.59 (7.73-11.89)	13.29 (8.36-21.13)	11.28 (9.76-13.04)	N/A	N/A
<b>C<sub>max</sub> (µg/mL)</b>						
Mean (CV%)	4.71 (25)	3.75 (30)	4.03 (34)	4.11 (30)	5.20 (37)	4.72 (29)
Geometric Mean (95% CI)	4.59 (3.76-5.61)	3.59 (2.93-4.40)	3.82 (2.61-5.60)	3.93 (3.46-4.46)	N/A	N/A
<b>t<sub>1/2</sub> (h)</b>						
Mean (CV%)	1.43 (11)	1.54 (23)	2.13 (41)	1.64 (33)	2.77 (13)	2.11 (21)
Geometric Mean (95% CI)	1.42 (1.29-1.56)	1.51 (1.32-1.73)	1.97 (1.26-3.08)	1.58 (1.41-1.76)	N/A	N/A
<b>t<sub>max</sub> (h)</b>						
Median (Range)	1.00 (0.98-2.00)	1.02 (0.98-2.08)	1.11 (0.97-2.05)	1.00 (0.97-2.08)	2.0 (0.75-2.50)	2.0 (1.00-2.00)
Mean (CV%)	1.14 (31)	1.30 (35)	1.25 (33)	1.24 (33)	1.82 (32)	1.67 (29)
<b>CL/F/kg (mL/min/kg)</b>						
Mean (CV%)	18.7 (21)	25.5 (35)	18.9 (41)	21.9 (36)	9.0 (21)	11.6 (31)
Geometric Mean (95% CI)	18.3 (15.0-22.3)	24.2 (19.5-29.9)	17.5 (11.0-27.8)	20.6 (17.8-23.8)	N/A	N/A

<sup>a</sup>N/A=not available  
 Source data: m5.3.3.3, Study HS210916, table 15

Comment: Average acyclovir systemic exposures following a single 20 mg/kg dose of valacyclovir oral suspension in children 1 to < 12 years of age with VZV

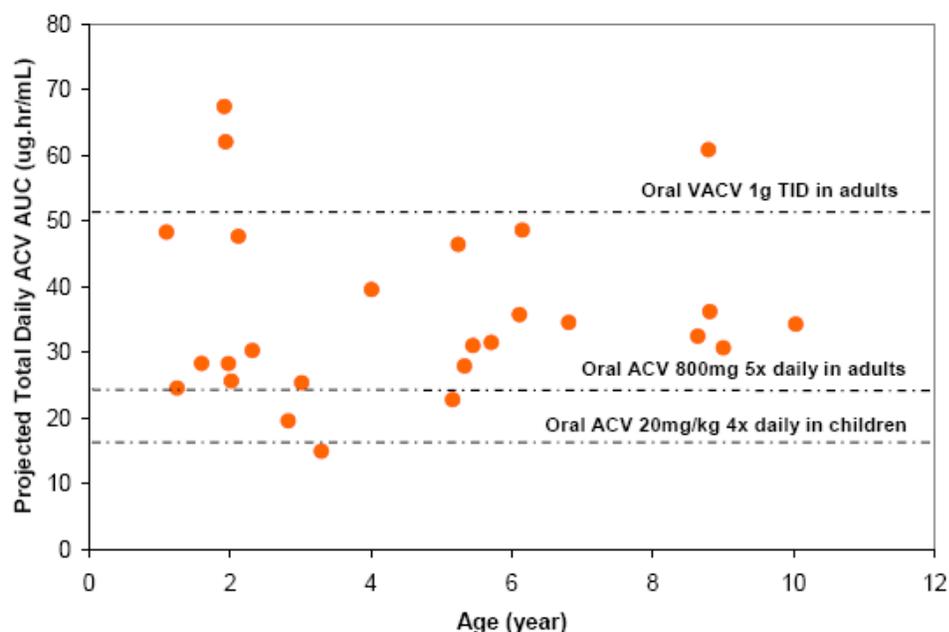
infections were lower ( $C_{max}$ : ↓13%, AUC: ↓30%) than the mean exposures in adults receiving a single 1 gram dose of Valtrex.

In addition to comparing the pharmacokinetic results of this study with those from adults who received Valtrex 1 gram, the Applicant compared the pediatric pharmacokinetic results of this study with the following historical acyclovir data obtained after:

- Oral acyclovir 800 mg five times daily in adults (acyclovir 800 mg five times daily for 7-10 days is approved for the treatment of herpes zoster in immunocompetent adults).
- Oral acyclovir 20 mg/kg four times daily (acyclovir 20 mg/kg four times daily for 5 days is approved for the treatment of chickenpox in immunocompetent children  $\geq 2$  years of age).

The results of this comparison are shown in Figure 2.

**Figure 2.** Projected individual total daily AUC of acyclovir from HS210916 compared with historical average results in adults and children.



**Comment:** The projected daily exposures in pediatric patients across all age groups (1 to < 12 years of age ) following a single 20 mg/kg dose of valacyclovir oral suspension were higher (daily AUC: ↑50%) than the daily exposures in adults receiving acyclovir 800 mg five times daily. The projected daily acyclovir exposures were also higher (daily AUC approximately 100% higher) than the exposures seen in immunocompetent pediatric patients receiving acyclovir 20 mg/kg four times daily for the treatment of chickenpox.

Based on these data, the applicant seeks approval of valacyclovir oral suspension administered 20 mg/kg three times daily for 5 days for the treatment of chickenpox in children  $\geq 1$  to < 12 years

of age.

### Safety results:

*Adverse events:* As previously stated, all subjects included in the safety analysis. A total of 6 subjects (22%) experienced at least one adverse event (pneumonia 1, headache 1, toothache 1, nausea 1, herpes labialis 1, and pyrexia, itching, and skin infection at the right calf 1). All adverse events were mild or moderate in severity. No adverse event was reported by more than one subject. Only one subject had an adverse event (nausea) considered by the investigator as possibly related to study drug.

No deaths were reported during the study and no subject experienced adverse event leading to premature discontinuation of study drug. One subject experienced a serious adverse event during the study which was not considered by the investigator to be drug related. This was a 2-year-old boy with a history of asthma and recurrent pneumonia who was hospitalized with pneumonia 10 days after the last dose of study drug. The patient was discharged the following day and the adverse event resolved 48 hours after the onset.

*Laboratory abnormalities:* No clinically important changes in chemistry or hematology values were observed during the study. One subject had schistocytes at screening and follow-up. This abnormality was not considered to be drug related.

### Conclusion:

Although the mean projected daily acyclovir exposures in pediatric patients across all age-groups (1 to <12 years of age) were lower ( $C_{max}$ : ↓13%, AUC: ↓30%) than the mean daily exposures in adults receiving valacyclovir 1 gram 3 times daily, the acyclovir exposures were higher (daily AUC: ↑50%) than the daily exposures in adults receiving acyclovir 800 mg 5 times daily. The projected daily exposures in pediatric patients were greater (daily AUC approximately 100% greater) than the exposures seen in immunocompetent pediatric patients receiving acyclovir 20 mg/kg 4 times daily for the treatment of chickenpox. Based on the provided pharmacokinetic and safety data and extrapolated efficacy data from 3 randomized, double-blind, placebo-controlled trials with oral acyclovir in pediatric patients at least 2 years of age with chickenpox, oral valacyclovir 20 mg/kg 3 times a day for 5 days is recommended for the treatment of chickenpox in pediatric patients 2 to <12 years of age. The efficacy and safety of oral formulations of acyclovir in pediatric patients younger than two years of age have not been established. Therefore, valacyclovir is not recommended for the treatment of chickenpox to children younger than two years of age. Valacyclovir is also not recommended for the treatment of herpes zoster in children because safety data up to 7 days duration are not available.

## 6 OVERALL ASSESSMENT

### 6.1 Conclusions

Pediatric use information for many of the approved drugs including antiviral drugs against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV) is needed. Children have less treatment options than adults due to lack of pediatric formulation and information to guide clinicians in dosing children.

This supplement includes pharmacokinetic and safety data from three studies conducted in response to the Pediatric Written Request. After a thorough review, the review team agrees the provided data are not sufficient to support the use of valacyclovir oral suspension in children 1 to < 12 years of age with recurrent genital herpes. Although the projected mean daily acyclovir exposures following valacyclovir oral suspension 10 mg/kg every 12 hours in children did not meet the targeted adult historical exposures from valacyclovir 500 mg twice daily, the mean exposures in children were comparable to historical data in adults receiving oral acyclovir 200 mg five times daily (an approved dose for the treatment of recurrent genital herpes in adults). However, clinical information on recurrent genital herpes in young children is limited; therefore, extrapolating efficacy data from adults to this population is not possible. Of note, none of the enrolled subjects in Study HS20915 had genital herpes.

(b) (4)



The review team also agrees the submitted data in this supplement are adequate to approve dose recommendations for the use of valacyclovir oral suspension in children 2 to < 12 years of age with chickenpox. This decision is based on a single-dose pharmacokinetic and multiple-dose safety data from an open-label study with valacyclovir and extrapolated efficacy data from 3 randomized, double-blind, placebo-controlled trials with oral acyclovir in pediatric patients at least 2 years of age with chickenpox. However, on May 2, 2008 the Applicant submitted for review pharmacokinetic data to support approval of valacyclovir for the treatment of chickenpox for children 12 to < 18 years of age. The Applicant and the Division agreed the May 2, 2008 submission is a major amendment and the Division decided to extend the review clock for three months for NDA 20-487/SE014 in order to review the submitted data. Therefore, no regulatory action was taken on June 10, 2008 for the use of valacyclovir in children for the treatment of chickenpox. An addendum to this review was added to summarize the data submitted to justify valacyclovir dosing in children 12 to < 18 years of age for the treatment of chickenpox.

Clinical Review  
Andreas Pikis, M.D.  
NDA 20-487, SE5-014 (b) (4)  
Valtrex® (valacyclovir hydrochloride)

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With respect to safety considerations, there were no unexpected adverse events. The overall adverse event profile of valacyclovir in children appears similar to that observed in adults.

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Concurrences:  
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## 7. ADDENDUM

### **Valacyclovir for the treatment of chickenpox in immunocompetent children 12 to < 18 years of age**

On June 9, 2008 the Applicant and the Division agreed that the pharmacokinetic data submitted on May 2, 2008 to support approval of valacyclovir for the treatment of chickenpox in immunocompetent children 12 to < 18 years of age are a major amendment and the Division decided to extend the review clock for three months for NDA 20-487/SE014 in order to review the submitted data. In addition, it was agreed that the Applicant should submit safety information from previously conducted clinical trials with acyclovir and valacyclovir to justify dosing in children 12 to < 18 years of age with chickenpox. The additional safety data were submitted on July 23, 2008.

This review summarizes the pharmacokinetic and safety data submitted to support approval of valacyclovir for the treatment of chickenpox in immunocompetent children 12 to < 18 years of age.

#### **Pharmacokinetic data:**

The Applicant believes pharmacokinetic data supporting valacyclovir dosing in children 12 to < 18 years of age with chickenpox could be interpolated from existing pharmacokinetic data from children < 12 years of age (included in the three pediatric studies conducted in response to the valacyclovir Pediatric Written Request) and pharmacokinetic data from adults. Based on these data, the Applicant proposes a valacyclovir dose of 20 mg/kg 3 times daily for 5 days (not to exceed 1 gram 3 times daily) for the treatment of chickenpox for this age group.

Pharmacokinetic results from Study HS210916 showed that the average acyclovir systemic exposures following a single 20 mg/kg dose of valacyclovir oral suspension in children 1 to <12 years of age were about 30% lower than historical mean exposures in adults receiving a single 1 gram dose of valacyclovir. However, the projected daily exposures in pediatric patients following a single 20 mg/kg dose of valacyclovir oral suspension were approximately 100% higher than the daily exposures seen in immunocompetent children receiving 20 mg/kg acyclovir 4 times daily for the treatment of chickenpox. Therefore, these exposures could be used to derive expected exposures that are effective in children 12 to < 18 years of age with chickenpox.

Existing pharmacokinetic data in children 1 month to < 12 years of age from the three studies conducted in response to the Pediatric Written Request (HS210914, HS210915, and HS210916) and pharmacokinetic data from historical valacyclovir studies in adults support dosing of valacyclovir for the treatment of chickenpox in children 12 to < 18 years of age. The following figures show the relationships between apparent oral acyclovir clearance (CL/F) versus age (Figure 1) and dose-normalized acyclovir AUC versus age (Figure 2).

Figure 1. Acyclovir clearance vs. age from valacyclovir administration

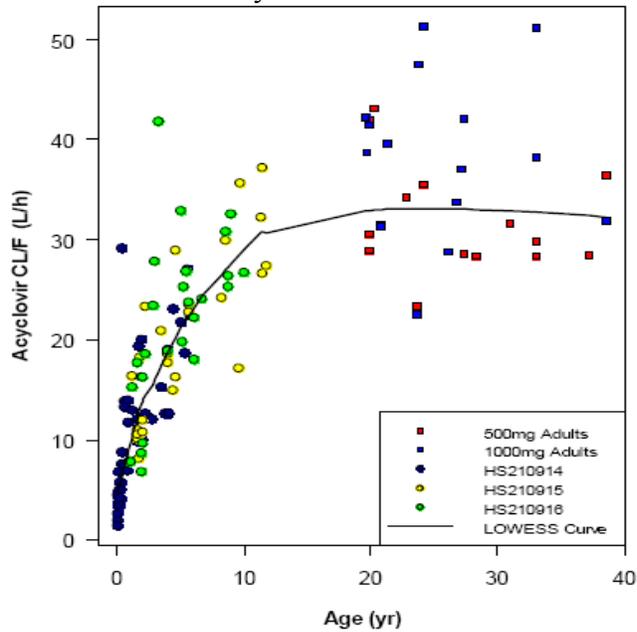
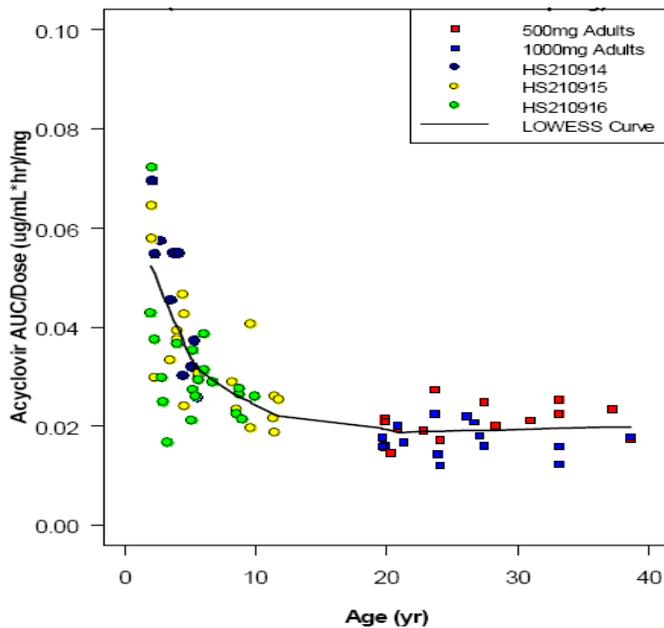


Figure 1 shows that the predicted clearance in adolescents is expected between the clearance of younger patients and the adult clearance values but closer to the adult values.

Figure 2. Dose-normalized acyclovir AUC vs. age



Source: Both figures are from Sponsor's submission dated 7/29/08

Figure 2 reveals that when a dose-normalized AUC exposure is compared against age, a 20 mg/kg dose in pediatric patients < 12 years of age produces higher exposures than adults

given a 500 or 1000 mg dose of valacyclovir. On a per mg dose basis, adolescents receiving a similar dose to that given in younger children would be expected to have slightly higher exposures than adults but lower exposures than younger children.

**Comment:** The above plotted pediatric and adult pharmacokinetic data provide a good estimate of the expected exposures and clearances in adolescents which they look similar to the adult valacyclovir doses at 500 or 1000 mg.

Based on these data, the Applicant proposes a valacyclovir dose of 20 mg/kg t.i.d. (not to exceed 1 gram three times daily) for 5 days for the treatment of chickenpox in children 12 to < 18 years of age.

Please refer to Dr. Shirley Lu's review for a more detailed review of the pharmacokinetic data submitted with this amendment.

### **Safety data:**

The Applicant supports additional safety studies in adolescents are not needed and a bridged safety justification and rationale for adolescents could be derived from the safety experience with acyclovir and valacyclovir studies. To support the dosing in children 12 to < 18 years of age with chickenpox, the Applicant submitted a summary safety review from the following studies:

#### Acyclovir

- Three acyclovir studies in immunocompetent children and adolescents with chickenpox

#### Valacyclovir

- Three pediatric studies in children < 12 years of age conducted in response to the valacyclovir Pediatric Written Request
- Two studies in children > 12 years of age and adults with herpes labialis
- Various adult studies in patients with HSV or VZV infections

Below is a brief summary of the submitted studies:

#### **Acyclovir studies**

Three randomized, double-blind, placebo-controlled trials were conducted in 993 pediatric patients aged 2 to 18 years with chickenpox. All patients were treated within 24 hours after the onset of rash. In two trials, acyclovir was administered at 20 mg/kg 4 times daily (up to 3,200 mg per day) for 5 days. In the third trial, doses of 10, 15, or 20 mg/kg were administered 4 times daily for 5 to 7 days. Treatment with acyclovir shortened the time to 50% healing; reduced the maximum number of lesions; reduced the median number of vesicles; decreased the median number of residual lesions on day 28; and decreased the proportion of patients with fever, anorexia, and lethargy by day 2. Follow are the safety results from the three studies:

### Study 176:

This was a double-blind, placebo-controlled trial of acyclovir for the treatment of chickenpox in children between 5 and 16 years of age. A total of 110 children were enrolled in the study and all were included in the safety analysis. The acyclovir dose is shown in Table 1.

**Table 1.** Acyclovir Dose

Age (years)	Acyclovir dose (mg/kg)
5.0 - 6.99	20
7.0 – 11.9	15
12.0 – 15.99	10

Study drug was administered four times a day for 5-7 days. Most patients (about 50%) were between 7-11 years of age and received the intermediate dose. The fewest patients were in the 12-16 years of age group and received the lowest dose. In fact, only 6 patients in this age group received acyclovir. A slight increase in the incidence of stomachache was observed in the acyclovir group (38 vs. 25%). Otherwise, there were no differences between the acyclovir and the placebo group and none of the adverse events and laboratory abnormalities was considered clinically significant.

### Study 183:

This was a double-blind, placebo-controlled trial of acyclovir for the treatment of chickenpox in immunocompetent children between 2 and 12 years of age. A total of 815 patients were randomized to receive either oral acyclovir or matching placebo. The study medication was 20 mg/kg four times daily for 5 days adjusted by weight according to the following table.

**Table 2.** Acyclovir pediatric suspension dosing

Weight range (kg)	Dose (mg)
5-10	200
11-15	300
16-20	400
21-25	500
26-30	600
31-35	700
36-40	800
> 40	800

According to the Sponsor, no significant differences in adverse events or laboratory abnormalities were noted between the acyclovir and the placebo groups. Three patients were discontinued from the study as a result of an adverse event. Two of the three patients had hives (one in each treatment group) and the third patient who was in the placebo group developed cerebellar ataxia as a complication of varicella. The only serious adverse event reported was ataxia and disorientation in the patient with cerebellar ataxia.

#### **Study 184:**

This was a double-blind, placebo-controlled study of acyclovir for the treatment of chickenpox in immunocompetent adolescents between 13 and 18 years of age. A total of 68 patients were randomized to receive either oral acyclovir (32) or matching placebo (36). The acyclovir dose was 800 mg four times daily for 5 days. All patients were included in the safety analysis.

As with the other two acyclovir studies, no significant differences in adverse events or laboratory abnormalities were noted between the acyclovir and the placebo groups.

**Comment:** The three acyclovir studies for the treatment of chickenpox in children between 2 and 18 years of age revealed that the frequency and intensity of adverse events and laboratory abnormalities were generally similar between the acyclovir and the placebo groups. However, it should be noted that the systemic daily acyclovir exposures after a valacyclovir dose of 20 mg/kg t.i.d. are expected to be approximately 100% higher than the acyclovir exposures seen in pediatric patients receiving acyclovir 20 mg/kg four times daily for the treatment of chickenpox.

#### **Valacyclovir studies**

##### **Valacyclovir pediatric studies conducted in response to the Pediatric Written Request.**

The three pediatric studies conducted in response to the Pediatric Written Request were described previously. In summary, a total of 112 patients, 1 month to < 12 years of age, participated in the three pharmacokinetic and safety studies and received valacyclovir oral suspension. Fifty-one of these 112 patients received oral suspension for 3 to 6 days. The frequency, intensity, and nature of clinical adverse events and laboratory abnormalities were similar to those seen in adults.

**Comment:** Only 20 of the 112 patients received valacyclovir oral suspension at the dose and duration that the Applicant seeks approval. More than half of the patients (65 of the 112) were enrolled in a single-dose pharmacokinetic and safety study.

##### **Studies in children > 12 years of age and adults with herpes labialis**

Two double-blind, placebo-controlled studies were conducted in 1,856 healthy adults and adolescents ( $\geq 12$  years of age) with a history of recurrent cold sores. Patients self-initiated

therapy at the earliest symptoms and prior to any signs of cold sores. Patients were randomized to valacyclovir 2 grams twice daily on Day 1 followed by placebo on Day 2, valacyclovir 2 grams twice daily on Day 1 followed by 1 gram twice daily on Day 2, or placebo on Days 1 and 2.

In these combined studies, 65 adolescents 12 to < 18 years of age received valacyclovir for 1 or 2 days and 30 received placebo. Of the 65 adolescents who received valacyclovir, 34 subjects received the valacyclovir 1-day regimen and 31 subjects received the valacyclovir 2-day regimen. Among the adolescents enrolled in the studies, no treatment limiting events were reported, no subjects were withdrawn from the study because of an adverse event, and no serious adverse events were reported. However, differences in the incidence of adverse reactions reported by adolescents receiving valacyclovir (n=65, across both dosing groups), or placebo (n=30), respectively, included headache (17%, 3%), and nausea (8%, 0%).

### **Studies in adults with genital herpes and herpes zoster infections**

The Applicant also presents a summary of the valacyclovir safety profile in adults from six studies with genital herpes and two studies with herpes zoster infections which are described in the valacyclovir prescribing information. These studies, demonstrate that the frequency, intensity, and nature of clinical and laboratory adverse events were similar between the valacyclovir and placebo groups.

According to the Applicant, the safety data provided from the:

- 3 acyclovir studies in children with chickenpox
- 3 valacyclovir studies in children 1 month to < 12 years of age conducted in response to the valacyclovir Pediatric Written Request
- 2 valacyclovir studies in adolescents and adults with herpes labialis, and
- 8 valacyclovir studies in adults with genital herpes and herpes zoster infections

support the safety profile of valacyclovir in adolescents by demonstrating that:

- The overall adverse event profile of valacyclovir is favorable with the frequency, intensity and nature of clinical and laboratory adverse events generally being similar between the valacyclovir and placebo groups.
- The safety data from the valacyclovir pediatric program are consistent with the safety data seen in the valacyclovir adult studies, with no new safety signals identified.
- The overall safety profile is similar across valacyclovir studies, regardless of disease indication, dose, or treatment duration.
- The totality of the safety data from the valacyclovir program (in children under the age of 12, in adolescents with herpes labialis, and in adults with herpes labialis, herpes zoster and genital herpes) is consistent with the safety data from the adolescent studies of acyclovir for the treatment of chickenpox.

## Conclusions and regulatory action

The pharmacokinetic and safety data submitted to support valacyclovir dosing in children 12 to < 18 years of age were discussed extensively during an internal meeting held on August 18, 2008. Despite the noted deficiencies (safety data at the recommended dose and duration available from a small number of patients < 12 years of age; safety experience with acyclovir studies in children with chickenpox limited by the lower acyclovir systemic exposures), the overall conclusion was that the totality of the available data satisfies expectations to support labeling. Therefore, valacyclovir 20 mg/kg three times daily for five days (not to exceed 1 gram three times daily) is recommended for the treatment of chickenpox in children 12 to < 18 years of age.

### 7.1 Labeling Review

The proposed label submitted with this sNDA has been reviewed by all disciplines involved in the review. The following outlines the agreed upon changes to the label after the May 2, 2008 major amendment to reflect the approval of valacyclovir for the treatment of chickenpox in children 2 to <18 years of age.

The major changes in the modified label involve the following sections:

#### INDICATIONS AND USAGE

This section was changed to add information on the use of valacyclovir in the treatment of chickenpox in children. The Pediatric Patients subsection reads as follows:

##### Pediatric Patients

Cold Sores (Herpes Labialis): VALTREX is indicated for the treatment of cold sores (herpes labialis) in pediatric patients  $\geq 12$  years of age. The efficacy of VALTREX initiated after the development of clinical signs of a cold sore (e.g., papule, vesicle, or ulcer) has not been established.

Chickenpox: VALTREX is indicated for the treatment of chickenpox in immunocompetent pediatric patients 2 to <18 years of age. Based on efficacy data from clinical studies with oral acyclovir, treatment with VALTREX should be initiated within 24 hours after the onset of rash [*see Clinical Studies (14.4)*].

#### DOSAGE AND ADMINISTRATION

This section was changed to add information on the use of valacyclovir in pediatric patients with chickenpox and to provide information on the extemporaneous preparation of valacyclovir oral suspension.

The Pediatric Dosing Recommendations subsection reads as follows:

Cold Sores (Herpes Labialis): The recommended dosage of VALTREX for the treatment of cold sores in pediatric patients  $\geq 12$  years of age is 2 grams twice daily for 1 day taken 12 hours apart. Therapy should be initiated at the earliest symptom of a cold sore (e.g., tingling, itching, or burning).

Chickenpox: The recommended dosage of VALTREX for treatment of chickenpox in immunocompetent pediatric patients 2 to  $<18$  years of age is 20 mg/kg administered 3 times daily for 5 days. The total dose should not exceed 1,000 mg 3 times daily. Therapy should be initiated at the earliest sign or symptom [see *Use in Specific Populations (8.4)*, *Clinical Pharmacology (12.3)*, *Clinical Studies (14.4)*].

The Extemporaneous Preparation of Oral Suspension reads as follows:

Extemporaneous Preparation of Oral Suspension

Ingredients and Preparation per USP-NF: VALTREX Caplets 500 mg, cherry flavor, and Suspension Structured Vehicle USP-NF (SSV). Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) should be prepared in lots of 100 mL.

Prepare Suspension at Time of Dispensing as Follows:

- Prepare SSV according to the USP-NF.
- Using a pestle and mortar, grind the required number of VALTREX 500 mg Caplets until a fine powder is produced (5 VALTREX Caplets for 25 mg/mL suspension; 10 VALTREX Caplets for 50 mg/mL suspension).
- Gradually add approximately 5 mL aliquots of SSV to the mortar and triturate the powder until a paste has been produced. Ensure that the powder has been adequately wetted.
- Continue to add approximately 5 mL aliquots of SSV to the mortar, mixing thoroughly between additions, until a concentrated suspension is produced, to a minimum total quantity of 20 mL SSV and a maximum total quantity of 40 mL SSV for both the 25 mg/mL and 50 mg/mL suspensions.
- Transfer the mixture to a suitable 100 mL measuring flask.
- Transfer the cherry flavor\* to the mortar and dissolve in approximately 5 mL of SSV. Once dissolved, add to the measuring flask.
- Rinse the mortar at least 3 times with approximately 5 mL aliquots of SSV, transferring the rinsing to the measuring flask between additions.
- Make the suspension to volume (100 mL) with SSV and shake thoroughly to mix.
- Transfer the suspension to an amber glass medicine bottle with a child-resistant closure.
- The prepared suspension should be labeled with the following information “Shake well before using. Store suspension between 2° to 8°C (36° to 46°F) in a refrigerator. Discard after 28 days.”

\*The amount of cherry flavor added is as instructed by the suppliers of the cherry flavor.

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