OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	20-487, S-014 (Dosing in pediatric patients)
Submission Dates:	December 10, 2007; May 2, 2008
Brand Name:	VALTREX
Generic Name:	Valacyclovir Hydrochloride
Reviewer:	Shirley K. Lu, Ph.D.
Team Leader:	Kellie S. Reynolds, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 4
OND Division:	Division of Antiviral Products
Sponsor:	GlaxoSmithKline
Submission Type; Code:	505 (b)(1); 1P
Formulation/Strength(s):	Extemporaneous Oral Suspension, 25 mg/mL and 50 mg/mL
Indications and Accompanying Dosing Regimens: (Approved in Adults)	**Herpes Zoster** 1 g TID for 7 days **Genital Herpes:** Initial episode 1 g BID for 10 days Recurrent episodes 500 mg BID for 3 days Suppressive therapy (immunocompetent) 1 g QD Suppressive therapy (alternative dose in immunocompetent adults with ≤9 recurrences/year) 500 mg QD Suppressive therapy in HIV (CD4 count ≥100 cells/mm^3) 500 mg BID Reduction of transmission for source partner 500 mg QD **Herpes Labialis (cold sores)** 2 g BID for 1 day
Proposed pediatric indications (from GSK):	Chickenpox for ages 2 to <18 y.o. (20 mg/kg orally 3 times daily for 5 days, not to exceed 1000 mg 3 times daily)

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1. Executive Summary

Valacyclovir (VACV, Valtrex®) is the L-valyl ester pro-drug of acyclovir (Zovirax). VACV is approved in adults for the treatment of herpes zoster, genital herpes (initial episodes, recurrent episodes, suppressive therapy, and reduction of transmission), and herpes labialis. VACV is currently approved for use in patients ≥12 years of age for the treatment of herpes labialis.

The sponsor has conducted three studies (HS210914, HS210915, and HS210916) in pediatric subjects to evaluate the pharmacokinetics and safety of a new extemporaneous oral suspension formulation. The overall purpose of these studies was to characterize acyclovir pharmacokinetics after administration of VACV to support dosing for treatment of relevant indications in pediatric patients. In order to obtain regulatory approval of an indication in pediatrics, the proposed doses should achieve acyclovir systemic exposures comparable to historical adult and/or pediatric exposures following administration of approved doses of either VACV or acyclovir (ACV, Zovirax®) and demonstrate adequate safety at the proposed dose for the proposed duration of treatment.

A single (b) (4) supplement was originally submitted on December 10, 2007 and included (b) (4) chickenpox in children ages (b) -12 years old. (b) (4) S-014 includes the request for the chickenpox indication. This review consists of an evaluation of the results of study HS210916 to support the chickenpox indication. The PDUFA due date for S-014 was extended by 3 months due to the submission of a major amendment on May 2, 2008 that included the pharmacokinetic rationale to support dosing in adolescents (ages 12-18) for the chickenpox indication. In addition, further clarification was needed for the sponsor's bioanalytical methods and was provided by the sponsor on August 5, 2008.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in this efficacy supplement and provides the following comments regarding the proposed indication:

- **Chickenpox in children ages 2 to <12 y.o.a.:** The PK and safety data are acceptable as support for approval of VACV for the chickenpox indication at a regimen of 20 mg/kg three times daily for 5 days in children ages 2 to <12 years old. Please refer to the medical officer's review for further details on safety information.

- **Chickenpox in adolescents ages 12 to <18 y.o.a.:** The extrapolated PK data and safety information are sufficient to support dosing in adolescents ages 12 to <18 years old.

1.2 Phase IV Commitments

(b) (4)

[redacted]

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Valacyclovir is approved for the following indications in adults with accompanying dosing regimens:

Indication	Valacyclovir Dose
Herpes Zoster	1 g TID for 7 days
Genital Herpes:	
Initial episode	1 g BID for 10 days
Recurrent episodes	500 mg BID for 3 days
Suppressive therapy (immunocompetent)	1 g QD
Suppressive therapy (alternative dose in immunocompetent adults with ≤9 recurrences/year)	500 mg QD
Suppressive therapy in HIV (CD4 count ≥100 cells/mm^3)	500 mg BID
Reduction of transmission for source partner	500 mg QD
Herpes Labialis* (cold sores)	2 g BID for 1 day

*Note: the indication for herpes labialis was approved after the issuance of the pediatric written request.

The three studies listed below were submitted in order to fulfill the pediatric written request (sent by the DAVP in a written request in 2001 and later amended in 2002) [redacted]. However, this review (of S-014) will include only a review of the third study.

Study #1 (HS210914): 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 (HS210915): A single-dose pharmacokinetic, multiple-dose safety study in immunocompetent and/or immunocompromised infants and children age 1-12 years who have HSV infections.

Study #3 (HS210916): A single-dose pharmacokinetic, multiple-dose safety study in immunocompetent and/or immunocompromised infants and children age 1-12 years who have varicella zoster virus (VZV) infections.

The major PK findings from study #3 are presented in the table below.

Mean (±SD) Plasma Acyclovir Pharmacokinetic Parameter Estimates Following First-Dose Administration of 20 mg/kg Valacyclovir Oral Suspension to Pediatric Patients vs. 1 g Valacyclovir Single Dose to Adults

Dose (mg/kg)	Parameter	Age			
		1 - <2 yr	2 - <6 yr	6 - <12 yr	Adult 1 g VACV solid dose*
20	N	6	12	8	15
	AUC (mcg•hr/mL)	14.4 (6.26)	10.1 (3.35)	13.1 (3.43)	17.2 (3.1)
	C_{max} (mcg/mL)	4.03 (1.37)	3.75 (1.14)	4.71 (1.20)	4.72 (1.37)

*Historical estimates using pediatric pharmacokinetic sampling schedule

The main conclusions from this study were:

- The daily acyclovir exposures in pediatric subjects with an active VZV infection given 20 mg/kg VACV are slightly greater than historical exposures in children at approved, effective doses of ACV for the treatment of chickenpox at a dose regimen of 20 mg/kg, 4 times daily for 5 days. The projected pediatric exposures are also greater than adult historical exposures given the approved dose regimen of ACV 800 mg, 5 times daily for 10 days for the treatment of herpes zoster. Thus, the exposures are at least as high as previously approved effective doses of ACV for the treatment of VZV infection.
- Adequate safety data are available for the proposed dosing duration. However, oral ACV is not approved for the treatment of chickenpox in children under 2 years old and thus safety and efficacy cannot be extrapolated to this age group.
- These PK and safety data are acceptable as support for the approval of VACV for the treatment of chickenpox at a regimen of 20 mg/kg three times daily for 5 days in children 2 to <12 years old.
- A regimen of 20 mg/kg three times daily for 5 days in adolescents ages 12 to <18 years old is supported by the interpolations derived from historical adult PK data and the pediatric PK data obtained in this study.

2 Question based review (QBR)

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Valacyclovir hydrochloride (Valtrex, VACV) is the hydrochloride salt of the L-valine ester pro-drug of acyclovir, a synthetic nucleoside analogue that is active against herpes simplex virus types 1 and 2 and varicella zoster virus. Each Valtrex caplet contains valacyclovir HCl equivalent to either 500 mg or 1 g valacyclovir free base. VACV is rapidly converted to acyclovir via first-pass intestinal and/or hepatic metabolism. Due to higher acyclovir bioavailability following oral administration of VACV (54.5% ± 9.1%) as compared with acyclovir administration (10-20%), VACV can achieve higher plasma concentrations of acyclovir with less frequent dosing.

Valacyclovir hydrochloride is a white to off-white powder with the molecular formula $C_{13}H_{20}N_6O_4$•HCl and a molecular weight of 360.80. The maximum solubility in water at 25°C is 174 mg/mL. The proposed final formulation of the extemporaneously prepared oral suspension of VACV is listed below. Detailed instructions on how to prepare the extemporaneous formulation will be included in the final labeling.

Composition of prepared VACV oral suspension

Ingredient	Formula Quantity per 100 mL	
	Valaciclovir Oral Suspension 25 mg/mL	Valaciclovir Oral Suspension 50 mg/mL
VALTREX CAPLETS 500mg	5 caplets	10 caplets
Cherry Flavor (b) (4) (b) (4)	(b) (4)	
Suspension Structured Vehicle USNF	To 100mL	To 100mL

(Components of the suspension structured vehicle: (b) (4)

Composition of 500 mg VACV caplets

Component	Quantity (mg/Caplet)	Reasonable Variation (mg)	Function
Core Valacyclovir Hydrochloride[1] Microcrystalline Cellulose, NF Crospovidone, NF (b) (4) Magnesium Stearate, NF/EP Silicon Dioxide Colloidal, NF (b) (4)	(b) (4)		
(b) (4)			
Approximate Coated Caplet Weight[6]	710.22	(b) (4)	-

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) both *in vitro* and *in vivo*. The following indications and dose regimens are approved in adults:

Indication	**Valacyclovir Dose**
Herpes Zoster	1 g TID for 7 days
Genital Herpes:	
Initial episode	1 g BID for 10 days
Recurrent episodes	500 mg BID for 3 days
Suppressive therapy (immunocompetent)	1 g QD
Suppressive therapy (alternative dose in immunocompetent adults with ≤9 recurrences/year)	500 mg QD
Suppressive therapy in HIV (CD4 count ≥100 cells/mm^3)	500 mg BID
Reduction of transmission for source partner	500 mg QD
Herpes Labialis	2 g BID for 1 day

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The following table shows the sponsor's proposed pediatric dosage and indication for Valtrex oral suspension.

Indication	**Age**	**Pediatric Dosage**
Chickenpox	2 to <18 y.o.a.	20 mg/kg orally 3times daily for 5 days, not to exceed 1000 mg 3 times daily

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

One study was conducted in support of the proposed chickenpox indication for children ages 1-12 years old. Study #HS210916 was a single-dose PK, multiple-dose safety study in immunocompetent and/or immunocompromised infants and children age 1-12 years who have varicella zoster virus (VZV) infections. Interpolated data from studies HS210914, HS210915, and HS210916 and historical adult PK data were used in support of dosing recommendations for adolescents ages 12 to <18 y.o.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

Clinical and micobiological responses would be appropriate endpoints for measurement for herpes virus indications. However, response endpoints were not evaluated in these pediatric studies as the overall goal was to match systemic exposures to those seen in historical adult and pediatric populations given approved VACV and ACV doses and to assess the safety of the proposed pediatric doses.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the sponsor has appropriately measured acyclovir levels in plasma as the primary moiety for PK evaluation. Plasma concentrations of VACV are low and transient, as it is rapidly converted to the active form, acyclovir. VACV typically becomes non-quantifiable by 3 hours post-administration.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Sufficient data are not available for determining exposure-response relationships for efficacy with VACV. The clinical endpoint is different for each herpes virus indication.

2.2.4.2. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

No data are available for exposure-response relationships for safety with VACV.

2.2.4.3. Does valacyclovir prolong QT or QTc interval?

Not applicable to this submission.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The doses selected by the sponsor reflect what is known about pediatric exposures at approved ACV doses, adult exposures at approved VACV and ACV doses, and the observed ACV exposure at the proposed regimen in pediatric patients.

PK and safety information for the chickenpox indication have been provided for adolescents ages 12 to <18 years. PK data to support dosing in the 12-18 year age group to treat chickenpox has been interpolated using existing PK data in children <12 years old and adult PK data.

2.2.5. What are the PK characteristics of valacyclovir?

VACV is rapidly absorbed in the GI tract and converted to acyclovir. The average oral bioavailability of acyclovir following administration of VACV is 54.5% as compared with 10-20% following administration of ACV. The following table shows the mean acyclovir AUC and Cmax exposures in healthy adults receiving doses between 100 mg and 1,000 mg of VACV (values are taken from the text of the current label). Cmax exposures do not increase proportionally with dose between the 250 and 1000 mg doses, however AUC increases very close to dose-proportionally.

Mean (±SD) Plasma Acyclovir Pharmacokinetic Parameters Following Administration of VALTREX to Healthy Adult Volunteers

	Single-Dose Administration (N = 8)		Multiple-Dose Administration* (N = 24, 8 per treatment arm)	
Dose	C_{max} (±SD) (mcg/mL)	AUC (±SD) (hr•mcg/mL)	C_{max} (±SD) (mcg/mL)	AUC (±SD) (hr•mcg/mL)
100 mg	0.83 (±0.14)	2.28 (±0.40)	ND	ND
250 mg	2.15 (±0.50)	5.76 (±0.60)	2.11 (±0.33)	5.66 (±1.09)
500 mg	3.28 (±0.83)	11.59 (±1.79)	3.69 (±0.87)	9.88 (±2.01)
750 mg	4.17 (±1.14)	14.11 (±3.54)	ND	ND
1,000 mg	5.65 (±2.37)	19.52 (±6.04)	4.96 (±0.64)	15.70 (±2.27)

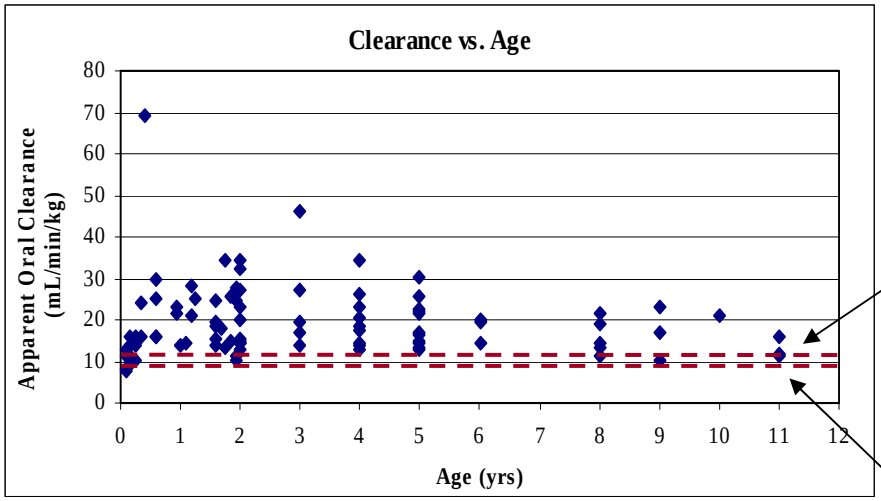
*Administered 4 times daily for 11 days.
ND = not done.

2.3 Intrinsic Factors

2.3.1. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Pediatric Patients: Children generally have higher weight-based clearance rates than adults because of age-related differences in renal function. Thus, on a per kg weight basis, pediatric patients require a higher dose in order to match adult systemic acyclovir exposures. The age groups between 3 months old and 6 years old tended to have higher clearances than the 1-3 month old infants and the oldest age group (6-12 years old). Clearance in the oldest age group approached adult clearance levels. The following figure depicts the relationship between clearance and age for the pediatric patients for all three studies.

Figure 1 **Apparent Oral Clearance for All Age Groups Across All Three Studies**



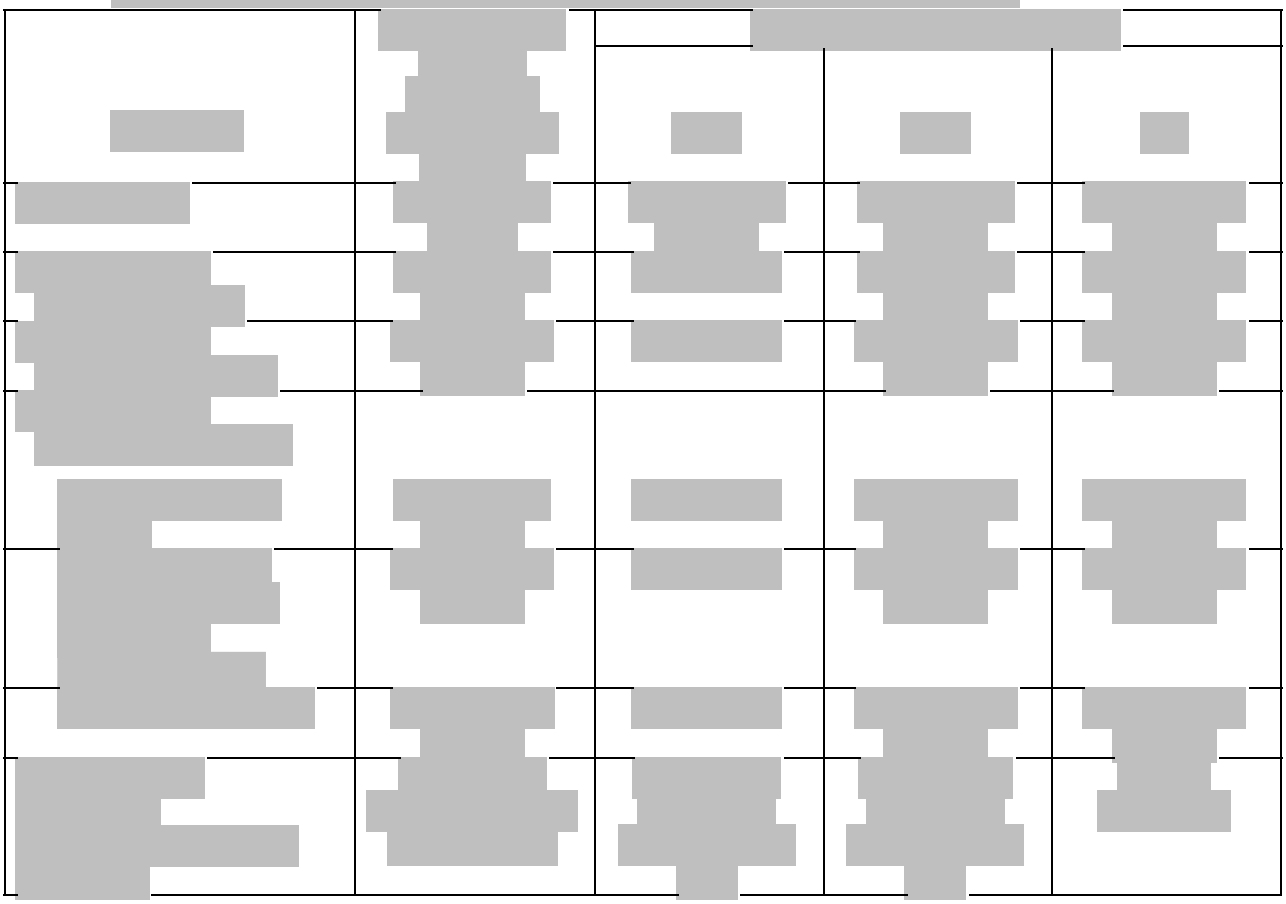
The following information is taken from the Valtrex label:

Geriatrics: Acyclovir plasma concentrations are higher in geriatric patients compared to younger adults, in part due to age-related changes in renal function. Dosage reduction may be required in geriatric patients with underlying renal impairment.

Adults with Impaired Renal Function: The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function.

According to the Valtrex label, precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Thus, not reducing the dose for patients with existing renal insufficiency may result in further renal toxicity or renal failure. The following dosage adjustment table for adults with renal impairment is contained within the Dosage and Administration section of the label.

(b) (4)



2.4 General Biopharmaceutics

2.4.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The information that is available from its solubility, permeability, and dissolution characteristics is inconclusive but would most likely indicate that valacyclovir is a BCS class III drug (low permeability, high solubility), although a BCS class I classification is not precluded.

Solubility: The solubility of valacyclovir in water is 174 mg/mL. At the highest dose strength, the BCS volume would be 5.75 mL (1000 mg ÷ 174 mg/mL). Solubilities in other pH media are not reported in the label or original OCPB review.

Permeability: The absolute bioavailability of VACV after oral administration is ~54%. However, this does not preclude VACV from being classified as BCS class 1 since bioavailability does not solely depict the extent of intestinal absorption, which is the main criteria for the "high permeability" designation.

Dissolution: Dissolution of VACV is pH-dependent. The sponsor's testing of the pure drug substance revealed that the dissolution rate was [redacted] in 0.1 N HCl than in water. Three batches of 500 mg VACV caplets of the same formulation were used in the BE study (conducted as part of the original NDA submission). The dissolution rates between the three batches were highly variable, ranging from [redacted] dissolved in water in 30 mins. and from [redacted] dissolved in 0.1 N HCl in 30 mins. The final specification was: NLT [redacted] (Q) dissolved in 45 minutes in 0.1 N HCl.

2.4.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The bioavailability of the caplet formulation of VACV is ~54.5%, but the bioavailability of the oral suspension has not been investigated. However, information on the relative bioavailability of the oral suspension formulation to the caplet are not critical because doses for children were determined following administration of the oral suspension, the intended formulation for that population.

2.4.3. What is the effect of food on the bioavailability (BA) of acyclovir from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The bioavailability of acyclovir from the administration of VACV caplets is not altered by administration with food in adults. However, the Tmax for acyclovir increased by 77% (from 1.3 to 2.3 hours) following a high-fat meal. Since the clinical significance of the delayed Tmax is not known, the label states that VACV may be given without regard to meals. The effect of food on the bioavailability of the oral suspension has not been studied.

2.5 Analytical Section

2.5.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Acyclovir and valacyclovir are extracted from plasma samples using a **(b) (4)** [redacted] procedure. The samples are then reconstituted and analyzed using HPLC/MS/MS.

2.5.2. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total concentrations of acyclovir and valacyclovir were measured.

2.5.3. Which metabolites have been selected for analysis and why?

Acyclovir metabolites were not measured in these studies.

2.5.4. What bioanalytical methods are used to assess concentrations?

Acyclovir and valacyclovir are extracted from plasma samples using a (b) (4) procedure. The samples are then reconstituted and analyzed using HPLC/MS/MS. The lower limit of quantitation for both analytes is 10 ng/mL using a 50-µL aliquot of human plasma.

3. Labeling Recommendations

Labeling sections pertaining to pediatric/adolescent dosing for the chickenpox indication and information summarizing the results of all three studies have been agreed upon with the sponsor. The sections containing clinical pharmacology information are represented below.

The use of VALTREX for treatment of chickenpox in pediatric patients 2 to <18 years of age is based on single-dose pharmacokinetic and multiple-dose safety data from an open-label trial with valacyclovir and supported by efficacy and safety data from 3 randomized, double-blind, placebo-controlled trials evaluating oral acyclovir in pediatric patients with chickenpox [see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)].

The efficacy and safety of valacyclovir have not been established in pediatric patients:

- *<12 years of age with cold sores*
- *<18 years of age with genital herpes*
- *<18 years of age with herpes zoster*
- *<2 years of age or ≥18 years of age with chickenpox*
- *for suppressive therapy following neonatal herpes simplex virus (HSV) infection.*

The pharmacokinetic profile and safety of valacyclovir oral suspension in children <12 years of age were studied in 3 open-label studies. No efficacy evaluations were conducted in any of the 3 studies.

Study 1 was a single-dose pharmacokinetic, multiple-dose safety study in 27 pediatric patients 1 to <12 years of age with clinically suspected varicella-zoster virus (VZV) infection [see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)].

Study 2 was a single-dose pharmacokinetic and safety study in pediatric patients 1 month to <6 years of age who had an active herpes virus infection or who were at risk for herpes virus infection. Fifty-seven subjects were enrolled and received a single dose of 25 mg/kg valacyclovir oral suspension. In infants and children 3 months to <6 years of age, this dose provided comparable systemic acyclovir exposures to that from a 1 gram dose of valacyclovir in adults (historical data). In infants 1 month to <3 months of age, mean acyclovir exposures resulting from a 25 mg/kg dose were higher (C_{max}: ↑30%, AUC: ↑60%) than acyclovir exposures following a 1 gram dose of valacyclovir in adults. 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.

Study 3 was a single-dose pharmacokinetic, multiple-dose safety study in 28 pediatric patients 1 to <12 years of age with clinically suspected HSV infection. None of the children enrolled in this study had genital herpes. Each subject was dosed with valacyclovir oral suspension, 10 mg/kg twice daily for 3 to 5 days. Acyclovir systemic exposures in pediatric patients following valacyclovir oral suspension were compared with historical acyclovir systemic exposures in immunocompetent adults receiving the solid oral dosage form of valacyclovir or acyclovir for the treatment of recurrent genital herpes. The mean projected daily acyclovir systemic exposures in pediatric patients across all age-groups (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. Insufficient data are available to support valacyclovir for the treatment of recurrent genital herpes in this age-group because 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.

4. Appendix

4.1 Individual Study Review

Study HS210916

"An open-label, multiple-dose, multicenter, pharmacokinetic, safety, and tolerability study of valacyclovir oral suspension in infants and children with VZV infection."

1. Objectives

- Primary objective:
  - To assess the pharmacokinetics of ACV after the first dose administration of VACV oral suspension (20 mg/kg) to VZV-infected infants and children.
- Secondary objectives:
  - To evaluate the safety and tolerability of VACV oral suspension, 20 mg/kg administered three times daily (TID) for five days, to VZV-infected infants and children.
  - To assess the PK of VACV after the first dose administration of VACV oral suspension (20 mg/kg) to VZV-infected infants and children.

2. Study Design

The study was a multicenter, open-label, multiple-dose study designed to include 26 evaluable VZV-infected infants and children that were to be dosed TID for 5 days. Three cohorts were planned and included children aged 1 year to <12 years old. The three cohorts were:

- Cohort 1 - Eight children aged 6 years to <12 years.
- Cohort 2 - Twelve children aged 2 years to <6 years.
- Cohort 3 - Six infants aged 1 year to <2 years.

Six subjects were enrolled for cohort 1 (all 6 included in PK evaluation), 13 subjects for cohort 2 (12 included in PK evaluation), and 8 subjects were enrolled for cohort 3 (8 subjects included in PK evaluation), for a total of 27 subjects enrolled (26 evaluable). Enrollment for each cohort met the FDA-recommended target numbers for enrollment from the pediatric written request.

3. Rationale for Dose Selection

For this study, the sponsor chose to target the acyclovir exposures of the adult dose of 1000 mg VACV. Valtrex is approved to treat herpes zoster in adults at a regimen of 1000 mg TID for 7 days. The sponsor predicted that 20 mg/kg TID in children would provide comparable systemic exposures to 1000 mg TID in adults.

Since weight-based renal clearance in children is generally higher than adults, an equation from Rowland and Tozer (1980) was used to estimate an appropriate pediatric dose for drugs that are predominantly cleared by the kidney. The equation is:

$$\text{Pediatric Dose (mg)} = (\text{Child's weight}/\text{Adult weight})^{0.7} * \text{Adult Dose (mg)}$$

For an average 70 kg adult, 1000 mg of VACV corresponds to a dose of 14.3 mg/kg. Pediatric subjects enrolled in this study were expected to weigh between 10 and 40 kg, which corresponds to doses ranging from 16.9 to 25.6 mg/kg (using the equation from above). Thus, the average dose chosen for the study was 20 mg/kg.

4. Drug Used in the Trial

An extemporaneous oral suspension formulation was used for this study as well as studies HS210914 and HS210915. VACV oral suspension was prepared by crushing 500-mg Valtrex caplets and suspending the resultant powder in the suspension structured vehicle USNF. Refer to table 1 for the components and composition of the vehicle.

VACV oral suspension in 25 mg/mL and 50 mg/mL strengths were prepared in lots of 100 mL using a mortar and pestle to grind Valtrex caplets into a fine powder and adding aliquots of vehicle. Cherry flavor (b) (4) was added to the last aliquot of vehicle that is added to the VACV. Refer to section 2.1.1 for the composition of the resultant suspension.

5. Sample Collection, Bioanalysis, PK Assessments, and Statistical Analysis

Sample Collection

Blood samples (1 mL each) were collected on Day 1 at pre-dose (within 15 minutes of dosing), 0.5, 1, 2, 4, and 6 hours post-dose. The subjects remained in the clinic facility for the duration of the blood collection period.

Bioanalysis

The bioanalytical portion of the study was conducted at (b) (4) . Sample analysis began on 5/3/03 and ended on 11/23/04 as samples were continuously being received from GSK. ACV and VACV along with their respective internal standards were extracted from samples using (b) (4) . Samples were quantitated using HPLC/MS/MS. The LLOQ for ACV and VACV is 10 ng/mL using a 50-µL aliquot of serum.

The calibration standard concentration levels were 10, 20, 50, 100, 200, 400, 600, 800, and 1000 ng/mL for both ACV and VACV. The QC sample concentrations were 30, 400, and 800 ng/mL for both analytes. Dilution validation samples were prepared at a 1:10 and 1:100 dilution.

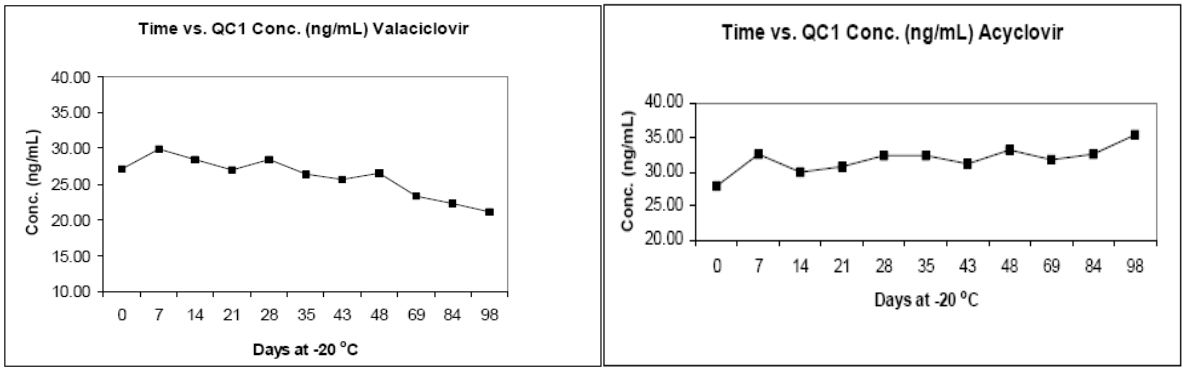
The mean interday precision (%CV) for each ACV QC was 6.95 (low), 5.6 (med), and 5.7 (high). The mean interday accuracy (%bias) for each ACV QC was 2.5 (low), 3.4 (med), and 2.9 (high). The interday precision (%CV) for each VACV QC was 5.9 (low), 5.7

(med), and 5.3 (high). The interday accuracy (%bias) for each VACV QC was 3.5 (low), 2.2 (med), and 4.2 (high).

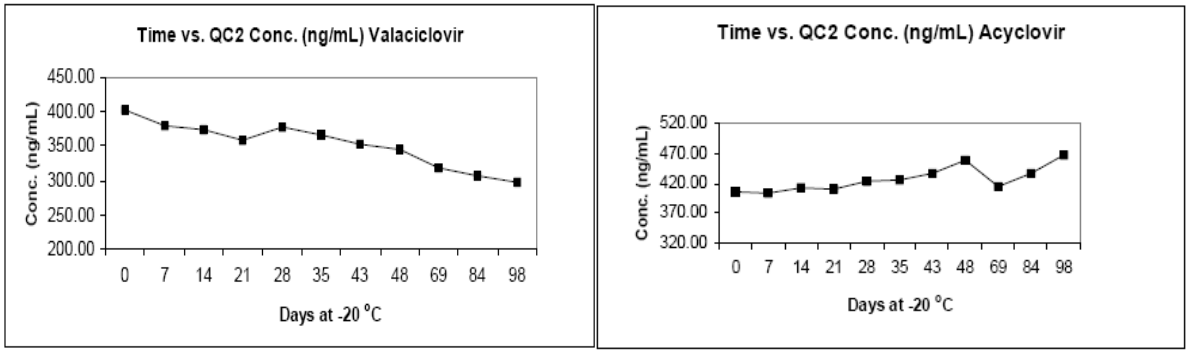
Due to stability issues with valacyclovir stored at -20° C, all study samples and QC samples were moved to -70° C on 1/7/04. The sponsor has stated that the protocol instructions for sample handling and storage conditions were followed. Upon blood collection at the study site, the samples were centrifuged at between 2-8° C within 30 minutes. The tubes of separated plasma were frozen at -20° C and shipped to the bioanalytical laboratory on dry ice. Thus, the plasma samples should have been in a frozen state from after the (b) (4) onward. However, upon analyses of their long-term stability studies, the bioanalytical firm discovered that the amount of valacyclovir in plasma samples was decreasing over time. This decrease in VACV was accompanied by a proportionate increase in ACV, suggesting that biotransformation of VACV was taking place in plasma when stored at -20° C. The cause of this loss of VACV over time is unknown. As figure 2 shows, all three quality control samples experienced a gradual and significant decline in concentrations. The stability of valacyclovir and acyclovir in human plasma could not be confirmed for any samples that were stored for longer than 48 days.

Figure 2 Concentrations of VACV and ACV in human plasma over time at -20° C

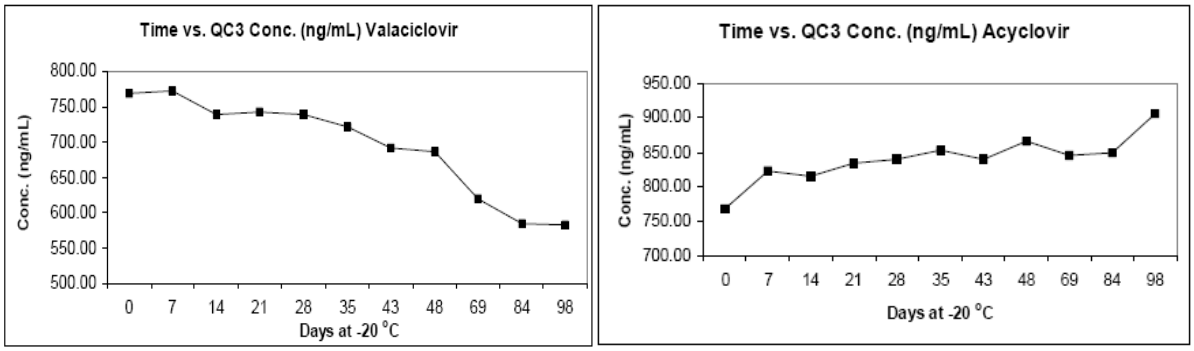
a.



b.



c.



Based on the assessment that drug levels in plasma samples stored at -20° C for longer than 48 days could potentially be unstable, the division requested that the sponsor list all samples (across all three studies) that had been stored at that temperature for a total of 48 days or more. A total of 136 samples were stored at -20° C for >48 days. The maximum VACV degradation in QC samples was (b) (4). Thus, the division requested that the sponsor re-calculate ACV and VACV PK parameters based on a maximum possible (b) (4) in VACV concentrations in those 136 affected samples. The AUC and Cmax mean values for ACV did not differ by more than 1% between the reported and re-calculated estimates. Therefore, it was determined that the change in ACV concentrations and clinical consequence would be minimal, if any. Table 1 shows the reported vs. re-calculated ACV PK parameters.

Table 1 Reported vs. re-calculated ACV PK parameter estimates

	ACV Reported			
	Cmax	Tmax	AUClast	AUCinf
Mean	3.96	1.23	10.10	11.10
Median	3.45	1.00	9.16	10.31
Minimum	1.51	0.50	3.24	3.58
Maximum	7.56	2.00	20.24	22.82

	ACV Estimated			
	Cmax	Tmax	AUClast	AUCinf
Mean	3.92	1.23	10.04	11.05
Median	3.41	1.00	9.10	10.22
Minimum	1.51	0.50	3.22	3.56
Maximum	7.51	2.00	20.11	22.69

	Percent Difference (Reported vs Estimated)			
	Cmax	Tmax	AUClast	AUCinf
Mean	0.85	0.00	0.56	0.47
Median	0.72	0.00	0.54	0.45
Minimum	0.00	0.00	0.00	-0.88
Maximum	2.33	0.00	1.05	2.04

Reviewer's Comments
-Although a proportionate increase of ACV in ACV QC samples was also observed following 48 days of storage, it was more relevant to investigate the impact of a decrease in VACV concentrations (rather than an increase in ACV concentrations) on plasma concentrations of VACV and ACV in plasma samples. This is due to the artificially high amount of VACV that was added to each QC sample that would not typically be found in plasma samples due to the rapid in vivo *conversion to ACV. Thus, a* (b) (4) *in VACV concentrations in a typical*

plasma sample does not necessarily equate to a (b) (4) *in ACV levels as there is a disproportionately higher amount of ACV than VACV in plasma.*
-Although the reported interday QC accuracy in the bioanalytical firm's original study report was relatively good, it is not certain on which days the firm measured those concentrations or at what temperature those QC samples were stored prior to analysis.

Pharmacokinetic Assessments

PK analyses for this study were conducted using a non-compartmental model using WinNonlin Professional Edition Version 4.1. Actual elapsed times from dosing were used to estimate individual PK parameters for evaluable subjects. In addition, when calculating oral clearance (and other related parameters), the actual individual dose administered was used instead of the nominal dose. PK assessments for dosing in adolescents were based on interpolations from pediatric exposures and clearance from the three pediatric studies (HS210914, HS210915, and HS210916) and historical adult PK data.

Statistical Analysis

Statistical analysis was not needed for this study as the intent was only to characterize acyclovir/valacyclovir PK and safety in children of various ages.

6. Results

Dosing in pediatric patients ages 2 to <12 years old

Each subject in this study was dosed with 20 mg/kg TID for 3 to 5 days. However, PK sampling was performed following the administration of the first dose of VACV on day 1. A total of 27 subjects were enrolled with 26 of them completing the study and 26 subjects included in the PK analysis. One subject withdrew consent at the first dose. A summary of the subject demographics is listed in Table 2.

Table 2 Summary of Demographic Characteristics

	Valaciclovir 20 mg/kg TID for 5 days			
Demographics	Total Population N=27	Cohort 1 Age 6-<12 yrs N=8	Cohort 2 Age 2-<6 yrs N=13	Cohort 3 Age 1-<2 yrs N=6
Age, months				
Mean	55.7	96.0	47.7	19.2
SD	32.7	17.8	17.4	4.7
Sex, n (%)				
Female	14 (52)	4 (50)	5 (38)	5 (83)
Male	13 (48)	4 (50)	8 (62)	1 (17)
Race, n (%)				
Asian	1 (4)	0	1 (8)	0
Black/African-American	2 (7)	0	2 (15)	0
White	19 (70)	7 (88)	6 (46)	6 (100)
Other	5 (19)	1 (13)	4 (31)	0
Ethnicity, n (%)				
Hispanic/Latino	0	0	0	0
Not Hispanic/Latino	27 (100)	8 (100)	13 (100)	6 (100)
Height[a], cm				
Mean	103.0	123.8	100.2	81.3
SD	18.9	8.5	13.9	5.0
Weight[a], kg				
Mean	17.2	23.7	16.2	10.8
SD	6.4	6.2	3.8	1.6

a. Measured at Screening.

As shown by the PK parameters in Table 3, VACV levels were low compared to acyclovir. Most subjects' VACV plasma concentrations dipped below the limit of quantitation after approximately 2 hours post-dose. Acyclovir pharmacokinetics in children receiving a 20 mg/kg dose are compared to adults given a 1000 mg dose (Table 4). The sponsor has included estimates of adult PK parameters using the pediatric PK sampling schedule to provide a more accurate comparison.

Table 3 Valacyclovir PK Parameter Estimates Following a Single 20 mg/kg Dose

Valaciclovir PK Parameter	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)
AUC(0-t) (μg•h/mL)				
Geometric Mean (95% CI)	0.21 (0.16-0.28)	0.24 (0.16-0.37)	0.36 (0.28-0.47)	0.26 (0.21-0.32)
Cmax (μg/mL)				
Geometric Mean (95% CI)	0.17 (0.13-0.22)	0.19 (0.13-0.28)	0.20 (0.14-0.28)	0.19 (0.15-0.22)
tmax (h)				
Median (Range)	0.50 (0.50-1.15)	0.83 (0.50-1.12)	0.61 (0.50-1.02)	0.60 (0.50-1.15)

Table 4 Acyclovir PK Parameter Estimates Following a Single 20 mg/kg Dose

	20 mg/kg Suspension in Pediatric Subjects (N=26)				1 g Solid Dose in Adults[a] (N=15)	
Acyclovir PK Parameter	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
AUC(0-∞) (μg•h/mL)						
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
Cmax (μg/mL)						
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
t½ (h)						
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
tmax (h)						
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)
CL/F/kg (mL/min/kg)						
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

N/A=not available

VACV 1 g TID for 7 days and ACV 200 mg 5 times daily are approved regimens for the treatment of herpes zoster in adults. Oral ACV 20 mg/kg 4 times daily is an approved regimen for the treatment of chickenpox in children. In this study, mean projected daily acyclovir AUC exposures in pediatric subjects receiving 20 mg/kg are lower than historical exposures in adults receiving VACV 1 g. However, nearly all pediatric subjects receiving 20 mg/kg have projected daily acyclovir AUC exposures that are comparable or higher than both approved ACV regimens (adults and children). Additionally, the pediatric patients in this study were confirmed to have active varicella zoster virus infection.

Figure 3 Mean Acyclovir and Valacyclovir Plasma Concentrations

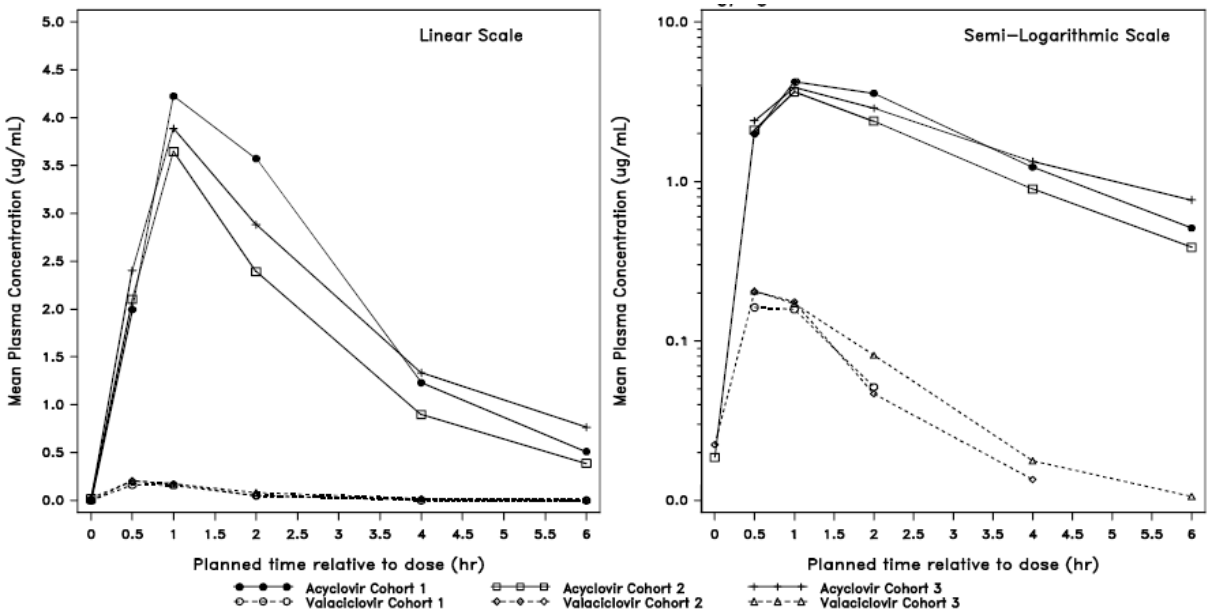


Figure 4 Comparison of Projected Daily ACV AUC Exposures following a single 20 mg/kg dose of Oral VACV in Children to Mean Historical Exposures

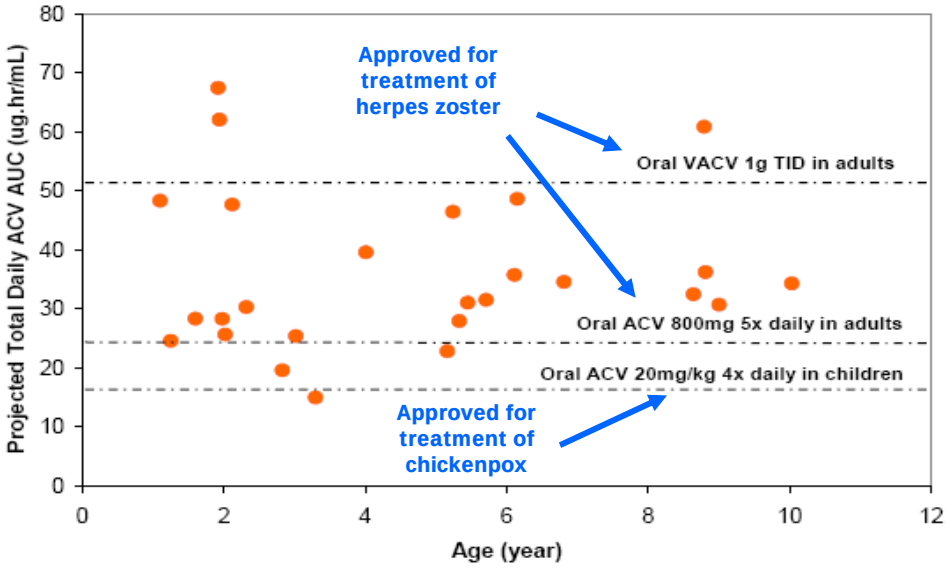
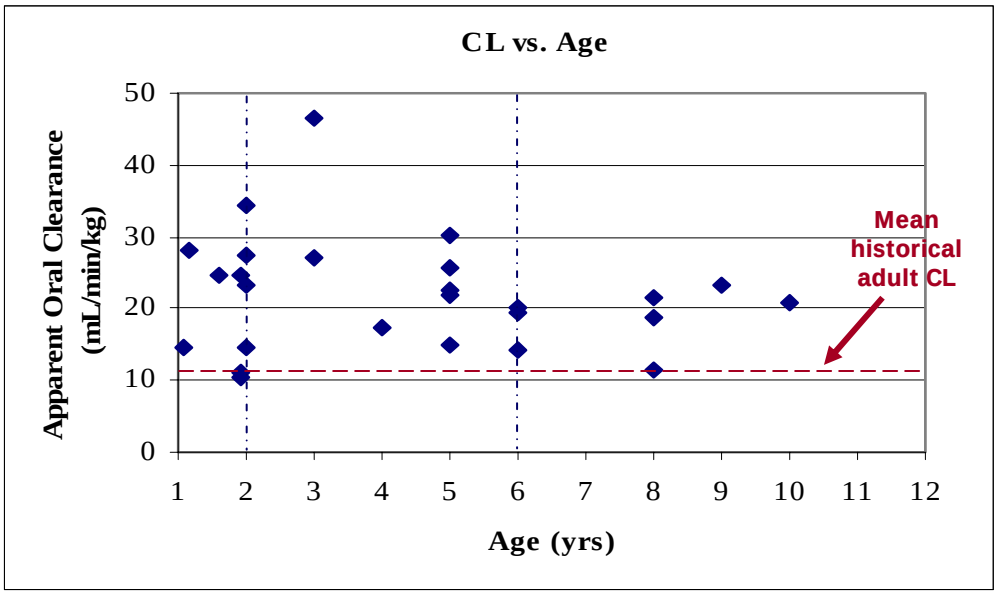


Figure 5 Weight-Normalized Oral Clearance for Each Pediatric Subject Following a Single 20 mg/kg dose of VACV



Dosing in adolescents ages 12 to <18 years old

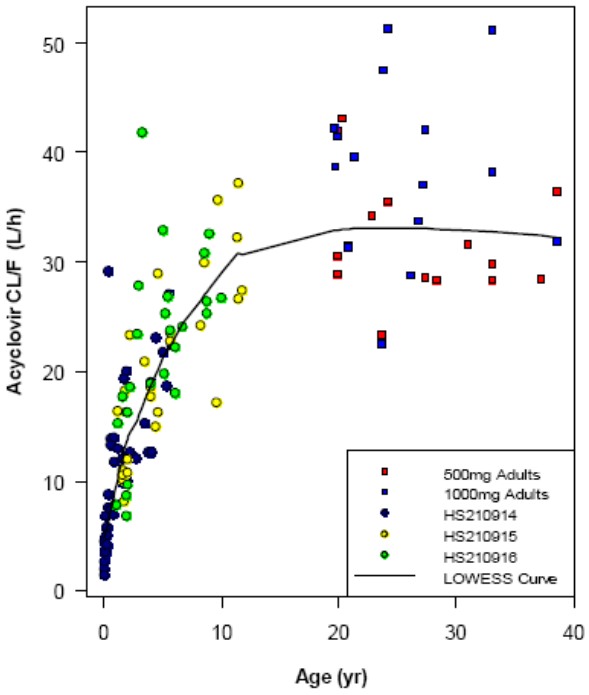
Since an indication for the treatment of chickenpox in pediatric patients ages 12 to <18 years old was lacking, PK and safety rationale in support for dosing in the adolescent age group was requested by the division as a major amendment. Additional efficacy studies were not needed, but safety data in this age group as well as extrapolation or interpolation of PK data was necessary for approval of this indication.

The suitability of using PK extrapolations should be considered when used in lieu of a pediatric study. In this case, the disease course of chickenpox is similar between young pediatric patients and adolescents, and a similar therapeutic outcome would be expected for both patient populations if similar ACV concentrations are achieved. Adolescents that are administered a similar dose given to pediatrics would be expected to have slightly lower exposures than adults, but higher exposures than young pediatric patients. Figure 6a and 6b shows that the predicted clearance in adolescents is expected to lie between the younger patients' and adult clearance values. Overall clearance is extremely low in very young patients and then follows an upward progression toward adult levels. Although the overall clearance for adolescents is expected to be slightly lower than adults, the per kg clearance is expected to be slightly higher in adolescents than in adults. Dosing recommendations for adolescents should follow the dose recommended for younger pediatric patients.

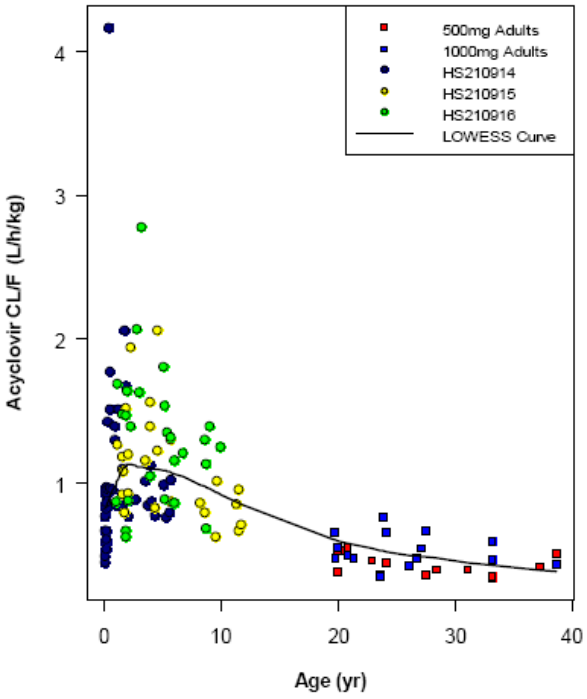
Reviewer's comments:
-It is important to note that extrapolating efficacy from PK data can be used in this case since VACV is a renally eliminated drug and would not likely have unexpected age-related differences in the elimination process in the adolescent age group (as could be the case with a metabolized drug).

Figure 6 Clearance data from VACV administration in pediatric patients and adults

a. Acyclovir clearance vs. age



b. Acyclovir weight-normalized clearance vs. age



(source: GSK amendment dated 7/29/08)

7. Safety Assessments

A total of eight adverse events were experienced by 6 subjects. No subject experienced serious adverse events or death in this study. No subject experienced an adverse event leading to discontinuation of the study treatment or the study itself. One adverse event was deemed related to study drug (nausea; 4% of total study population) by the investigator. Safety data are available for a mean duration of 5.1 days of treatment.

The safety data to support dosing in adolescents comes from the study supporting approval of the herpes labialis indication (65 adolescents given 2 g VACV twice daily for 1 day + VACV 1 g twice daily for 1 day) and study 184 in which 800 mg of ACV was administered 4 times daily to 68 adolescents for 5 days. For a more detailed analysis, please refer to the medical officer's review.

8. Conclusions

The mean projected daily acyclovir exposures in pediatric subjects (who have an active VZV infection) given 20 mg/kg of VACV match or exceed historical exposures in adults and children at approved, effective doses of ACV for the treatment of herpes zoster and chickenpox, respectively (Figure 4). On average, the 2-6 yr. old age group had the highest clearance (mL/min/kg) following a single 20 mg/kg dose (Figure 5).

PK interpolations were used to provide estimates of adolescent exposures and clearances in support of adolescent dosing in the treatment of chickenpox. Clearances in the adolescent age group would be expected to be higher than adults, but slightly lower than younger children on a per kg weight basis. Dosing recommendations can be made based on extrapolation from young pediatric patients as the disease course of chickenpox is generally similar between younger pediatrics and adolescents and the same therapeutic outcome is expected. The disease course is not the same between the approved indication of herpes zoster in adults and chickenpox in pediatrics.

Adequate safety data are available for the proposed dosing duration. However, oral ACV is not approved for the treatment of chickenpox in children under 2 years old and thus safety and efficacy cannot be extrapolated to this age group. These PK and safety data are acceptable as support for approval of VACV for the chickenpox indication at a regimen of 20 mg/kg three times daily for 5 days in children ages 2 to <18 years old.

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