CLINICAL PHARMACOLOGY MEMO

NDA:	22-257
Generic Name:	Valganciclovir hydrochloride
Formulation:	Powder for oral solution; 50 mg/ml
Sponsor:	Roche
Submission Date:	April 30, 2008
Pharmacometrics Reviewer:	Kevin M. Krudys, Ph.D.
Pharmacometrics Team Leader:	Pravin Jadhav, Ph.D.
Clinical Pharmacology Reviewer:	Vikram Arya, Ph.D.
Clinical Pharmacology Team Leader:	Kellie S. Reynolds, Pharm.D.

This document serves as an addendum to the Clinical Pharmacology Review dated Novermber 25, 2008.

EXECUTIVE SUMMARY

The sponsor has adequately resolved the outstanding deficiency noted by the Division of Scientific Investigations, namely to:

> "Identify a set of integrations parameters and re-integrate all the chromatograms within a run in a consistent manner. This procedure should be repeated for all the chromatograms generated in studies WV16726 and CASG109. Use the resulting concentrations to repeat the pharmacokinetic and/or pharmacodynamic evaluation in studies WV16726 and CASG109."

The original pharmacokinetic analysis using manually integrated data was repeated with automatically integrated data. The results indicated a 0% to 4.4% change in $AUC_{0\text{-}24h}$ and a 0% to 16% change in C_{max} in selected transplant type/age groups. Therefore, the recommendations in the original Clinical Pharmacology Review are final:

- The clinical pharmacology and biopharmaceutics information provided to support the dosing recommendations of valganciclovir powder for oral solution in pediatric (4 months -16 years) solid organ transplant recipients for the prophylaxis of CMV disease is acceptable. The reviewer explored other simplified dosing schemes but they were not superior to the sponsor's proposal. The information provided supports the following dosing recommendation:

$$\text{Pediatric Dose (mg)} = 7 \times BSA \times CrCL$$

where

$$\text{Mosteller BSA } (\text{m}^2) = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$$

and

$$\text{Modified Schwartz Creatinine Clearance}\,(mL/\min/1.73m^2) = \frac{k \times Height(cm)}{SerumCreatinine(mg/dL)}$$

where k = 0.45 for patients < 2 years, 0.55 for boys ages 2 to < 13 years and girls ages 2 to 16 years, and 0.7 for boys ages 13 to 16 years. The calculated dose should be rounded to the nearest 25 mg increment for the actual deliverable powder for oral solution dose. If the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered.

- The clinical pharmacology and biopharmaceutics information provided to support the dosing recommendations of valganciclovir powder for oral solution in pediatric patients from birth to less than 3 months for the treatment of congenital CMV is acceptable. However, the safety and efficacy of intravenous ganciclovir (reference treatment used in the study) has not been previously established, (b) (4) The study will be described in section 8.4 (pediatric use) of the package insert to indicate there is similar ganciclovir exposure following administration of 16 mg/kg of valganciclovir and 6 mg/kg IV ganciclovir.
- (b) (4)
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Summary of Important Clinical Pharmacology Findings

WV16726

Automatic re-integration of the chromatograms resulted in one failed run. As a result, 37 pharmacokinetic samples from 9 patients in study WV16726 were excluded from the pharmacokinetic analysis. Two subjects (1101 and 6301) were entirely removed from the pharmacokinetic database. Removal of these 37 samples did not have a significant impact on individual pharmacokinetic parameter estimates in subjects who were affected (Table 1). Similarly in the entire WV16726 population, pharmacokinetic parameters using

automatic integration were similar to the original values estimated with manually integrated data (Table 2).

Table 1. Individual Pharmacokinetic Parameters (Manual vs. Automatic) in Subjects who had Pharmacokinetic Data Excluded from Analysis

ID	Number of PK samples removed	Number of PK samples remaining	CL (manual integration)	CL (automatic integration)	$V_{central}$ (manual integration)	$V_{central}$ (automatic integration)
1101	6	0	3.30	-	16.09	-
1102	6	1	8.33	9.93	28.39	20.80
3101	3	4	5.09	5.41	15.62	14.98
3301	4	2	3.11	2.68	4.19	4.99
6301	4	0	5.10	-	7.69	-
6401	4	3	11.20	12.18	23.54	29.99
5101	4	3	9.24	9.75	17.34	18.65
5102	4	3	8.73	9.44	18.13	22.72
1103	2	3	5.18	4.72	10.67	10.30

Table 2. Comparison of Pharmacokinetic Parameter Estimates from Study WV16726. (Parameter estimates derived from manually integrated data are in black font; parameter estimated derived from automatically integrated data are below in red font.)

	PK Parameter	Age Group (Years)		
		≤ 2 (n=2)	**> 2 to < 12 (n=12)***	**≥ 12 (n=19)**
Kidney	$AUC_{0\text{-}24h}$ (µg·h/mL)	65.2 (16.6)	55.0 (11.9)	50.0 (11.6)
		67.6 (13.0)	55.9 (12.1)	47.8 (12.4)
(N=33)	C_{max} (µg/mL)	10.0 (0.04)	8.74 (2.49)	7.85 (2.10)
		10.4 (0.4)	8.7 (2.1)	7.7 (2.1)
	$t_{1/2}$ (h)	3.10 (0.59)	4.40 (1.41)	5.67 (1.06)
		4.5 (1.5)	4.8 (1.0)	6.0 (1.3)
		≤ 2 (n=9)	**> 2 to < 12 (n=6)**	**≥ 12 (n=2)**
Liver	$AUC_{0\text{-}24h}$ (µg·h/mL)	69.4 (35.4)	58.4 (6.18)	35.6 (2.76)
		69.9 (37.0)	59.4 (8.1)	35.4 (2.8)
(N=17)	C_{max} (µg/mL)	11.7 (3.59)	9.35 (2.33)	5.55 (1.34)
		11.9 (3.7)	9.5 (2.3)	5.5 (1.1)
	$t_{1/2}$ (h)	2.72 (1.32)	3.61 (0.80)	4.50 (0.25)
		2.8 (1.5)	3.8 (0.7)	4.4 (0.2)
		≤ 2 (n=6)	**> 2 to < 12 (n=2)**	**≥ 12 (n=4)**
Heart	$AUC_{0\text{-}24h}$ (µg·h/mL)	56.3 (23.2)	60.0 (19.3)	61.2 (26.0)
		55.4 (22.8)	59.6 (21.0)	60.6 (25.0)
(N=12)	C_{max} (µg/mL)	8.22 (2.44)	12.5 (1.02)	9.50 (3.34)
		8.2 (2.5)	12.5 (1.2)	9.5 (3.3)
	$t_{1/2}$ (h)	3.60 (1.73)	2.62 (0.65)	5.05 (0.70)
		3.8 (1.7)	2.8 (0.9)	4.9 (0.8)

* n = 10 for automatic integration.

CASG109

Pharmacokinetic parameters from study CASG109 using automatic integration were similar to the original values estimated using manually integrated data (Table 3).

Table 3. Comparison of Relevant Pharmacokinetic Parameters in CASG109

Dosing Regimen	AUC_{0-12} (manual integration) Median [range]	AUC_{0-12} (automatic integration) Median [range]
16 mg/kg Valcyte	23.9 [16.7 – 35.4]	23.6 [16.8 – 35.5]
6 mg/kg iv ganciclovir	25.5 [2.45 – 191]	25.3 [2.4 – 89.7]

LABELING RECOMMENDATIONS

As requested by the Division of Anti-Viral Products, the sponsor has updated sections 8.4 and 12.3 (Table 10) of the label to reflect the results using the automatically integrated data. These updates are acceptable and the relevant sections are reproduced below.

8.4 Pediatric Use

The pharmacokinetic results showed that in infants > 7 days to 3 months of age, a dose of 16 mg/kg twice daily of Valcyte for oral solution provided ganciclovir systemic exposures (median AUC_{0-12h} = 23.6 [range 16.8 – 35.5] µg h/mL; n = 6) comparable to those obtained in infants up to 3 months from a 6 mg/kg dose of intravenous ganciclovir twice daily (AUC_{0-12h} = 25.3 [range 2.4 – 89.7] µg h/mL; n = 18) or to the ganciclovir systemic exposures obtained in adults from a 900 mg dose of oral Valcyte twice daily.

12.3 Pharmacokinetics

Table 10 Mean (SD) Pharmacokinetics of Ganciclovir by Age in Pediatric Solid Organ Transplant Patients

	PK Parameter	Age Group in Years		
		≤ 2 (n=2)	**> 2 to < 12 (n=10)[a,b]**	**≥ 12 (n=19)**
Kidney (N=31)	AUC_{0-24h} (µg·h/mL)	67.6 (13.0)	55.9 (12.1)	47.8 (12.4)
	C_{max} (µg/mL)	10.4 (0.4)	8.7 (2.1)	7.7 (2.1)
	$t_{1/2}$ (h)	4.5 (1.5)	4.8 (1.0)	6.0 (1.3)
		≤ 2 (n=9)	**> 2 to < 12 (n=6)**	**≥ 12 (n=2)**
Liver (N=17)	AUC_{0-24h} (µg·h/mL)	69.9 (37.0)	59.4 (8.1)	35.4 (2.8)
	C_{max} (µg/mL)	11.9 (3.7)	9.5 (2.3)	5.5 (1.1)
	$t_{1/2}$ (h)	2.8 (1.5)	3.8 (0.7)	4.4 (0.2)
		≤ 2 (n=6)	**> 2 to < 12 (n=2)**	**≥ 12 (n=4)**
Heart (N=12)	AUC_{0-24h} (µg·h/mL)	55.4 (22.8)	59.6 (21.0)	60.6 (25.0)
	C_{max} (µg/mL)	8.2 (2.5)	12.5 (1.2)	9.5 (3.3)
	$t_{1/2}$ (h)	3.8 (1.7)	2.8 (0.9)	4.9 (0.8)

[a] There was one subject in this age group who received both a kidney and liver transplant. The pharmacokinetic profile for this subject has not been included in this table as it is not possible to determine whether the effects observed are from the kidney/liver transplant or neither.

[b] The pharmacokinetic profiles for two subjects in this age group who received kidney transplants have not been included in this table as the data were determined to be non-evaluable.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22257	ORIG 1	HOFFMAN-LA ROCHE INC	VALCYTE
NDA 22257	ORIG 1	HOFFMAN-LA ROCHE INC	VALCYTE

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/s/

KEVIN M KRUDYS
08/26/2009

VIKRAM ARYA
08/26/2009

PRAVIN R JADHAV
08/26/2009

SARAH M ROBERTSON
08/26/2009
Signing for Kellie Reynolds