Public Assessment Report

EU worksharing project paediatric data

Valcyte®

Valganciclovir

Currently approved indication(s):	Valcyte is indicated for the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). Valcyte is indicated for the prevention of CMV disease in CMV-positive donor and CMV-negative recipient solid organ transplant patients.
Pharmaceutical form(s) affected by this project:	Film-coated tablets
Strength(s) affected by this variation:	450 mg
Marketing authorisation holder	Roche, NL
Start 1st round **Clock-off period** **Procedure re-start date**	18 September 2006 15 December 2006 – 27 February 2008 27 February 2008
Date of this report	31 October 2008
Rapporteur	Medicines Evaluation Board, The Netherlands
Co-Rapporteur	National Institute of Pharmacy, Hungarye

I. INTRODUCTION

Based on the review of the paediatric data on safety and pharmacokinetics, the Rapporteur considers that the variation application for Valcyte, in the treatment of the following therapeutic indication

Valcyte is indicated for the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

Valcyte is indicated for the prevention of CMV disease in CMV-positive donor and CMV-negative recipient solid organ transplant patients

is sufficient. In later phase, when more pharmacokinetic, safety and efficacy data will be available from other studies (to be reported in line with article 46 (of the Paediatric Regulation)), a decision will be made about paediatric labelling in section 4.2, 5.1 and 5.2 of the SmPC.

I.1 Scope of the variation

Roche was requested to submit all available paediatric data for Valcyte® (as mentioned in the FDA list) to be submitted to the EU Member States, as part of the worksharing project assessment of paediatric data of existing products.

In November 2001 Roche agreed to conduct 4 clinical studies to assess the safety and pharmacokinetics of a valganciclovir oral solution in the paediatric population. Currently only one study (WP16296) has been submitted (study WP16296: an open label, dose escalation pharmacokinetic study of valganciclovir in paediatric renal transplant recipients).

Within 6 months after completion of these studies, the MAH will inform the EU Member States in line with Art 46 of the Paediatric Regulation. A Paediatric Investigation Plan (PIP) containing all of these 4 studies will be presented once completed to the Paediatric Committee.

The MAH stated that no recommendation can be made in respect of a change to the EU SmPC at this time to include specific paediatric information in the SmPC/Labelling.

II. SCIENTIFIC DISCUSSION

II.1 Quality aspects

N/A

II.2 Non-clinical aspects

N/A

II.3 Clinical aspects

Completed study with Valcyte® in Children

Study #1 (WP16296) is an open label, dose escalation pharmacokinetic study of valganciclovir in paediatric renal transplant recipients. The study which explored the clinical pharmacokinetics of valganciclovir oral solution (strawberry formulation) was completed and provided to the FDA in December 2005. The same study report is included in this submission.

III.3.1 Clinical pharmacology

Study WP16296

The objective of this study was to determine the once daily dose and the pharmacokinetics of oral valganciclovir syrup that will achieve a ganciclovir 24 hour AUC equivalent to that achieved with once daily standard dosage regimens of i.v. ganciclovir. In this study 25 paediatric kidney transplant recipients with stable renal function, aged between 1 and 16 years, and at risk of developing CMV disease (CMV D+ / R+, D+ / R- or D-/R+) were included. 6 patients were < 6 years of age and 19 patients > 6 years. Creatinine clearance ranged from 45 – 233 ml/min/1.73m^2. The reference dose for i.v. ganciclovir was 200 mg/m^2, based on a standard adult dose of 5 mg/kg, was adjusted based on a weight of 70 kg and a BSA of 1.73 m2. In order to estimate the most appropriate dose of valganciclovir syrup in children, two dose levels of valganciclovir were used. The adult dose of valganciclovir tablets is 900 mg. The lower reference dose of valganciclovir syrup used was 260 mg/m^2, equivalent to half the adult dose (i.e. 450 mg, adjusted for a BSA of 1.73 m^2). The higher reference dose of 520 mg/m^2, was equivalent of the adult dose (i.e. 900 mg, adjusted for a BSA of 1.73 m^2). The doses for both i.v. ganciclovir and oral valganciclovir syrup were adjusted according to renal function. Blood samples were taken at day 2 – 4 (see table below)

Study Day	PK blood sampling schedule, in hours post dose
Dosing day 1	None
Dosing day 2	Pre-dose*, and at 1 (immediately BEFORE the end of the infusion), 2-3, 5-7, 10-12 hours post-dose
Dosing day 3	Pre-dose*, and at 0.25-0.75, 1-3, 5-7, 10-12 hours post-dose
Dosing day 4	Pre-dose*, and at 0.25-0.75, 1-3, 5-7, 10-12 hours post-dose
Follow-up (on day of last PK blood sampling)	22-24 hours, (optional samples at 34-36, 46-50 hours) post-dose

* The pre-dose blood sample on dosing days 2, 3 and 4 was taken at any time within 2 hours prior to dosing. Post-dose blood samples were taken at any time within the windows specified.

Data were analysed by a population pharmacokinetic analysis. Based on previous population pharmacokinetic analyses for ganciclovir and valganciclovir a 2-compartmental model for ganciclovir was considered appropriate. Since the conversion of valganciclovir to ganciclovir is very rapid, no attempt was made to model the concentration time profile of valganciclovir. The overall process of absorption of valganciclovir in tablets and its conversion to ganciclovir can be described by both first and zero order processes. As first order absorption was used in the pharmacokinetic model for the adult SOT study, PV16000, it was included in the basic pharmacokinetic model for children. NONMEM software was used for the modeling. The more accurate first order conditional estimation method (FOCE) was used instead of the first order (FO) method since the run times were short and no numerical problems occurred. In the initial covariate model, CrCL was used as a predictor of clearance according to a power model ($CL = CL_0 \times CrCL^{\alpha}$). Inter-subject variability of all parameters selected was modeled as a log-normal distribution. CrCL was estimated using the Schwartz, rather than the Cockroft-Gault formula, as it is better suited to paediatric data. Since the Schwartz formula produces BSA-normalized CrCL, the results were multiplied by BSA in order to determine actual CrCL in units of mL/min. Body-weight, age and BSA were all evaluated as covariates representing size. Amongst other criteria, such as visual inspection of residual plots, the relevant influence of a covariate was based on the change in objective function between models of increasing complexity.
The basic PK parameters of the final population PK model are listed in the table below:

Description	PK parameter	Estimate	Standard error of estimate	Inter-subject CV (%)
Absorption constant	Ka (L/h)	0.751	0.141	61
Bioavailability	F1	0.534	0.0273	21
Lag Time	Tlag (h)	0.216	0.136	
Clearance	CL (L/h)	$5.93*(CrCLS/65.09)^{0.659}$	0.352 (0.162)	26
Central Volume	V_{cent} (L)	$19.6*(Age/12)^{0.755}$	2.50 (0.128)	32
Peripheral Volume	V_{periph} (L)	$17.5*(Age/12)^{0.755}$	-	77
Intercomp Clearance	Q (L/h)	$4.80*(Age/12)^{0.755}$	-	32

The bioavailability (0.534) of ganciclovir from the valganciclovir syrup was in accordance to that predicted from adults (about 60%, see previous assessments). No dependence on age was observed. In the table below the summary of the individual derived PK parameters by age group are shown:

PK Parameter	Age Group	Arith Mean	CV [%]	Geom. Mean	Median	Min	Max
AUC_{0-24} (mg.h/L) i.v. ganciclovir (200 mg/m^2)	0-5	22.15	20	21.82	22.18	17.13	27.1
	6-11	34.43	37	32.89	37.86	15.78	43.59
	12-16	41.57	38	38.98	38.58	21.01	89.29
AUC_{0-24} (mg.h/L) valganciclovir (520 mg/m^2)	0-5	21.28	19	21.02	22.22	16.15	24.52
	6-11	39.54	49	36.68	43.78	14.45	55.07
	12-16	41.61	32	39.75	39.88	20.95	70.64
C_{max} (mg/mL) i.v. ganciclovir (200 mg/m^2)	0-5	10.46	12	10.40	10.19	9.17	12.29
	6-11	9.07	17	8.97	9.03	6.79	11.28
	12-16	9.99	43	9.21	9.40	3.51	25.26
C_{max} (mg/mL) valganciclovir (520 mg/m^2)	0-5	5.72	32	5.51	5.10	4.20	8.50
	6-11	5.94	37	5.64	6.01	3.37	9.08
	12-16	5.32	21	5.22	5.40	3.56	7.92
$t_{½}$ term (h)	0-5	3.71	57	3.33	3.28	1.97	6.31
	6-11	6.28	52	5.64	4.41	3.06	12.77
	12-16	7.29	52	6.25	5.62	3.32	27.04
CL (L/h)	0-5	4.62	13	4.59	4.71	3.83	5.23
	6-11	5.42	35	5.15	4.92	3.62	8.75
	12-16	7.09	40	6.62	7.40	3.39	12.93

Clearance increased with increasing age group and was lower than the Cl observed in adults (about 9.4 l/h, see previous assessment, study WP15711). AUC after i.v. (200 mg/m^2 dose) and oral administration (520 mg/m^2 dose) were comparable at each age group. The BSA dosing algoritm resulted in lower exposure in younger children compared to adolescents (22.15 vs. 41.57 after iv administration, and 21.28 vs. 41.61 after oral administration).

When the protocol for this study was prepared the exposure was assumed to be proportional to BSA and this should be compared to the effect of dosing proportional to body weight. To assess the effect of dosing per kg body weight versus dosing per m^2 BSA, the doses were calculated for both dosing formulas. Since the AUC is proportional to the dose it is sufficient to compare the doses for both dose adjustments. Dosing per kg body weight would have reduced the AUC of valganciclovir by a median value of 28% over all age groups, by 45% in the age group 0-5, by 34% in the age group 6-11 and by

27% in the age group 12-16. The median AUC_{0-24h} would have been 13, 28 and 30 mg*h/l for the age groups 0-5, 6-11 and 12-16 years, respectively. Therefore dosing proportional to body weight would have reduced the exposure and increased the differences between the age groups.
In the final model CL was not estimated to be proportional to BSA or body weight. The exponent of the influence of unadjusted CrCL on CL was estimated as 0.659. Fixing this value to 1 would increase the OF by 11.9 which corresponds to a p value < 0.001 (F022). If the dosing would have been chosen proportional to $(\text{unadjusted CrCL})^{0.659}$ it would have increased the dose and the exposure of valganciclovir in the median by 51% over all age groups, by 156% in the age group 0-5 years, by 75% in the age group 6-11 and by 26% in the age group 12-16. In this simulation a dose of 900 mg valganciclovir was chosen for a CrCL of 90. The median AUC_{0-24h} would have been 54, 77 and 49 mg*h/l for the age groups 0-5, 6-11 and 12-16 years, respectively. Therefore, dosing proportional to $(\text{unadjusted CrCL})^{0.659}$ would have increased the exposure and decreased the differences between the age groups. The exposures are comparable to the median exposure in adults of 44 mg*h/l (study PV16000, see previous assessment), except for the age group 6-11 years.

Assessor's comments:
Dosing based on BSA provided satisfactory exposure in children aged 6-11 and 12-16 yrs, but obviously for the very young the mg/m² dose was too low.
Dosing based on renal clearance would provide higher exposure in all age groups, but data simulations demonstrate that over-exposure may occur, especially in the two youngest age groups (0-5 and 6-11 yrs, AUC 54 and 77 mg*hr/l, versus adult reference value of 44 mg*hr/l). From safety viewpoint, dosing by renal clearance seems not very feasible.

Neither do the Rapporteurs agree with the Company that dosing based on renal clearance would provide more comparable AUC's over the different age group. The AUCs based on mg/m² dose provided similar AUC levels for the 6-11 and 12-16 y sub-groups.

The Rapporteurs have observed more often with other products that infants may have relative higher clearance capacity of drugs (per kg BW) compared to older children. Maybe age should be taken into account in the dose recommendation.

In addition, the Rapporteurs would like to remark that tablets are better tolerated by children than syrups (especially by older children, when the volume of the dose increases) (see PEG Reflection paper Formulation of Choice for the Paediatric Population, EMEA/CHMP/PEG/194810/2005).

Request for supplementary information and assessment of information provided

1. Dosing based on BSA provided satisfactory exposure in children aged 6-11 and 12-16 yrs, but obviously for the very young the mg/m² dose was too low.
   Dosing based on renal clearance would provide higher exposure in all age groups, but data simulations demonstrate that over-exposure may occur, especially in the two youngest age groups (0-5 and 6-11 yrs, AUC 54 and 77 mg*hr/l, versus adult reference value of 44 mg*hr/l). From safety viewpoint, dosing by renal clearance seems not very feasible.

Assessment of the MAH's response:
The MAH refers to comparable exposure in adults and in addition to the safety profile in adults. Extrapolation of the safety profile to children should be considered with care as this is a different patient group. However, limited data obtained in study WP16296 did not indicate safety concerns. Additional (supportive) data will be provided from the ongoing study WV16726.
As concluded in the previous assessment report, in later phase, when more safety and efficacy data will be available from the other studies, a decision will be made about paediatric labelling in section 4.2 and 5.1.

2. The Rapporteur do not agree with the Company that dosing based on renal clearance would provide more comparable AUC's over the different age group. The AUCs based on mg/m² dose provided similar AUC levels for the 6-11 and 12-16 y sub-groups.

Assessment of the MAH's response:
Although dosing based upon renal clearance results in less comparable AUCs amongst the different age groups, it is acknowledged that under exposure should be prevented. The safety aspects are addressed in question 1. When more data will be available from the other studies, a final decision will be made regarding this issue.

3. The Rapporteurs have observed more often with other products that infants may have relative higher clearance capacity of drugs (per kg BW) compared to older children. Maybe age should be taken into account in the dose recommendation.

Assessment of the MAH's response:
As recognised in study WP16296 no dependence on age was observed regarding bioavailability. As indicated a new dosing algorithm will be developed based upon the ongoing study WP16726. These results will be awaited for further discussion.

4. When doses will be adjusted for the very young, it should be taken into account that Cmax was relatively high in children <6 years old in the study submitted. Maybe infusion period or dosing frequency should be adapted to prevent high Cmax after dose increments.

MAH response:
Based on the pharmacokinetic data from study WP16296, on average, the value for the ganciclovir Cmax within each formulation is very similar across the investigated age range. However, the Cmax achieved following oral administration is approximately 2-fold lower compared to the intravenous administration and therefore reducing any potential safety concern (Table 1.).

Table 1 Comparison of Ganciclovir Cmax values after intravenous and oral administration of ganciclovir and valganciclovir, respectively, by age group in study WP16296: Median (Min – Max)

	Age Group		
PK Parameter	**0-5 years**	**6-11 years**	**12-16 years**
C_{max} (mg/L)	10.19	9.03	9.40
i.v. ganciclovir (200 mg/m$^{2)}$	(9.17, 12.29)	(6.79, 11.28)	(3.51, 25.26)
C_{max} (mg/L)	5.10	6.01	5.40
valganciclovir (520 mg/m^2)	(4.20, 8.50)	(3.37, 9.08)	(3.56, 7.92)

Increasing the dosing frequency is a problem because of the difficulty of administering any oral drugs to young children. In addition, because of the more rapid elimination in this age group increasing the dosing frequency may lead to lower mean plasma ganciclovir concentrations over time and consequent reduced efficacy compared to once daily administration.

Assessment of the MAH's response:
The response of the applicant is considered acceptable. No further comments.

5. The Rapporteurs would like to remark that tablets are better tolerated by children than syrups (especially by older children, when the volume of the dose increases) (see PEG Reflection paper Formulation of Choice for the Paediatric Population, EMEA/CHMP/PEG/194810/2005). The Company is encouraged to investigate PK profile and tolerability of solid tablet formulations in paediatric patients as well.

MAH response:
The pharmacokinetic profile and tolerability of valganciclovir in paediatric SOT patients (n=63) is presently under investigation in the paediatric safety study (WV16726). Depending on the age, paediatric patients are administered their daily dose of valganciclovir comprised of either oral solution or tablets (450 mg). A total daily valganciclovir dose combining the two formulations is not allowed. During the 100 day treatment period in this study, however, a change from oral solution to tablet formulation and vice versa is allowed.

Assessment of the MAH's response:
No further comments.

6. The data from this study are relevant for clinical practice. Even though these data are preliminary as studies are still in process, the preliminary PK outcomes, including a table of the PK data to allow the information to be easily assimilated by potential prescribers should be reported in section 5.2 of the SmPC. In later phase, when more safety and efficacy data will be available from the other studies, a decision will be made about paediatric labelling in section 4.2 and 5.1.

Assessment of the MAH's response:
The Rapporteur understands the point of the applicant regarding the lack of availability of an oral solution and the possible confusion. As currently studies are ongoing and data can be more substantiated, the Rapporteur agrees to update the SmPC at a later time point.

III.3.2 Clinical efficacy

<N/A>

III.3.3 Clinical safety

Patient exposure

Number of subjects study WP16296:
Twenty six patients from 3 months to 16 years of age, with the following number of patients in the specific groups listed below:

Six patients ≤ 6 years.
Nineteen patients > 6 years but pre-pubescent (puberty defined as Tanner Scale stage 5).
One patient aged 16 years and pubescent.

Of the 26 patients enrolled into the study, 25 received the full course of study treatment, comprising a single dose equivalent to 5 mg/kg i.v. ganciclovir on study days 1 and 2, a single dose equivalent to 450 mg valganciclovir syrup on study day 3, and a single dose equivalent to 900 mg valganciclovir syrup on study day 4, as adjusted for BSA and renal function. The remaining patient only received the first 2 doses of i.v. ganciclovir (adjusted for BSA and renal function) on study days 1 and 2, and did not receive either dose of valganciclovir syrup.

Adverse events

During the treatment phase of the study (on treatment), a higher proportion of patients (50% vs. 32%) experienced at least one adverse event while receiving i.v. ganciclovir compared with oral valganciclovir syrup. The most common adverse events experienced by patients on treatment were gastrointestinal disorders (particularly diarrhea, nausea and vomiting), with the incidence of vomiting being higher during treatment with valganciclovir syrup (12.0%, vs. 0%) than during treatment with i.v. ganciclovir. The incidence of all other adverse events appeared broadly comparable during treatment with both study medications. The overall pattern of adverse events remained consistent during the follow-up phase of the

study (off treatment), with gastrointestinal disorders remaining the most frequent adverse event experienced by patients off treatment

Four patients experienced adverse events which were considered by the investigator to be related to trial treatment. Three patients experienced four related adverse events (headache, nausea and vomiting) during treatment with valganciclovir syrup. One patient experienced headaches on dosing days 3 and 4 which were considered by the investigator to be remotely related to trial treatment. One patient experienced headache prior to dosing on day 4 and nausea post-dose on day 4, which were considered possibly and probably related to trial treatment, respectively. One patient experienced vomiting post-dose on day 3, which was considered by the investigator to be possibly related to trial treatment. One patient experienced thrombocytopenia during treatment with i.v. ganciclovir which was considered remotely related to trial treatment
(Table below). No events occurred during the follow-up period (off treatment) that were considered related to prior treatment with i.v. ganciclovir or valganciclovir syrup.

Table 9 Summary of All Related Adverse Events Occurring On Treatment (All Patients)

aell_a4_on Summary of Adverse Events by Body System and Trial Treatment
Summary of Related Adverse Events - On Treatment
Related Adverse Events
Protocol(s): WP16296
Analysis: ALL PATIENTS Center: ALL CENTERS
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Body System/ Adverse Event	All Periods IV GCV N = 26 No. (%)	All Periods VGCV N = 26 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	1 (3.8)	3 (12.0)
Total Number of AEs	1	4
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	-	2 (8.0)
NAUSEA	-	1 (4.0)
VOMITING NOS	-	1 (4.0)
Total Number of AEs	-	2
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	-	2 (8.0)
HEADACHE	-	2 (8.0)
Total Number of AEs	-	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	1 (3.8)	-
THROMBOCYTOPENIA	1 (3.8)	-
Total Number of AEs	1	-

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once under a given treatment.
AE11C 27MAR2003:14:30:58 (1 of 1)

Serious adverse events and deaths

Four patients experienced a total of six serious adverse events during the course of the study, all of these events were considered unrelated to the trial treatment.

Two of these serious adverse events occurred during trial treatment: one patient experienced deep vein thrombosis on dosing day 3 after receiving the first dose of valganciclovir, and one patient experienced sepsis on day 5 before receiving the second dose of valganciclovir.

Four serious adverse events (lymphocele, transplant rejection, urinary tract infection, and wound dehiscence) occurred during the follow-up phase of the study (off treatment)

There were no premature withdrawals due to adverse events, and there were no deaths during the study.

Laboratory findings

The incidence of shifts in grade of laboratory test data is graded according to ACTG grades. There were no patients who exhibited a worsening of 3 grades or more during the treatment period of the study. One patient experienced a worsening of 3 grades between follow-up and the safety review visit (i.e. off treatment): one patient experienced a reduction in neutrophil count (shift from grade 0 to grade 3). The patient experienced no adverse events, and completed the study although reduced neutrophil count remained unresolved. There was no assessment of causality assigned by the investigator.

Long-term safety data; effect on development (growth, motor, mentally, sexually) and cognition

Not available

Conclusions

During the treatment phase of the study (on treatment), the most common adverse events were disorders of the gastrointestinal system (diarrhea, nausea and vomiting), with the incidence of vomiting being higher during treatment with valganciclovir (12%, vs. 0% during treatment with i.v. ganciclovir). The incidence of all other adverse events was comparable during treatment with both study drugs. The overall pattern of adverse events remained consistent during the follow-up phase of the study (off treatment), with gastrointestinal disorders remaining the most frequent adverse event experienced by patients off treatment. The majority of adverse events were considered by the investigators to be unrelated to trial treatment, and either mild or moderate in intensity.

Assessor's comments

The results of the study did not lead to new safety issues. So far, the reported reactions are similar to the reactions reported by adults.

III. OVERALL CONCLUSION <AND BENEFIT-RISK ASSESSMENT>

Dosing based on BSA provided satisfactory exposure in children aged 6-11 and 12-16 yrs, but obviously for the very young the mg/m² dose was too low.
Dosing based on renal clearance would provide higher exposure in all age groups, but data simulations demonstrate that over-exposure may occur, especially in the two youngest age groups (0-5 and 6-11 yrs). From safety viewpoint, dosing by renal clearance seems not very feasible.

The results of the study did not lead to new safety issues. So far, the reported reactions are similar to the reactions reported by adults.

In later phase, when more pharmacokinetic, safety and efficacy data will be available from other studies (within 6 months after completion of these studies the MAH will inform the EU member states in line with article 46 (of the Paediatric Regulation)), a decision will be made about paediatric labelling in section 4.2, 5.1 and 5.2 of the SmPC.