Valcyte®

Valganciclovir

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antiviral

ATC code: J05AB14

1.2 Type of Dosage Form

Film-coated tablet

Powder for oral solution

1.3 Route of Administration

Oral

1.4 Sterile / Radioactive Statement

Not applicable

1.5 Qualitative and Quantitative Composition

Active ingredient: valganciclovir (as valganciclovir hydrochloride).

Film-coated tablets: 450 mg.

Powder for oral solution: 50 mg/ml.

Excipients:

Tablet:

Tablet core: povidone, crospovidone, microcrystalline cellulose, stearic acid powder.

Tablet coat: hydroxypropyl methylcellulose, titanium dioxide (E171), polyethylene glycol, red iron oxide (E172), polysorbate.

Powder:

1 ml of reconstituted solution contains 50 mg valganciclovir (as hydrochloride).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

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

Valcyte is indicated for the prevention of CMV disease in adult and pediatric solid organ transplant (SOT) patients who are at risk.

2.2 Dosage and Administration

Caution – Strict adherence to dosage recommendations is essential to avoid overdose.

Standard Dosage

Valcyte is administered orally, and should be taken with food (see sections 3.2.1 Absorption and 3.2.5 Pharmacokinetics in Special Populations).

Valcyte is rapidly and extensively converted into the active ingredient ganciclovir. The bioavailability of ganciclovir from Valcyte is up to 10-fold higher than from oral ganciclovir.

The dosage and administration of Valcyte tablets or powder for oral solution as described below should be closely followed (see sections 2.4 Warnings and Precautions and 2.7 Overdose).

The ganciclovir systemic exposure following administration of 900 mg Valcyte powder for oral solution is equivalent to a 900 mg Valcyte dose administered as two 450 mg tablets.

An oral dosing dispenser with 25 mg graduations up to 500 mg is provided with the powder for oral solution. It is recommended that this dispenser is used to measure and administer the dose.

Treatment of cytomegalovirus (CMV) retinitis

Adult patients

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is 900 mg twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity (see section 2.4 Warnings and Precautions).

Maintenance treatment of CMV retinitis

Following induction treatment, or in adult patients with inactive CMV retinitis, the recommended dose is 900 mg once daily. Patients whose retinitis worsens may repeat induction treatment (see *Induction treatment of CMV retinitis*).

The duration of maintenance treatment should be determined on an individual basis.

Pediatric patients

The safety and efficacy of Valcyte in the treatment of CMV retinitis have not been established in adequate and well-controlled clinical studies in pediatric patients.

Prevention of CMV disease in transplantation

Adult patients

For kidney transplant patients, the recommended dose is 900 mg once daily starting within 10 days post-transplantation and continuing until 200 days post-transplantation.

For patients who have received a solid organ transplant other than kidney, the recommended dose is 900 mg once daily starting within 10 days post-transplantation and continuing until 100 days post-transplantation.

Pediatric patients

In pediatric solid organ transplant patients from birth, who are at risk of developing CMV disease, the recommended once daily dose of Valcyte is based on body surface area (BSA) and creatinine clearance (Clcr) derived from Schwartz formula (ClcrS), and is calculated using the equation below:

Pediatric dose (mg) = 7 x BSA x ClcrS (see Mosteller BSA formula and Schwartz Creatinine Clearance formula below). If the calculated Schwartz creatinine clearance exceeds 150 ml/min/1.73m^2, then a maximum value of 150 ml/min/1.73m^2 should be used in the equation.

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

$$Schwartz\ Creatinine\ Clearance\ (ml/min/1.73m^2\ ) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dl)}$$

where k = 0.45* for patients aged < 2 years, 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and 0.7 for boys aged 13 to 16 years. Refer to adult dosing for patients older than 16 years of age.

- The k values provided are based on the Jaffe method of measuring serum creatinine, and may require correction when enzymatic methods are used.

- * A lowering of k value may also be necessary for appropriate sub-populations.

For pediatric kidney transplant patients, the recommended once daily mg dose (7x BSA x ClcrS) should start within 10 days post-transplantation and continue until 200 days post-transplantation.

For pediatric patients who have received a solid organ transplant other than kidney, the recommended once daily mg dose (7x BSA x ClcrS) should start within 10 days post transplantation and continue until 100 days post transplantation.

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte tablets may be used if the calculated doses are within 10% of available tablet

doses, and the patient is able to swallow tablets. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.

It is recommended to monitor serum creatinine levels regularly and consider changes in height and body weight and adapt the dose as appropriate during prophylaxis period.

2.2.1 Special Dosage Instructions

Pediatric Patients

Dosing of pediatric SOT patients is individualized based on a patient's renal function and size (see Section 2.2 Dosage and Administration).

Geriatric Use

Safety and efficacy have not been established in this patient population. No studies have been conducted in adults older than 65 years of age. Since renal clearance decreases with age, Valcyte should be administered to elderly patients with special consideration of their renal status (see Table 1 and section 3.2.5 Pharmacokinetics in special populations, Geriatric Population).

Adult patients with renal impairment

Serum creatinine or estimated creatinine clearance levels should be monitored carefully. Dosage adjustment is required for adult patients based on creatinine clearance as shown in Table 1 and Table 2 below (see sections 2.4 Warnings and Precautions and 3.2.5 Pharmacokinetics in Special Populations).

Table 1 Valcyte tablets dose for renally impaired patients

ClCr (ml/min)	**Induction dose of Valcyte tablets**	**Maintenance/Prevention dose of Valcyte tablets**
≥ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days
10 – 24	450 mg every 2 days	450 mg twice weekly
< 10	not recommended	not recommended

Table 2 Valcyte powder for oral solution dose for renally impaired patients

ClCr (ml/min)	**Induction dose of Valcyte oral solution**	**Maintenance/Prevention dose of Valcyte oral solution**
≥ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily

25 – 39	450 mg once daily	225 mg once daily
10 – 24	225 mg once daily	125 mg once daily
<10	200 mg (3 x weekly after dialysis)	100 mg (3 x weekly after dialysis)

Estimated creatinine clearance is calculated from serum creatinine by the following formulae:

For males:

$$\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (0.011 \times \text{serum creatinine [micromol/l]})}$$

For females:

0.85 x male value

Hepatic impairment

The safety and efficacy of Valcyte have not been established in patients with hepatic impairment. (see section 3.2.5 *Pharmacokinetics in special populations, hepatic impairment).*

2.3 Contraindications

Valcyte is contraindicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any of the excipients.

2.4 Warnings and Precautions

2.4.1 General

Cross hypersensitivity

Due to the similarity of the chemical structure of ganciclovir and that of aciclovir and penciclovir, a cross-hypersensitivity reaction between these drugs is possible. Caution should therefore be used when prescribing Valcyte to patients with known hypersensitivity to aciclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively).

Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception

In animal studies ganciclovir was found to be mutagenic, teratogenic, carcinogenic and to impair fertility. Valcyte should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. Prior to initiation of valganciclovir treatment, patients should be advised of the potential risks to the fetus and to use contraceptive measures. Based on clinical and nonclinical studies, Valcyte may cause temporary or permanent inhibition of spermatogenesis (see Sections

2.5.1 Females and Males of Reproductive Potential, 2.5.2 Pregnancy, 2.5.3 Lactation, 2.6 Undesirable Effects 3.3 Nonclinical Safety and 4.2, Special Instructions for Use, Handling and Disposal).).

Myelosuppression

Valcyte should be used with caution in patients with pre-existing hematological cytopenia or a history of drug-related hematological cytopenia and in patients receiving radiotherapy.

Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anemia have been observed in patients treated with Valcyte (and ganciclovir). Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µl or the platelet count is less than 25000/µl or the hemoglobin is less than 8 g/dl (see sections 2.2.1 Special Dosage Instructions, 2.4 Warnings and Precautions and 2.6 Undesirable Effects).

It is recommended that complete blood counts and platelet counts be monitored in all patients during therapy, particularly in patients with renal impairment and in neonates and infants (see Sections 2.4.4 Laboratory Tests and 2.5.4 Pediatric use).

In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia treatment with hematopoietic growth factors and/or the interruption of therapy is recommended (see sections 2.6 Undesirable Effects).

Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir. Valcyte should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).

Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).

Didanosine plasma concentrations may increase during concomitant use with Valcyte; therefore patients should be closely monitored for didanosine toxicity (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).

Concomitant use of other drugs that are known to be myelosuppressive or associated with renal impairment with Valcyte may result in added toxicity (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).

2.4.2 Drug Abuse and Dependence

No information is available for drug abuse and dependence with Valcyte.

2.4.3 Ability to Drive and Use Machines

Adverse reactions such as seizures, dizziness, and confusion have been reported with the use of Valcyte and/or ganciclovir (see Section 2.6 Undesirable Effects). If they occur,

such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility

In animal studies ganciclovir was found to impair fertility (see section 3.3.3 Impairment of Fertility). In a clinical study, renal transplant patients receiving Valcyte for CMV prophylaxis for up to 200 days were compared to an untreated control group. Spermatogenesis was inhibited during treatment with Valcyte. At follow-up, approximately six months after treatment discontinuation, the mean sperm density in treated patients was comparable to that observed in the untreated control group. In Valcyte treated patients, all patients with normal sperm density (n=7) and 8/13 patients with low sperm density at baseline, had normal density after treatment cessation. In the control group, all patients with normal sperm density (n=6) and 2/4 patients with low sperm density at baseline, had normal density at the end of follow-up.

Contraception

Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment. Sexually active men are recommended to use condoms during and for at least 90 days after cessation of treatment with Valcyte, unless it is certain that the female partner is not at risk of becoming pregnant (see Sections 2.4 Warnings and Precautions and 3.3.4 Reproductive Toxicity).

2.5.2 Pregnancy

The safety of Valcyte for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. The use of Valcyte should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the fetus.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity (see section 3.3.4 Reproductive Toxicity).

The safe use of Valcyte during labor and delivery has not been established.

2.5.3 Lactation

Peri- and postnatal development has not been studied with valganciclovir or with ganciclovir but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Human data are not

available but animal data indicates that ganciclovir is excreted in the milk of lactating rats. Therefore, a decision should be made to discontinue the drug or discontinue nursing taking into consideration the potential benefit of Valcyte to the nursing mother.

2.5.4 Pediatric Use

A higher risk of hematological cytopenias in neonates and infants warrants careful monitoring of blood counts in these age groups. Monitoring of liver function abnormalities, renal function and gastrointestinal fluid loss is also recommended in pediatric patients.

See sections 2.1 Therapeutic Indications, 2.2 Dosage and Administration, Standard Dosage, Pediatric patients, 2.6.1 Clinical Trials, Pediatric patients, 3.2.5 Pharmacokinetics in Special Populations and 3.1.2 Clinical/Efficacy Studies for information on pediatric use.

2.5.5 Geriatric Use

Safety and efficacy have not been established in this patient population (see section 2.2.1 Special Dosage Instructions , and 3.2.5 Pharmacokinetics in Special Populations).

2.5.6 Renal Impairment

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations).

2.5.7 Hepatic Impairment

Safety and efficacy have not been established in this patient population (see Section 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations).

2.6 Undesirable Effects

2.6.1 Clinical Trials

Valganciclovir is a prodrug of ganciclovir, which is rapidly converted to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir usage can therefore be expected to occur with Valcyte. All of the adverse drug reactions observed in Valcyte clinical studies have been previously observed with ganciclovir.

Therefore, adverse drug reactions reported with IV or oral ganciclovir (no longer available) or with valganciclovir are included in the table of adverse reactions (see Table 3).

In patients treated with valganciclovir/ganciclovir the most serious and frequent adverse drug reactions are hematological reactions and include neutropenia, anemia and thrombocytopenia.

The frequencies presented in the table of adverse reactions are derived from a pooled population of patients (n=1704) receiving maintenance therapy with ganciclovir (GAN 1697, GAN 1653, 2304, GAN 1774, GAN 2226, AVI 034, GAN 041) or valganciclovir

(WV15376, WV15705). Exception is made for anaphylactic reaction, agranulocytosis and granulocytopenia the frequencies of which are derived from post-marketing experience. Frequencies are presented as percentages and as CIOMS frequency categories defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

The overall safety profile of ganciclovir/valganciclovir is consistent in HIV and transplant populations except that retinal detachment has only been reported in patients with CMV retinitis. However, there are some differences in the frequency of certain reactions. Valganciclovir is associated with a higher risk of diarrhea compared to intravenous ganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC <500/µl) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

Table 3 Frequency of Ganciclovir/Valganciclovir ADRs Reported in HIV Patients Receiving Maintenance Therapy (n=1704)

ADR (MedDRA) System Organ Class	**Percentage**	**Frequency Category**
Infections and infestations:		
Candida infections including oral candidiasis.	22.42%	Very common
Upper respiratory tract infection	16.26%	
Sepsis	6.92%	Common
Influenza	3.23%	
Urinary tract infection	2.35%	
Cellulitis	1.47%	
Blood and lymphatic disorders:		
Neutropenia	26.12%	Very common
Anemia	19.89%	
Thrombocytopenia	7.34%	Common
Leukeopenia	3.93%	
Pancytopenia	1.06%	
Bone marrow failure	0.29%	Uncommon
Aplastic anemia	0.06%	Rare
Agranulocytosis*	0.02%	
Granulocytopenia*	0.02%	
Immune system disorders:		
Hypersensitivity	1.12%	Common
Anaphylactic reaction*	0.02%	Rare
Metabolic and nutrition disorders:		

Decreased appetite	12.09%	Very common
Weight decreased	6.46%	Common
Psychiatric disorders:		
Depression	6.69%	Common
Confusional state	2.99%	
Anxiety	2.64%	
Agitation	0.59%	Uncommon
Psychotic disorder	0.23%	
Thinking abnormal	0.18%	
Hallucinations	0.18%	
Nervous system disorders:		
Headache	17.37%	Very common
Insomnia	7.22%	Common
Neuropathy peripheral	6.16%	
Dizziness	5.52%	
Paraesthesia	3.58%	
Hypoaesthesia	2.58%	
Seizures	2.29%	
Dysgeusia (taste disturbance)	1.35%	
Tremor	0.88%	Uncommon
Eye disorders:		
Visual impairment	7.10%	Common
Retinal detachment**	5.93%	
Vitreous floaters	3.99%	
Eye pain	2.99%	
Conjunctivitis	1.58%	
Macular edema	1.06%	
Ear and labyrinth disorders:		
Ear pain	1.17%	Common
Deafness	0.65%	Uncommon
Cardiac disorders*:*		
Arrhythmia	0.47%	Uncommon
Vascular disorders*:*		
Hypotension	2.05%	Common
Respiratory, thoracic and mediastinal disorders:		
Cough	18.31%	Very common
Dyspnea	11.80%	
Gastrointestinal disorders:		
Diarrhea	34.27%	Very common
Nausea	26.35%	
Vomiting	14.85%	
Abdominal pain	10.97%	
Dyspepsia	4.81%	Common
Flatulence	4.58%	

Abdominal pain upper	4.58%	
Constipation	3.70%	
Mouth ulceration	3.17%	
Dysphagia	2.93%	
Abdominal distention	2.41%	
Pancreatitis	1.64%	
Hepato-biliary disorders:		
Blood alkaline phosphatase increased	3.58%	Common
Hepatic function abnormal	3.23%	
Aspartate aminotransferase increased	1.88%	
Alanine aminotransferase increased	1.23%	
Skin and subcutaneous tissues disorders:		
Dermatitis	11.80%	Very common
Night sweats	7.92%	Common
Pruritus	4.58%	
Rash	2.52%	
Alopecia	1.29%	
Dry skin	0.94%	Uncommon
Urticaria	0.70%	
Musculo-skeletal and connective tissue disorders:		
Back pain	4.46%	Common
Myalgia	3.52%	
Arthralgia	3.35%	
Muscle spasms	2.99%	
Renal and urinary disorders:		
Renal impairment	2.52%	Common
Creatinine clearance renal decreased	2.35%	
Blood creatinine increased	1.88%	
Renal failure	0.76%	Uncommon
Hematuria	0.70%	
Reproductive system and breast disorders:		
Infertility male	0.23%	Uncommon
General disorders and administration site conditions:		
Pyrexia	33.51%	Very common
Fatigue	18.96%	
Pain	5.81%	Common
Chills	5.40%	
Malaise	2.11%	
Asthenia	2.00%	
Chest pain	0.88%	Uncommon

** The frequencies of these adverse reactions are derived from post-marketing experience*

***Retinal detachment has only been reported in HIV patients treated for CMV retinitis*

Description of selected adverse reactions

Neutropenia

The risk of neutropenia is not predictable on the basis of the number of neutrophils before treatment. Neutropenia usually occurs during the first or second week of induction therapy. The cell count usually normalizes within 2 to 5 days after discontinuation of the drug or dose reduction (see Section 2.4, Warnings and Precautions).

Thrombocytopenia

Patients with low baseline platelet counts (< 100,000 / µl) have an increased risk of developing thrombocytopenia. Patients with iatrogenic immunosuppression due to treatment with immunosuppressive drugs are at greater risk of thrombocytopenia than patients with HIV (see Section 2.4, Warnings and Precautions). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Influence of treatment duration or indication on adverse reactions

Severe neutropenia (ANC <500/µl) is seen more frequently in CMV retinitis patients (16%) undergoing treatment with valganciclovir than in solid organ transplant patients receiving valganciclovir or oral ganciclovir. In patients receiving valganciclovir or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia was 5% and 3% respectively, whilst in patients receiving valganciclovir until Day 200 post-transplant the incidence of severe neutropenia was 10%.

There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 or Day 200 post-transplant with both valganciclovir and oral ganciclovir when compared to CMV retinitis patients. However, impaired renal function is a feature more frequent in solid organ transplantation patients.

The overall safety profile of Valcyte did not change with the extension of prophylaxis up to 200 days in high risk kidney transplant patients. Leukopenia was reported with a slightly higher incidence in the 200 days arm while the incidence of neutropenia, anaemia and thrombocytopenia were similar in both arms.

Laboratory Abnormalities

Laboratory abnormalities reported in adult CMV retinitis patients and SOT patients receiving valganciclovir until Day 100 post-transplant are listed in Table 4. The incidence of laboratory abnormalities was comparable with the extension of prophylaxis up to 200 days in high risk kidney transplant patients.

Laboratory abnormalities reported in pediatric SOT patients are listed in Table 5. The incidence of severe neutropenia (ANC<500/µL) was higher in pediatric kidney transplant patients treated until Day 200 as compared to pediatric kidney transplant patients treated until Day 100 and to adults kidney transplant patients treated until Day 100 or Day 200.

Table 4 Laboratory Abnormalities in Adult Patients

Laboratory abnormalities	**CMV Retinitis Patients [6]**	**Solid Organ Transplant Patients (Dosing until Day 100 Post-Transplant) [2]**	
	Valganciclovir (n=370)	**Valganciclovir (n=244)**	**Oral ganciclovir (n=126)**
	%	**%**	**%**
Neutropenia (ANC/µL)			
<500	16	5	3
500 - <750	17	3	2
750 - <1000	17	5	2
Anemia (hemoglobin g/dL)			
<6.5	7	1	2
6.5 - <8.0	10	5	7
8.0 - <9.5	14	31	25
Thrombocytopenia (platelets/µL)			
<25000	3	0	2
25000 - <50000	5	1	3
50000 - <100000	21	18	21
Serum creatinine (mg/dL)			
>2.5	2	14	21
>1.5 – 2.5	11	45	47

Table 5 Laboratory Abnormalities in Pediatric Solid Organ Transplant patients

Laboratory abnormalities	**Valganciclovir in Pediatric SOT patients**	
	Dosing until Day 100 Post-Transplant [44] n=63	**Dosing until Day 200 Post-Transplant [49] n=56**
	%	**%**
Neutropenia (ANC/µL)		
<500	**5**	**30**
500 - <750	**8**	**7**
750 - <1000	**5**	**11**
Anemia (hemoglobin g/dL)		
<6.5	**0**	**0**
6.5 - <8.0	**14**	**5**
8.0 - <9.5	**38**	**29**
Thrombocytopenia (platelets/µL)		
<25000	**0**	**0**
25000 - <50000	**10**	**0**
50000 - <100000	**3**	**4**
Serum creatinine (mg/dL)		
>2.5	**2**	**5**
>1.5 – 2.5	**11**	**20**

Pediatric patients

Valcyte has been studied in 179 pediatric solid organ transplant patients who are at risk of developing CMV disease (aged 3 weeks to 16 years) and in 133 neonates with symptomatic congenital CMV disease (aged 2 to 31 days), with duration of ganciclovir exposure ranging from 2 to 200 days (see section 3.1.2 Clinical/Efficacy Studies).

The overall safety profile was similar in pediatric patients as compared to adults. Neutropenia was also reported with slightly higher incidence in the two pediatric studies as compared to adults but neutropenia and infectious adverse events were generally not correlated in the pediatric populations.

In kidney transplant pediatric patients, prolongation of valganciclovir exposure to 200 days was not associated with increased incidence of adverse events.

Congenital CMV

Congenital CMV is not an approved indication for Valcyte. However, studies conducted in neonates and infants with congenital CMV do provide safety data in this patient population. Studies suggest that the safety of Valcyte and Cymevene appear consistent with the known safety profile of valganciclovir/ganciclovir. The primary toxicity is neutropenia, in one study 9 of 24 subjects (38%) developed Grade 3 or 4 neutropenia while on ganciclovir therapy (one patient required treatment cessation). Most events were manageable with continuation of antiviral therapy. Growth (head circumference, weight and height) of all neonates, who had growth measurements recorded, increased over time in this non-comparative study. The most frequent treatment related AEs associated with oral valganciclovir were neutropenia, anemia, liver function abnormality and diarrhea, all seen more frequently in the placebo group. The only treatment-related SAEs were neutropenia and anemia, both seen more frequently in the placebo arm. No statistically or clinically significant differences were observed in the rate of growth (average head circumference, weight and length) over time at each time point between the two treatment groups.

2.6.2 Postmarketing Experience

Safety reports from the postmarketing setting are consistent with safety data from clinical trials with valganciclovir and ganciclovir (see Section 2.6.1 Undesirable Effects - Table 3).

2.7 Overdose

Overdose experience with valganciclovir and intravenous ganciclovir

It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity (see sections 2.2 Dosage and Administration and 2.4 Warnings and Precautions).

Reports of overdose with intravenous ganciclovir, some with fatal outcomes, have been received from clinical trials and during post-marketing experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:

– Hematological toxicity: myelosuppression including pancytopenia, bone marrow failure, leukopenia, neutropenia, granulocytopenia.

– Hepatotoxicity: hepatitis, liver function disorder

– Renal toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine.

– Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting.

– Neurotoxicity: generalised tremor, seizure.

Hemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see Section 3.2.5 Pharmacokinetics in Special Populations).

2.8 Interactions With Other Medicinal Products And Other Forms Of Interaction

Drug interactions with Valcyte

Valcyte is the pro-drug of ganciclovir; therefore interactions associated with ganciclovir are expected.

Imipenem-cilastatin

Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly and a pharmacodynamic interaction between these two drugs cannot be discounted. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see Section 2.4 Warnings and Precautions).

Potential drug interactions

Toxicity may be enhanced when ganciclovir / valganciclovir is co-administered with other drugs known to be myelosuppressive or associated with renal impairment. This includes nucleoside analogues (e.g. zidovudine, didanosine, stavudine), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vinblastine, vincristine, hydroxyurea) and anti-infective agents (trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these drugs should only be considered for concomitant use with valganciclovir

if the potential benefits outweigh the potential risks (see Section 2.4 Warnings and Precautions).

Zidovudine

Both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, a pharmacodynamic interaction may occur during concomitant administration of these drugs, some patients may not tolerate concomitant therapy at full dosage (see Section 2.4 Warnings and Precautions).

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with IV ganciclovir. At intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38 to 67% has been observed confirming a pharmacokinetic interaction during the concomitant administration of these drugs. There was no significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis) (see Section 2.4 Warnings and Precautions).

Probenecid

Probenecid given with oral ganciclovir resulted in statistically significantly decreased renal clearance of ganciclovir (20%) leading to statistically significantly increased exposure (40%). These changes were consistent with a mechanism of interaction involving competition for renal tubular excretion. Therefore patients taking probenecid and valganciclovir should be closely monitored for ganciclovir toxicity.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir, which after oral administration is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of herpes viruses *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir mono-phosphate by the viral protein kinase, UL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly. This has been shown to occur in HSV- and HCMV-infected cells with half-lives of 18 and between 6 and 24 hours respectively after removal of extracellular ganciclovir. As phosphorylation is largely dependent on the viral kinase, the phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase and (b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited further viral DNA elongation. Typical antiviral IC_{50} against CMV *in vitro* is in the range 0.08 μM (0.02 μg/ml) to 14 μM (3.5 μg/ml).

The clinical antiviral effect of Valcyte has been demonstrated in the treatment of AIDS patients with newly diagnosed CMV retinitis (clinical trial WV15376). CMV shedding was decreased from 46% (32/69) of patients at study entry to 7% (4/55) of patients following 4 weeks of Valcyte treatment.

3.1.2 Clinical / Efficacy Studies

Adult patients

Treatment of CMV retinitis

Clinical studies of Valcyte have been conducted in patients with AIDS and CMV retinitis. Valcyte has shown comparable efficacy for induction treatment of CMV retinitis to intravenous ganciclovir.

Patients with newly diagnosed CMV retinitis were randomised in one study to induction therapy with either Valcyte or intravenous ganciclovir. The proportion of patients with progression of CMV retinitis at week 4 was the same in both treatment groups.

Following induction treatment dosing, patients in this study received maintenance treatment with Valcyte given at the dose of 900 mg daily. The mean (median) time from randomisation to progression of CMV retinitis in the group receiving induction and maintenance treatment with Valcyte was 226 (160) days and in the group receiving induction treatment with intravenous ganciclovir and maintenance treatment with Valcyte was 219 (125) days.

Valcyte allows systemic exposure of ganciclovir similar to that achieved with recommended doses of intravenous ganciclovir, which has been shown to be efficacious in the treatment of CMV retinitis. Ganciclovir AUC has been shown to correlate with time to progression of CMV retinitis.

Prevention of CMV disease in transplantation

A double-blind, double-dummy clinical active comparator study has been conducted in heart, liver and kidney transplant patients at high risk of CMV disease (D+/R–) who received either Valcyte (900 mg od) or oral ganciclovir (1000 mg tid) starting within 10 days of transplantation until day 100 post-transplant. The incidence of CMV disease (CMV syndrome + tissue invasive disease), as adjudicated by an independent Endpoint Committee, during the first 6 months post-transplant was 12.1% in the Valcyte arm (n=239) compared with 15.2% in the oral ganciclovir arm (n=125). The majority of cases occurred following cessation of prophylaxis (post day 100) with cases in the valganciclovir arm occurring on average later than those in the oral ganciclovir arm. The incidence of acute rejection in the first 6 months was 29.7% in patients randomised to valganciclovir compared with 36.0% in the oral ganciclovir arm.

A double-blind, placebo controlled study has been conducted in 326 kidney transplant patients at high risk of CMV disease (D+/R–) to assess the efficacy and safety of extending Valcyte CMV prophylaxis from 100 to 200 days post-transplant. Patients were randomised (1:1) to receive Valcyte tablets (900 mg od) within 10 days of transplantation either until day 200 post-transplant or until day 100 post-transplant followed by 100 days of placebo.

Extending CMV prophylactic therapy with Valcyte until day 200 post-transplant demonstrated superiority in preventing CMV disease within the first 12 months post-transplant in high-risk kidney transplant patients compared to the 100-day dosing regimen.

The proportion of patients who developed CMV disease during the first 12 months post-transplant is shown in Table 6.

Table 6 Percentage of kidney transplant patients with CMV disease[1], 12-month ITT population

	Valganciclovir 900 mg od 100 days	**Valganciclovir 900 mg od 200 days**	**Cochran-Mantel-Haenszel p-value**
Patients with confirmed or assumed CMV disease[2]	71/163 (43.6%)	36/155 (23.2%)	0.0001
Patients with confirmed CMV disease	60/163 (36.8%)	25/155 (16.1%)	<0.0001

[1] CMV Disease is defined as either CMV syndrome or tissue invasive CMV. [2] Confirmed CMV is a clinically confirmed case of CMV disease. Patients were assumed to have CMV disease if there was either no week 52 assessment or no confirmation of CMV disease before this time point.

The graft survival rate at 12 months post-transplant was 98.2% (160/163) for the 100-day dosing regimen and 98.1% (152/155) for the 200-day dosing regimen. The incidence of biopsy proven acute rejection at 12 months post-transplant was 17.2% (28/163) for the 100-day dosing regimen and 11.0% (17/155) for the 200-day dosing regimen.

Pediatric patients

Prevention of CMV disease in transplantation

Valganciclovir powder for oral solution has been studied in five open-label, multi-center clinical trials in pediatric solid organ transplant (SOT) patients.

Three of these studies assessed only the pharmacokinetics and safety of oral valganciclovir in SOT patients requiring anti-CMV prophylaxis ranging in age from birth to 16 years of age (see section 3.2.5 Pharmacokinetics in Special Populations). One study enrolled 20 liver transplant patients with a median age of 2 years (6 months to 16 years) who received a single daily dose of valganciclovir on 2 consecutive days. A second study enrolled 26 kidney patients with a median age of 12 years (1 to 16 years) who received multiple doses of valganciclovir on 2 consecutive days. The third study enrolled 14 heart transplant patients with a median age of 13 weeks (3 weeks to 125 days) who received a single daily dose of valganciclovir on 2 consecutive days.

The other two studies assessed the development of CMV disease, as a measure of efficacy, following prophylaxis of valganciclovir for up to 100 days and 200 days post transplant using the pediatric dosing algorithm described in section 2.2 Dosage and Administration. One solid organ transplant study enrolled 63 pediatric kidney, liver or heart patients with a median age of 9 years (4 months to 16 years) who received daily doses of valganciclovir for up to 100 days. There was no CMV event reported during the study that would fulfil the definition of CMV disease. CMV events were reported in 7 patients during the study of which 3 did not require adjustment to study drug or were not treated and, therefore, were not considered clinically significant (see section 2.6.1 Clinical Trials and 3.2.5 Pharmacokinetics in Special Populations). The second study in solid organ transplant enrolled 57 pediatric kidney patients with a median age of 12 years (1 to 16 years) who received daily doses of valganciclovir for up to 200 days. There was no CMV event reported during the study that would fulfill the definition of CMV disease. While 4 patients reported CMV events, one could not be confirmed by the central laboratory and of the 3 remaining events one did not require treatment and, therefore, was not considered clinically significant (see section 2.6.1 Clinical Trials).

Congenital CMV

The efficacy and safety of ganciclovir and/or valganciclovir were studied in neonates and infants with congenital symptomatic CMV infection in two studies, with patients receiving up to 6 weeks or 6 months of treatment. The dose of valganciclovir that was determined in the first study and carried forward to the second study was twice daily doses of Valcyte oral solution based on body weight using the following equation: Dose (mg) = 16 mg per kg of body weight.

Efficacy was evaluated using relevant endpoints such as hearing outcomes, neurodevelopmental outcomes and correlations of CMV blood viral load with ganciclovir plasma concentrations and hearing (see section 2.6.1 Clinical Trials).

Viral resistance

Viruses resistance to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in either the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation or the viral polymerase gene (UL54). UL97 mutations arise earlier and more frequently than mutations in UL54. Virus containing mutations in the UL97 gene is resistant to ganciclovir alone, with M460V/I, H520Q, C592G, A594V, L595S, C603W being the most frequently reported ganciclovir resistance-associated substitutions. Mutations in the UL54 gene may show cross-resistance to other antivirals targeting the viral polymerase, and vice versa. Amino acid substitutions in UL54 conferring cross-resistance to ganciclovir and cidofovir are generally located within the exonuclease domains and region V, however amino acid substitutions conferring cross resistance to foscarnet are diverse, but concentrate at and between regions II (codon 696-742) and III (codon 805-845).

Treatment of CMV retinitis (Adult patients)

Genotypic analysis of CMV in polymorphonuclear leukocytes (PMNL) isolates from 148 patients with CMV retinitis enrolled in one clinical study has shown that 2.2%, 6.5%, 12.8% and 15.3% contain UL97 mutations after 3, 6, 12 and 18 months, respectively, of valganciclovir treatment.

Prevention of CMV disease in transplantation

Resistance was studied by genotypic analysis of CMV in PMNL samples collected i) on day 100 (end of study drug prophylaxis), and ii) in cases of suspected CMV disease up to 6 months after transplantation. From the 245 patients randomised to receive valganciclovir, 198 day 100 samples were available for testing and no ganciclovir resistance mutations were observed. This compares with 2 ganciclovir resistance mutations detected in the 103 samples tested (1.9%) for patients in the oral ganciclovir comparator arm.

Of the 245 patients randomised to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 125 patients in the ganciclovir comparator arm, samples from 29 patients with suspected CMV disease were tested, from which 2 resistance mutations were observed, giving an incidence of resistance of 6.9%.

Resistance was evaluated in a study that extended valganciclovir CMV prophylaxis from 100 days to 200 days post-transplant in adult kidney transplant patients at high risk for CMV disease (D+/R-) (see section 3.1.2 Clinical/Efficacy Studies). Five subjects from the 100 day group and four subjects from the 200 day group meeting the resistance analysis criteria had known ganciclovir resistance-associated amino acid substitutions detected. In six subjects, the following resistance associated amino acid substitutions were detected within pUL97: 100 day group: A440V, M460V, C592G; 200 day group: M460V, C603W. In three subjects, the following resistance-associated amino acid substitutions were detected within pUL54: 100 day group: E315D, 200 day group: E315D, P522S. Overall, the detection of known ganciclovir resistance-associated amino acid substitutions was observed more frequently in patients during prophylaxis therapy than after the completion of prophylaxis therapy (during therapy: 5/12 [42%] versus after therapy: 4/58 [7%]). The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

3.1.3 Immunogenicity

Not applicable.

3.2 Pharmacokinetic Properties

The pharmacokinetic properties of valganciclovir have been evaluated in HIV- and CMV-seropositive patients, patients with AIDS and CMV retinitis and in solid organ transplant patients.

The parameters which control the exposure of ganciclovir from valganciclovir are bioavailability and renal function. The bioavailability of ganciclovir from valganciclovir is comparable across all the patient populations studied (adults and pediatrics). The

systemic exposure of ganciclovir to heart, kidney, and liver transplant recipients was similar after oral administration of valganciclovir according to the adult renal function dosing algorithm and pediatric dosing algorithm (see section 2.2 Dosage and Administration).

Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir in the dose range 450 to 2625 mg was demonstrated only under fed conditions.

3.2.1 Absorption

Valganciclovir is a prodrug of ganciclovir, which is well absorbed from the gastro-intestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The bioavailability of ganciclovir from oral dosing of valganciclovir is approximately 60%. Systemic exposure to valganciclovir is transient and low, $AUC_{0\text{-}24h}$ and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

When valganciclovir was given with food at the recommended dose of 900 mg, increases were seen in both mean ganciclovir $AUC_{0\text{-}24h}$ (approximately 30%) and mean ganciclovir C_{max} values (approximately 14%). Therefore, it is recommended that Valcyte be administered with food (see section 2.2 Dosage and Administration).

3.2.2 Distribution

Because of the rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. The steady-state volume of distribution of ganciclovir after intravenous administration was 0.680 ±0.161 l/kg.

For IV ganciclovir, the volume of distribution is correlated with body weight with values for the steady state volume of distribution ranging from 0.54-0.87 l/kg. Ganciclovir penetrates the cerebrospinal fluid. Binding to plasma proteins was 1%-2% over ganciclovir concentrations of 0.5 and 51 µg/ml.

3.2.3 Metabolism

Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected.

Ganciclovir itself is not metabolized to a significant extent.

3.2.4 Elimination

Following dosing with oral valganciclovir, the drug is rapidly hydrolyzed to ganciclovir. Ganciclovir is eliminated from the systemic circulation by glomerular filtration and active tubular secretion. In patients with normal renal function greater than 90% of IV administered ganciclovir was recovered un-metabolized in the urine within 24 hours. In patients with normal renal function the post-peak plasma concentrations of valganciclovir decline with a half-life ranging from 0.4 h to 2.-0 h. In these patients ganciclovir concentrations decline with a half-life ranging from 3.5 to 4.5 hours similarly to that observed after direct IV administration of ganciclovir.

3.2.5 Pharmacokinetics in Special Populations

Pediatric Population

Prevention of CMV disease in transplantation

The pharmacokinetics of ganciclovir following the administration of valganciclovir were characterized using a population PK model based on data from four studies in pediatric solid organ transplant (SOT) patients aged 3 weeks to 16 years. PK data were evaluable from 119 of the 123 patients enrolled. In these studies, patients received daily intravenous doses of ganciclovir to produce exposure equivalent to an adult 5 mg/kg intravenous dose (70 kg reference body weight) and/or received oral doses of valganciclovir to produce exposure equivalent to an adult 900 mg dose.

The model indicated that clearance is influenced by body weight and creatinine clearance while the central and peripheral volumes of distribution were influenced by body weight (see section 2.2 Dosage and Administration, Pediatric Patients).

The mean ganciclovir Cmax, AUC and half-life by age and organ type in studies using the pediatric dosing algorithm are listed in Table 7 and are consistent with estimates obtained in adult SOT patients.

Table 7 Summary of Model-Estimated Mean (±SD) Pharmacokinetics of Ganciclovir in Pediatric Patients by Age

Transplant Subgroups	**PK Parameter**	**Age Group**			
		Heart Transplant Recipients < 4 months of age [48]		**Solid Organ Transplant Patients 4 months to 16 years [44]**	
		< 4 months (n=14)	**4 months ≤ 2 years (n=2)**	**> 2- < 12 years (n=12)***	**≥ 12 years (n=19)**
Kidney	$AUC_{0\text{-}24h}$ (µg·h/ml)	**---**	65.2 (16.6)	55.0 (11.9)	50.0 (11.6)
(N=33)	C_{max} (µg/ml)	**---**	10.0 (0.04)	8.74 (2.49)	7.85 (2.10)
	$t_{1/2}$ (h)	**---**	3.10 (0.59)	4.40 (1.41)	5.67 (1.06)
		---	**4 months ≤2 years (n=9)**	**>2 - < 12 years (n=6)**	**≥ 12 years (n=2)**
Liver	$AUC_{0\text{-}24h}$ (µg·h/ml)	**---**	69.4 (35.4)	58.4 (6.18)	35.6 (2.76)
(N=17)	C_{max} (µg/ml)	**---**	11.7 (3.59)	9.35 (2.33)	5.55 (1.34)
	$t_{1/2}$ (h)	**---**	2.72 (1.32)	3.61 (0.80)	4.50 (0.25)
		< 4 months (n=14)	**4 months ≤2 years (n=6)**	**> 2 - < 12 years (n=2)**	**≥ 12 years (n=4)**
Heart	$AUC_{0\text{-}24h}$ (µg·h/ml)	68.1(19.8) †	56.3 (23.2)	60.0 (19.3)	61.2 (26.0)
(N=26)	C_{max}	10.5 (3.35)	8.22 (2.44)	12.5 (1.02)	9.50 (3.34)

Transplant Subgroups	PK Parameter	Age Group			
		Heart Transplant Recipients < 4 months of age [48]		Solid Organ Transplant Patients 4 months to 16 years [44]	
	(µg/ml)				
	$t_{1/2}$ (h)	2.00 (0.19)	3.60 (1.73)	2.62 (0.65)	5.05 (0.70)

* There was one subject who received both a kidney and liver transplant. The PK 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.

†n = 18 observations, 3 patients contributed more than one value

Congenital CMV

Ganciclovir pharmacokinetics following valganciclovir administration were also evaluated in 133 neonates aged 2 to 31 days with symptomatic congenital CMV disease in two studies.

In the first study, all patients received 6 mg/kg intravenous ganciclovir twice daily. Patients were then treated with oral valganciclovir, where the dose of valganciclovir powder for oral solution ranged from 14 mg/kg to 20 mg/kg twice daily. A dose of 16 mg/kg twice daily of valganciclovir powder for oral solution provided comparable ganciclovir exposure as 6 mg/kg intravenous ganciclovir twice daily in neonates, and also achieved ganciclovir exposure similar to the effective adult 5 mg/kg intravenous dose. In the second study, all patients received valganciclovir powder for oral solution at a dose of 16 mg/kg twice daily for 6 weeks and subsequently 96 out of 109 enrolled patients were randomized to continue receiving valganciclovir or placebo for 6 months.

The mean ganciclovir AUC0-12hr after oral dose administration of valganciclovir was approximately 23.2 µg.h/ml (equivalent to 46.4 µg.h/ml in AUC0-24hr) in the first study. Similar exposure was also observed in the second study.

Geriatric Populaion

No investigations on valganciclovir or ganciclovir pharmacokinetics in adults older than 65 years of age have been undertaken. However as valganciclovir is a pro-drug of ganciclovir and because ganciclovir is mainly renally excreted and since renal clearance decreases with age, a decrease in ganciclovir total body clearance and a prolongation of ganciclovir half-life can be anticipated in elderly (see Section 2.2.1 Special Dosage Instructions)

Patients with renal impairment

The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir were evaluated in 24 otherwise healthy individuals with renal impairment.

Table 8: Pharmacokinetic parameters of ganciclovir from a single oral dose of 900 mg Valcyte tablets in patients with various degrees of renal impairment

Estimated	N	Apparent	$AUC_{0-\infty}$	Half-life (hours)

Creatinine Clearance (mL/min)		**Clearance (mL/min) Mean ± SD**	**(µg·h/mL) Mean ± SD**	**Mean ± SD**
51-70	6	249 ± 99	50.5 ± 23	4.9 ± 1.4
21-50	6	136 ± 64	100 ± 54	10.2 ± 4.4
11-20	6	45 ± 11	252 ± 64	21.8 ± 5.2
≤10	6	12.8 ± 8	407 ± 83	68.1 ± 35

Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see sections 2.2.1 Special Dosage Instructions and 2.4 Warnings and Precautions).

Patients undergoing hemodialysis

Ganciclovir is readily removable by hemodialysis. Data obtained during intermittent haemodialysis in patients dosed with valganciclovir showed estimated dialysis clearance as 138 ml/min ± 9.1% (N = 3) and intra-dialysis half-life estimated to 3.47 h (N = 6).

55% of ganciclovir was removed during a 3 hour dialysis session.

Stable liver transplant patients

The pharmacokinetics of ganciclovir from valganciclovir in stable liver transplant patients were investigated in one open-label 4-part cross-over study (n = 28). The bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed conditions, was approximately 60%. Ganciclovir $AUC_{0\text{-}24h}$ was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant patients.

Hepatic impairment

No pharmacokinetic study has been conducted and no population PK data was collected in patients with hepatic impairment undergoing valganciclovir therapy.

Patients with cystic fibrosis

In a phase I pharmacokinetic study, steady state systemic exposure to ganciclovir was assessed in lung transplant recipients with or without cystic fibrosis (N=31) who were receiving 900 mg/day of Valcyte as part of their post-transplant prophylaxis. The study indicated that cystic fibrosis had no statistically significant influence on the overall average systemic exposure to ganciclovir in lung transplant recipients. Ganciclovir exposure in lung transplant recipients was comparable to that shown to be efficacious in the prevention of CMV disease in other solid organ transplant recipients.

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

Valganciclovir and ganciclovir were mutagenic in mouse lymphoma cells and clastogenic in mammalian cells. Such results are consistent with the positive mouse carcinogenicity study with ganciclovir. Ganciclovir is a potential carcinogen.

3.3.2 Genotoxicity

Valganciclovir and ganciclovir were mutagenic in mouse lymphoma cells and clastogenic in mammalian cells.

3.3.3 Impairment of Fertility

Ganciclovir causes impaired fertility and teratogenicity in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. The same reprotoxicity warning is seen as applying to both drugs (see section 2.4 Warning and Precautions).

Based upon animal studies where aspermia was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir (and valganciclovir) could cause temporary or permanent inhibition of human spermatogenesis (see Section 2.5.1 Females and Males of Reproductive Potential, Fertility).

3.3.4 Reproductive Toxicity

Ganciclovir causes teratogenicity in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. The same reprotoxicity warning is seen as applying to both drugs (see section 2.4 Warning and Precautions).

3.3.5 Other

No additional information is available.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Film-coated tablets

Shelf life: As registered locally

Storage: As registered locally

Powder for oral solution

Powder for oral solution:

Shelf life: As registered locally

Storage: As registered locally

Reconstituted solution:

After reconstitution with purified water the solution should not be used for longer than 49 days.

The reconstituted solution should be stored in a refrigerator (2ºC–8°C).

4.2 Special Instructions for Use, Handling and Disposal

Stability

Tablets should not be broken or crushed. Since Valcyte is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets or Valcyte powder for oral solution (see section 2.4 Warnings and Precautions). Avoid direct contact of broken or crushed tablets, powder or reconstituted solution with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water or plain water if sterile water is not available.

It is recommended that Valcyte powder for oral solution be reconstituted by the pharmacist prior to dispensing to the patient. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution.

Preparation of solution

1 Measure 91 ml of purified water in a graduated cylinder.
2 Remove the child-resistant cap and add the water to the bottle. Shake the closed bottle until the powder is dissolved.
3 Remove the child-resistant cap and push the bottle adapter into the neck of the bottle.
4 Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.
5 Write the date of expiration of the reconstituted solution on the bottle label. [The shelf life of the reconstituted solution is 49 days. The reconstituted solution should be stored in a refrigerator (2ºC–8°C).

This medicine should not be used after the expiry date (EXP) shown on the pack.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

4.3 Packs

Film-coated tablets 450mg 60

1 bottle of 12 g powder for oral solution, a bottle adapter and 2 oral dispensers

Medicine: keep out of reach of children

Current at July 2017

Made for F. Hoffmann- La Roche Ltd., Basel, Switzerland
by Patheon Inc., Mississauga, Canada