Valcyte®

Valganciclovir

1. DESCRIPTION

1.1. Therapeutic / Pharmacologic Class of Drug

Antiviral

ATC code: J05AB14

1.2. Type of Dosage Form
Film-coated tablet

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. The tablets are pink, film-coated, and convex oval with 'VGC' embossed on one side and '450' on the other side.

2. Clinical Particulars

2.1 Therapeutic Indications
Valcyte tablets are indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

Valcyte is indicated for the prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant patients at high risk. (Donor CMV seropositive/ Recipient CMV seronegative [(D+/R-)]).

Valcyte is not indicated for use in liver transplant patients.

The safety and efficacy of Valcyte for the prevention of CMV disease in other solid organ transplant patients such as lung transplant patients have not been established.

2.2. Dosage and administration
Caution – Strict adherence to dosage recommendations is essential to avoid overdose. Valcyte tablets cannot be substituted for ganciclovir tablets on a one-to-one basis.

2.2.1 Standard Dosage
Valcyte is administered orally, and should be taken with food (see Pharmacokinetics in Special Populations, 3.2.1 Absorption). After oral administration, Valcyte is rapidly and extensively converted into ganciclovir. The bioavailability of ganciclovir from Valcyte is up to 10-fold higher than from ganciclovir capsules. Therefore the dosage and administration of Valcyte tablets as described below should be closely followed (see 2.4 Special Warnings and Special Precautions for Use and 2.7 Overdosage).

For the treatment of CMV retinitis in patients with normal renal function

Adults

Induction

For patients with active CMV retinitis, the recommended dose is 900 mg (two 450 mg tablets) twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity (see section 2.4 Special Warnings and Special Precautions for use).

Maintenance:

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg (two 450 mg tablets) once daily with food. Patients whose retinitis worsens may repeat induction treatment (see Induction).

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

For the prevention of CMV disease in heart, kidney, and kidney-pancreas transplantation

For kidney transplant patients, the recommended dose is 900 mg (two 450 mg tablets) once daily with food starting within 10 days post-transplantation and continuing until 100 days post-transplantation. Prophylaxis may be continued until 200 days post-transplantation (See 2.4 Special Warnings and Special Precautions for Use, 2.6 Undesirable Effects and 3.1.2 Efficacy/Clinical Studies).

For patients who have received a heart, or kidney-pancreas transplant, the recommended dose is 900 mg (two 450 mg tablets) once daily with food starting within 10 days post-transplantation and continuing until 100 days post-transplantation.

2.2.2 Special dosage instructions
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).

Patients with renal impairment

Serum creatinine or estimated creatinine clearance levels should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in the table below (see 3.2.5 Pharmacokinetics in special populations and 2.4 Special Warnings and Special Precautions for Use).

Table 1 Valcyte Tablets Dose for Renally Impaired Patients

CrCl (ml/min)	Induction dose	Maintenance dose/ Prevention dose
³ 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

Estimated creatinine clearance can be calculated from serum creatinine by the following formula:

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

For females = 0.85 x male value

Patients undergoing hemodialysis

For patients on hemodialysis (CrCl < 10 ml/min) a dose recommendation cannot be given. Thus Valcyte should not be used in these patients (see 3.2.5 Pharmacokinetics in special populations and 2.4 Special Warnings and Special Precautions for Use).

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).

Children

Safety and efficacy have not been established in this patient population. The use of Valcyte in children is not recommended because the pharmacokinetic characteristics of Valcyte have not been established in this patient population (see 2.4 Special Warnings and Special Precautions).

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

Due to the similarity of the chemical structure of Valcyte and that of aciclovir and penciclovir, a cross-hypersensitivity reaction between these drugs is possible.

2.4 Special Warnings and Special Precautions for Use
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 in males (see 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).

Myelosuppresssion

Valcyte should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological 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/㎥ or the platelet count is less than 25000 /㎥ or the hemoglobin is less than 8 g/dl. Valcyte tablets should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or are receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may increase with continued dosing. Cell counts usually begin to recover within 3 to 7 days of discontinuing drug. (see 2.2.2 Special dosage instructions, 2.4 Special Warnings and Special Precautions and 2.6 Undesirable effects)

The use of Valcyte in children is not recommended (see 2.2.2 Special dosage instructions).

The diagnosis of CMV retinitis should be made by indirect opthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis include candidiasis, toxoplasmosis, histoplasmosis, retinal scars and cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason it is essential that the diagnosis of CMV be established by an ophthalmologist familiar with the presentation of these conditions. The diagnosis of CMV retinitis may be supported by culture of CMV in the urine, blood throat, or other sites, but a negative culture does not rule out CMV retinitis. The bioavailability of ganciclovir from Valcyte is 10-fold higher than from ganciclovir capsules. Valcyte cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte tablets (see 2.2 Dosage and administration and 2.7 Overdosage).

It is recommended that complete blood counts and platelet counts be monitored in all patients during therapy, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/µl at the beginning of the treatment and in neonates and infants. In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia, treatment with hematopoietic growth factors and/or the interruption of therapy is recommended (see 2.5.4 Pediatric use and 2.6 Undesirable effects). In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see 2.2.2 Special dosage instructions and 3.2.5. Pharmacokinetics in special populations).

For patients on hemodialysis (CrCl < 10 ml/min) a dose recommendation cannot be given. Thus, Valcyte should not be used in these patients. (see 2.2.2 Special dosage instructions and 3.2.5 Pharmacokinetics in special populations).

Use with other medicines

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 2.8 Interactions with other Medical 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 2.8 Interactions with other Medical 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 2.8 Interactions with other Medical 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 2.8 Interactions with other Medical Products and other Forms of Interaction).

2.4.1. Drug Abuse and Dependence
No information is available for drug abuse and dependence with Valcyte.

2.4.2. 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 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 2.4 Special Warnings and Special 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 3.3.4 Reproductive Toxicity).

The safety 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.

2.5.5. Geriatric Use
Safety and efficacy have not been established in this patient population (see section 2.2.1. Special Dosage Instructions).

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

2.6. Undesirable effects
2.6.1. Clinical trials
Experience with Valcyte

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 2).

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) [2, 6, 44, 49] and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

Table 2 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
Leukopenia	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. Cell counts usually begin to recover within 3 to 7 days of discontinuing drug (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 adults CMV retinitis patients and solid organ transplant patients receiving valganciclovir until Day 100 post-tranplant are listed below. The incidence of laboratory abnormalities was comparable with the extension of prophylaxis up to 200 days in high risk kidney transplant patients.

Table 3 Laboratory Abnormalities

Laboratory abnormalities	Patients with CMV retinitis	Solid Organ Transplant Patients	
	Valganciclovir	Valganciclovir	Oral Ganciclovir
	(n = 370) %	(n=244) %	(n=126) %
Neutropenia: ANC / ㎥			
<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 / ㎥			
<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

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 (5%) or oral ganciclovir (3%) until Day 100 post-transplant or valganciclovir (10%) until Day 200 post-transplant. 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. Impaired renal function is a feature common to 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.

The incidence of adverse events in this patient population from the clinical study is shown in Tables 4 and 5. Table 4 shows adverse events occurring in the first 100 days of the study when all patients were receiving valganciclovir prophylaxis. While, Table 5 shows adverse events occurring after day 100 of the study when only patients in the 200 days arm were receiving valganciclovir (patients in the 100 day arm were receiving placebo.)

Table 4 Adverse Events Occurring in ≥5% of High Risk Kidney Transplant Patients Treated with valganciclovir (Days 1-100)

System organ class	100-day arm (*n* = 164) *n* (%)	200-day arm (*n* = 156) *n* (%)
Gastrointestinal disorders		
Diarrhoea	29 (18)	42 (27)
Constipation	22 (13)	14 (9)
Nausea	14 (9)	13 (8)
Abdominal pain	7 (4)	10 (6)
Dyspepsia	3 (2)	10 (6)
Vomiting	5 (3)	8 (5)
Blood and lymphatic system disorders		
Leucopenia	33 (20)	31 (20)
Anaemia	21 (13)	20 (13)
Neutropenia	20 (12)	15 (10)
General disorders and administration site conditions		
Oedema peripheral	29 (18)	26 (17)
Pyrexia	11 (7)	10 (6)
Fatigue	4 (2)	12 (8)
Infections and infestations		
Urinary tract infection	17 (10)	30 (19)
Nasopharyngitis	14 (9)	3 (2)
Upper respiratory tract infection	10 (6)	4 (3)
Nervous system disorders		
Tremor	15 (9)	23 (15)
Headache	14 (9)	9 (6)
Insomnia	10 (6)	10 (6)
Metabolism and nutrition disorders		
Hypophosphataemia	19 (12)	18 (12)
Hyperkalaemia	18 (11)	15 (10)
Hypomagnesaemia	16 (10)	7 (4)
Hyperglycaemia	9 (5)	4 (3)
Vascular disorders		
Hypertension	19 (12)	12 (8)
Hypotension	9 (5)	2 (1)
Investigations		
Blood creatinine increased	16 (10)	11 (7)
Renal and urinary disorders		
Haematuria	7 (4)	10 (6)
Immune system disorders		
Transplant rejection	9 (5)	6 (4)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	8 (5)	6 (4)
Cough	8 (5)	3 (2)

Table 5 Adverse Events Occurring in ≥ 5% of High Risk Kidney Transplant Patients Treated with valganciclovir (Day 101 onwards)

System organ class	100-day arm (*n* = 164) *n* (%)	200-day arm (*n* = 156) *n* (%)
Blood and lymphatic system disorders		
Leucopenia	7 (4)	30 (19)
Neutropenia	5 (3)	8 (5)
Gastrointestinal disorders		
Diarrhoea	18 (11)	15 (10)
Infections and infestations		
Urinary tract infection	11 (7)	11 (7)
Cytomegalovirus infection	20 (12)	1 (<1)
Nasopharyngitis	7 (4)	10 (6)
Upper respiratory tract infection	4 (2)	11 (7)
Cytomegalovirus syndrome	12 (7)	-
General disorders and administration site conditions		
Pyrexia	10 (6)	6 (4)
Respiratory, thoracic and mediastinal disorders		
Cough	9 (5)	4 (3)

2.6.2. Post Marketing Experience
Safety reports from the postmarketing setting are consistent with the safety data from clinical trials with valganciclovir and ganciclovir (see Section 2.6.1 Undesirable Effects-Table 2)

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 2.4 Special Warnings and Special Precautions and 2.2 Dosage and administration).

Reports of overdoses 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*: generalized tremor, seizure.

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

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 a 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 monophosphate 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 the phosphorylation is largely dependent on the viral kinase, 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 anti-viral IC_{50} against CMV *in vitro* is in the range 0.08 mM (0.02 mg/ml) to 14 mM (3.5 mg/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 four weeks of Valcyte treatment.

3.1.2 Efficacy/ Clinical Studies
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 randomized 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 randomization 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. Safety and efficacy of valganciclovir have not been demonstrated in transplant patients.

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 three times a day) 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 randomized to valganciclovir compared with 36.0% in the oral ganciclovir arm. However, in liver transplant patients, the incidence of tissue-invasive CMV disease was significantly higher in the Valcyte group (14%) compared with the ganciclovir group (3%).

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 valganciclovir CMV prophylaxis from 100 to 200 days post-transplant.

The inclusion criteria in this study required the patients to have adequate haematological (absolute neutrophil count > 1000 cells/μL, platelets > 25,000/μL, haemoglobin > 8 g/dL) and renal function (creatinine clearance > 15 mL/min and improving) in the immediate post-transplant period. The mean age of the patients who participated in this trial was about 48 years.

Patients were randomised (1:1) to receive VALCYTE tablets (900 mg once daily) within 10 days of transplantation until Day 200 post-transplant or until Day 100 post-transplant followed by 100 days placebo.

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	Treatment difference (95% CI)
Patients with confirmed or assumed CMV disease[2]	71/163 (43.6%)	36/155 (23.2%)	-20.3% (-30.8%, -9.9%)
Patients with confirmed CMV disease	60/163 (36.8%)	25/155 (16.1%)	-20.7% (-30.4%, -10.9%)

[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.

Viral Resistance
Viruses resistant 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 foscamet are diverse, but concentrate at and between regions II (codon 696-742) and III (codon 805-845).

Treatment of CMV retinitis
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 randomized 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 randomized to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 127 patients on the ganciclovir comparator arm, samples from 29 patients with suspected CMV disease were tested, from which two 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 *Efficacy/Clinical 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 Pharmacokinetics Properties

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

The parameters which control the exposure of ganciclovr from valganciclovir are bioavailability and renal function. The bioavailability of ganciclovr from valganciclovir is comparable across all the patient populations studied. The systemic exposure of ganciclovir to heart, kidney and liver transplant recipients was similar after oral administration of valganciclovir according to the renal function dosing algorithm.

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 gastrointestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir is approximately 60%. Systemic exposure to valganciclovir is transient and low. AUC_{24} 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_{24} (approximately 30%) and mean ganciclovir C_{max} values (approximately 14%). Also the inter-individual variation in exposure of ganciclovir decreases when taking Valcyte with food. Valcyte has only been administered with food in clinical studies. Therefore, it is recommended that Valcyte be administered with food. For ganciclovir, average AUC_{0-24} has been shown to correlate with time to progression of CMV retinitis. (see 2.2 Dosage and administration).

3.2.2 Distribution
Because of 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. Post peak plasma concentrations of valganciclovir decline with a half-life of 0.4 to 2-0 h in subjects with normal renal function. 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
Geriatric Population
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 7 Pharmacokinetic parameters of ganciclovir from a single oral dose of 900 mg Valcyte tablets in patients with various degrees of renal impairment

Estimated Creatinine Clearance (mL/min)	N	Apparent Clearance (mL/min) Mean ± SD	$AUC_{0-\infty}$ (μg·h/mL) Mean ± SD	Half-life (hours) 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 2.2.2 Special dosage instructions and 2.4 Special Warnings and Special 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 crossover 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_{0-24} was comparable to that achieved by 5mg/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.

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. Valganciclovir, like 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
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 (2.4 Special Warnings and Special Precautions. Ganciclovir causes impaired fertility and teratogenicity in animals.

Based upon animals 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 (2.4 Special Warnings and Special Precautions).

4. Pharmaceutical Particulars

4.1 List of Excipients:
Tablet core: povidone, crospovidone, microcrystalline cellulose, stearic acid powder

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

4.2 Stability
See also outer pack for storage remark.

4.3 Special remarks
4.3.1 Instructions for Use, Handling and Disposal
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 (see 2.4 Special Warnings and Special Precautions). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with plain water.

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.

5. Packs

Tablets 450 mg 60

Medicine: keep out of reach of children

Current at March 2018

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland