

Data Sheet

Valcyte[®]

Valganciclovir

Antiviral

Pharmaceutical Form

Tablet.

Qualitative and Quantitative Composition

Active ingredient

valganciclovir hydrochloride 450 mg

Excipients

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

Tablet coat: hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, red iron oxide, polysorbate

Appearance

Pink convex oval tablets with "VGC" on one side and "450" on the other

Clinical Particulars

Therapeutic Indications

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

Valcyte is indicated for the prevention of CMV disease in solid organ transplant patients at risk.

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 Absorption and 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 as described below should be closely followed (see Warnings and Precautions, and Overdose).

Adults

Induction treatment of CMV retinitis

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

Maintenance treatment of CMV retinitis

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

Prevention of CMV disease in transplantation

For kidney transplant patients, the recommended dose is 900 mg (two 450 mg tablets) once daily with food, starting within 10 days of transplantation until 200 days post-transplantation.

For patients who have received a solid organ transplant other than kidney, the recommended dose is 900 mg (two 450 mg tablets) once daily with food, starting within 10 days of transplantation until 100 days post-transplantation.

Special dosage instructions

Patients with renal impairment

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

CrCl (mL/min)	Induction dose	Maintenance / Prevention dose
≥ 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

An estimated creatinine clearance can be related to 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:

$$0.85 \times \text{male value}$$

Patients undergoing haemodialysis

For patients on haemodialysis (CrCl < 10 mL/min) a dose recommendation cannot be given. Thus Valcyte should not be used in these patients (see Pharmacokinetics in special populations and Warnings and Precautions).

Patients with severe leukopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia 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/microlitre or the platelet count is less than 25,000/microlitre or the haemoglobin is less than 8 g/dL (see Warnings and Precautions and Undesirable Effects).

Elderly

Safety and efficacy have not been established in this patient population.

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 Warnings and Precautions).

Contraindications

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

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

Warnings and Precautions

General

In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic. Valcyte should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see Instructions for use, handling and disposal). It is also considered likely that Valcyte causes temporary or permanent inhibition of spermatogenesis (see Pharmacokinetic Properties: Preclinical safety, Use in Special Populations: Pregnancy and Undesirable Effects).

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia 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/microlitre or the platelet count is less than 25,000/microlitre or the haemoglobin is less than 8 g/dL (see Special dosage instructions, and Undesirable Effects).

It is recommended that complete blood counts and platelet counts be monitored during therapy. In patients with severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended

that treatment with haematopoietic growth factors and/or dose interruption be considered (see Special dosage instructions and Undesirable Effects).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see Special dosage instructions and Pharmacokinetics in special populations).

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

Convulsions 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 Interactions with other Medicinal Products and other Forms of Interaction).

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

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

Ability to Drive and Use Machines

Convulsions, sedation, dizziness, ataxia, and/or confusion have been reported with the use of Valcyte and/or ganciclovir. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

Interactions with other Medicinal Products and other Forms of Interaction

Medicine interactions with Valcyte

In a rat *in situ* model of intestinal permeability, there was no interaction of valaciclovir, didanosine, nelfinavir, cyclosporin, omeprazole and mycophenolate mofetil with valganciclovir.

Valcyte is metabolised to ganciclovir; therefore interactions associated with ganciclovir will be expected for Valcyte.

Medicine interactions with ganciclovir

Binding of ganciclovir to plasma proteins is only about 1 to 2%, and medicine interactions involving binding site displacement are not anticipated.

Imipenem-cilastatin

Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These medicines should not be used concomitantly unless the potential benefits outweigh the potential risks (see 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 Valcyte should be closely monitored for ganciclovir toxicity.

Zidovudine

When zidovudine was given in the presence of oral ganciclovir there was a small (17%), but statistically significant, increase in the AUC of zidovudine. There was also a trend towards lower ganciclovir concentrations when administered with zidovudine although this was not statistically significant. However, since both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, some patients may not tolerate concomitant therapy at full dosage (see Warnings and Precautions).

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both intravenous and oral). At ganciclovir oral doses of 3 and 6 g/day, an increase in the AUC of didanosine ranging from 84 to 124% has been observed, and likewise 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. This increase cannot be explained by competition for renal tubular secretion, as there was an increase in the percentage of didanosine dose excreted. This increase could arise from either increased bioavailability or decreased metabolism. There was no clinically significant effect on ganciclovir concentrations. However, given the increase in didanosine plasma concentrations in the presence of ganciclovir, patients should be closely monitored for didanosine toxicity (see Warnings and Precautions).

Mycophenolate mofetil

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil (MMF) and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that co-administration of these agents (which have the potential to compete for renal tubular secretion) will result in increases in phenolic glucuronide of mycophenolic acid (MPAG) and ganciclovir concentration. No substantial alteration of mycophenolic acid (MPA) pharmacokinetics is anticipated and MMF dose adjustment is not required. In patients with renal impairment in which MMF and ganciclovir are co-administered, the dose recommendation of ganciclovir should be observed and patients monitored carefully.

Zalcitabine

Zalcitabine increased the AUC_{0-8h} of oral ganciclovir by 13%. There were no statistically significant changes in any of the other pharmacokinetic parameters assessed. Additionally, there were no clinically relevant changes in zalcitabine pharmacokinetics in the presence of oral ganciclovir although a small increase in the elimination rate constant was observed.

Stavudine

No statistically significant pharmacokinetic interaction was observed when stavudine and oral ganciclovir were given in combination.

Trimethoprim

Trimethoprim statistically significantly decreased the renal clearance of oral ganciclovir by 16.3% and this was associated with a statistically significant decrease in the terminal elimination rate and corresponding increase in half-life by 15%. However, these changes are unlikely to be clinically significant, as AUC_{0-8h} and C_{max} were unaffected. The only statistically significant change in trimethoprim pharmacokinetic parameters when co-administered with ganciclovir was a 12% increase in C_{min} . However, this is unlikely to be of clinical significance and no dose adjustment is recommended.

Ciclosporin

There was no evidence that introduction of ganciclovir affects the pharmacokinetics of ciclosporin based on the comparison of ciclosporin trough concentrations. However, there was some evidence of increases in the maximum serum creatinine value observed following initiation of ganciclovir therapy.

Other potential medicine interactions

Toxicity may be enhanced when ganciclovir is co-administered with other medicines known to be myelosuppressive or associated with renal impairment (such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, nucleoside analogues and hydroxyurea). Therefore, these medicines should be considered for concomitant use with valganciclovir only if the potential benefits outweigh the potential risks (see Warnings and Precautions).

Use in Special Populations

Pregnancy

Pregnancy category D

Ganciclovir has been shown to be teratogenic and embryotoxic in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir.

Women of childbearing potential should be advised to use effective contraception during treatment. Male patients should be advised to practice barrier contraception during and for at least 90 days following treatment with Valcyte (see Pharmacokinetic Properties: Preclinical safety).

The safety of Valcyte for use in human pregnancy has not been established. The use of Valcyte should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the foetus.

Nursing mothers

Peri- and post-natal development has not been studied with valganciclovir or with ganciclovir but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Therefore, a decision should be made to discontinue the medicine or discontinue nursing taking into consideration the potential benefit of Valcyte to the nursing mother.

Paediatric use

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

Geriatric use

Safety and efficacy have not been established in this patient population (see Special dosage instructions).

Renal impairment

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see Special dosage instructions and Pharmacokinetics in special populations).

Undesirable Effects

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 events observed in Valcyte clinical studies have been previously observed with ganciclovir.

Treatment of CMV retinitis in AIDS patients

The safety profiles of valganciclovir and intravenous ganciclovir during 28 days of randomised study phase (21 days induction dose and 7 days maintenance) in 79 patients each were comparable. The most frequently reported events were diarrhoea, neutropenia and pyrexia. More patients reported diarrhoea, oral candidiasis, headache and fatigue in the oral valganciclovir arm, and nausea and injection site-related events in the intravenous ganciclovir arm (see Table 1).

Table 1 Percentage of patients with selected adverse events occurring during the randomised study phase.

Adverse event	Valganciclovir arm <i>n</i> = 79	Intravenous ganciclovir arm <i>n</i> = 79
Diarrhoea	16%	10%
Oral candidiasis	11%	6%
Headache	9%	5%
Fatigue	8%	4%
Nausea	8%	14%
Venous phlebitis and thrombophlebitis	—	6%

Table 2 below shows adverse events regardless of seriousness and medicine relationship with an incidence of $\geq 5\%$ obtained either from trials looking at the use of valganciclovir in patients with CMV retinitis or the use of valganciclovir in solid organ transplant patients.

The information in Table 2 pertaining to the patients with CMV retinitis is based on two clinical trials (*n* = 370) where patients with CMV retinitis received Valcyte at a dosage of 900 mg twice daily or once daily, corresponding to the induction or maintenance regimen, respectively. Approximately 65% of these patients received valganciclovir for more than nine months (maximum duration was 30 months).

The most frequently reported adverse events (% of patients), regardless of seriousness and medicine relationship in patients taking Valcyte reported from these two clinical trials ($n = 370$) were diarrhoea (38%), pyrexia (26%), nausea (25%), neutropenia (24%) and anaemia (22%). The majority of the adverse events were of mild or moderate intensity. The most frequently reported adverse reactions (% of patients), regardless of seriousness that were considered related (remotely, possibly or probably) to Valcyte by the investigator were neutropenia (21%), anaemia (14%), diarrhoea (13%) and nausea (9%).

Prevention of CMV disease in transplantation

Table 2 shows the adverse events regardless of seriousness and medicine relationship with an incidence of $\geq 5\%$ from a clinical trial (up to 28 days after study treatment) where solid organ transplant patients received valganciclovir ($n = 244$) or oral ganciclovir ($n = 126$) starting within 10 days of transplantation until Day 100 post-transplant. The most frequently reported adverse events (% of patients), regardless of seriousness and medicine relationship in patients taking Valcyte reported in this clinical trial ($n = 244$) were diarrhoea (30%), tremors (28%), graft rejection (24%), nausea (23%), headache (22%), oedema lower limb (21%), constipation (20%), back pain (20%), insomnia (20%), hypertension (18%) and vomiting (16%). These events were also seen with oral ganciclovir at a comparable incidence. The majority of the adverse events were of mild or moderate intensity.

Events seen in the solid organ transplant clinical trial (100-day dosing regimen) not seen in CMV retinitis clinical trials at a frequency $\geq 2\%$ included hypertension (18%), blood creatinine raised (10%), metabolism disorders – e.g., hyperkalaemia (14%) and hepatic function abnormal (9%). These events occurred at a similar rate with oral ganciclovir and could be considered a reflection of the underlying disease process.

The most frequently reported adverse reactions (% of patients), regardless of seriousness, that were considered related (remotely, possibly or probably) to Valcyte by the investigator in solid organ transplant patients treated until Day 100 post-transplant were leucopenia (9%), diarrhoea (7%), nausea (6%), neutropenia (5%).

Table 2 Percentage of patients with adverse events occurring in $\geq 5\%$ of patients in either CMV retinitis or solid organ transplantation clinical trials treated with valganciclovir or ganciclovir

	Patients with CMV retinitis	Solid Organ Transplant Patients Dosing until Day 100 Post-Transplant	
	Valganciclovir	Valganciclovir	Oral ganciclovir
System organ class	($n = 370$) %	($n = 244$) %	($n = 126$) %
Gastrointestinal disorders			
Diarrhoea	38	30	29
Nausea	25	23	23
Vomiting	20	16	14
Abdominal pain	13	14	14
Constipation	6	20	20
Abdominal pain upper	6	9	6
Dyspepsia	4	12	10
Abdominal distention	2	6	6

	Patients with CMV retinitis	Solid Organ Transplant Patients Dosing until Day 100 Post-Transplant	
	Valganciclovir	Valganciclovir	Oral ganciclovir
System organ class	(n = 370) %	(n = 244) %	(n = 126) %
Ascites	-	9	6
General disorders and administration site conditions			
Pyrexia	26	13	14
Fatigue	20	13	15
Oedema lower limb	5	21	16
Pain	3	5	7
Oedema	1	11	9
Oedema peripheral	1	6	7
Weakness	4	6	6
Blood and lymphatic system disorder			
Neutropenia	24	8	3
Anaemia	22	12	15
Thrombocytopenia	5	5	5
Leucopenia	4	14	7
Infections and infestations			
Oral candidiasis	20	3	3
Pharyngitis/nasopharyngitis	12	4	8
Sinusitis	10	3	-
Upper respiratory tract infection	9	7	7
Influenza	9		
Pneumonia	7	4	2
Bronchitis	6	-	1
Pneumocystis carinii pneumonia	6	-	-
Urinary tract infection	5	11	9
Nervous system disorders			
Headache	18	22	27
Insomnia	14	20	16
Peripheral neuropathy	7	1	1
Paraesthesia	6	5	5
Tremors	2	28	25
Dizziness (excl. vertigo)	9	10	6
Skin and subcutaneous tissue disorders			
Dermatitis	18	4	5
Night sweats	7	3	4
Pruritus	6	7	4
Acne	<1	4	6
Respiratory, thoracic and mediastinal disorders			
Cough	16	6	8
Dyspnoea	9	11	10
Productive cough	5	2	2
Rhinorrhoea	2	4	6
Pleural effusion	<1	7	8
Eye Disorders			
Retinal detachment	13	-	-
Vision blurred	6	1	4

	Patients with CMV retinitis	Solid Organ Transplant Patients Dosing until Day 100 Post-Transplant	
	Valganciclovir	Valganciclovir	Oral ganciclovir
System organ class	(n = 370) %	(n = 244) %	(n = 126) %
Psychiatric disorders			
Depression	9	7	6
Investigations			
Weight decrease	9	3	3
Blood creatinine increased	1	10	14
Musculoskeletal and connective tissue disorders			
Back pain	8	20	15
Arthralgia	6	7	7
Muscle cramps	2	6	11
Pain in limb	3	5	7
Renal and urinary disorders			
Renal impairment	1	7	12
Dysuria	2	7	6
Immune system disorders			
Graft rejection	-	24	30
Metabolism and nutrition disorders			
Anorexia	5	3	-
Cachexia	5	-	-
Hyperkalaemia	<1	14	14
Hypokalaemia	2	8	8
Hypomagnesaemia	<1	8	8
Hyperglycaemia	1	6	7
Appetite decreased	8	4	5
Dehydration	6	5	6
Hypophosphataemia	<1	9	6
Hypocalcaemia	<1	4	6
Hepatobiliary disorders			
Hepatic function abnormal	3	9	11
Surgical and medical procedures			
Post-operative complications	1	12	8
Post-operative pain	2	13	7
Post-operative wound infection	1	11	6
Injury, poisoning and procedural complication			
Wound drainage increased	-	5	9
Wound dehiscence	<1	5	6
Vascular disorders			
Hypotension	1	3	8
Hypertension	3	18	15

Serious adverse events considered related by the company to the use of Valcyte reported from these three clinical trials ($n = 614$) with a frequency of less than 5% and which are not mentioned in the two tables above, are listed below:

- Haemic and lymphatic system: pancytopenia, bone marrow depression, aplastic anaemia.
- Urogenital system: decreased renal creatinine clearance.

- Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia.
- Central and peripheral nervous system: convulsion, psychotic disorder, hallucinations, confusion, agitation.
- Body as a whole: valganciclovir hypersensitivity.

Severe neutropenia (< 500 ANC/microlitre) 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. There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 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. The incidence of adverse events in this patient population from the IMPACT study is shown in Tables 3 and 4. Table 3 shows adverse events occurring in the first 100 days of the study when all patients were receiving valganciclovir prophylaxis. While, Table 4 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 3 Adverse Events Occurring in ≥ 5% of High Risk Kidney Transplant Patients Treated with valganciclovir (IMPACT Study, 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)

System organ class	100-day arm (n = 164) n (%)	200-day arm (n = 156) n (%)
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 4 Adverse Events Occurring in ≥ 5% of High Risk Kidney Transplant Patients Treated with valganciclovir (IMPACT Study, 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)

Experience with ganciclovir

Valcyte is rapidly converted to ganciclovir. Adverse events reported with ganciclovir, and not mentioned above, are listed below:

Gastrointestinal system disorders

Abdominal distension, cholangitis, dyspepsia, dysphagia, eructation, oesophagitis, faecal incontinence, flatulence, gastritis, gastrointestinal disorder, gastrointestinal haemorrhage, mouth ulceration, pancreatitis, tongue disorder.

Body as a whole - general disorders

Acites, asthenia, bacterial, fungal and viral infections, haemorrhage, malaise, mucous membrane disorder, pain, photosensitivity reaction, rigors, sepsis.

Hepatic system disorders

Hepatitis, jaundice.

Skin and appendages disorders

Alopecia, dry skin, sweating increased, urticaria.

Central and peripheral nervous system disorders

Abnormal dreams, amnesia, anxiety, ataxia, coma, dry mouth, emotional disturbance, hyperkinetic syndrome, hypertonia, libido decreased, myoclonic jerks, nervousness, somnolence, thinking abnormal.

Musculoskeletal system disorders

Musculoskeletal pain, myasthenic syndrome.

Urogenital system disorders

Haematuria present, impotence, renal failure, urinary frequency.

Metabolic and nutritional disorders

Blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood glucose decreased, blood lactic dehydrogenase increased, diabetes mellitus, hypoproteinemia.

Special senses

Amblyopia, blindness, earache, eye haemorrhage, eye pain, deafness, glaucoma, taste disturbance, tinnitus, vision abnormal, vitreous disorder.

Haemic and lymphatic

Eosinophilia, leukocytosis, lymphadenopathy, splenomegaly.

Cardiovascular system disorders

Arrhythmia (including ventricular arrhythmia), migraine, phlebitis, tachycardia, thrombophlebitis deep, vasodilatation.

Respiratory system disorders

Sinus congestion.

Laboratory abnormalities

Laboratory abnormalities reported with valganciclovir are listed in Table 5.

Table 5 Laboratory abnormalities

Laboratory abnormalities	CMV Retinitis Patients	Solid Organ Transplant Patients	
	Valganciclovir (n = 370) %	Valganciclovir (n = 244) %	Oral ganciclovir (n = 126) %
Neutropenia (ANC/microlitre)			
< 500	16	5	3
500 - < 750	17	3	2
750 - < 1000	17	5	2
Anaemia (haemoglobin g/dL)			

Laboratory abnormalities	CMV Retinitis Patients	Solid Organ Transplant Patients	
	Valganciclovir (n = 370) %	Valganciclovir (n = 244) %	Oral ganciclovir (n = 126) %
< 6.5	7	1	2
6.5 - < 8.0	10	5	7
8.0 - < 9.5	14	31	25
Thrombocytopenia (platelets/microlitre)			
< 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

Post-marketing

Experience with ganciclovir

Adverse events from post-marketing spontaneous reports with intravenous and oral ganciclovir not mentioned in any section above, and for which a causal relationship cannot be excluded are listed below. As Valcyte is rapidly and extensively converted to ganciclovir, such adverse events might also occur with Valcyte.

- Anaphylaxis
- Decreased fertility in males

Adverse events that have been reported during the post-marketing period are consistent with those seen in clinical trials with Valcyte and ganciclovir.

Overdose

Overdose experience with valganciclovir

One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's degree of renal impairment (decreased creatinine clearance).

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

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see Pharmacokinetic properties: Patients undergoing haemodialysis).

Overdose experience with intravenous ganciclovir

Reports of overdoses with intravenous ganciclovir 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:

- *Haematological toxicity*: pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia.
- *Hepatotoxicity*: hepatitis, liver function disorder.
- *Renal toxicity*: worsening of haematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine.
- *Gastrointestinal toxicity*: abdominal pain, diarrhoea, vomiting.
- *Neurotoxicity*: generalised tremor, convulsion.

Pharmacological Properties & Effects

Pharmacodynamic Properties

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 monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised 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 IC₅₀ 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 four weeks of Valcyte treatment.

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 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.

Study PV16000: Prevention of CMV disease in solid organ 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 once daily) or oral ganciclovir (1000 mg three times daily) 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 large 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.

IMPACT Study (Study NT18435): Prevention of CMV Disease in Kidney Transplant Patients

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/ μ L, platelets > 25,000/ μ L, 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 Disease¹, 12 Month ITT Population

	100-day group	200-day group	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 98.1% (160/163) for the 100-day dosing regimen and 98.2% (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

Virus 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). Virus containing mutations in the UL97 gene is resistant to ganciclovir alone, whereas virus with mutations in the UL54 gene may show cross-resistance to other antivirals targeting the viral polymerase, and vice versa.

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 medicine 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 on 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%.

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. 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.

Absorption

Valganciclovir is a prodrug of ganciclovir, which is well absorbed from the gastrointestinal tract and rapidly metabolised 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_{24h} and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

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

Distribution

Because of rapid conversion of valganciclovir to ganciclovir, protein binding of Valcyte was not determined. Plasma protein binding of ganciclovir was 1% to 2% over concentrations of 0.5 and 51 µg/mL. The steady state volume of distribution of ganciclovir after intravenous administration was 0.680 ± 0.161 L/kg.

Metabolism

Valganciclovir is rapidly hydrolysed to ganciclovir; no other metabolites have been detected. No metabolite of orally administered radio labelled ganciclovir (1000 mg single dose) accounted for more than 1% to 2% of the radioactivity recovered in the faeces or urine.

Elimination

Following dosing with Valcyte, renal excretion as ganciclovir by glomerular filtration and active tubular secretion is the major route of elimination of Valcyte. Renal clearance accounts for 81.5% ± 22% of the systemic clearance of ganciclovir.

Pharmacokinetics in special populations

Patients with renal impairment

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 Special dosage instructions and Warnings and Precautions).

Patients undergoing haemodialysis

For patients receiving haemodialysis (CrCl < 10 mL/min), a dose recommendation cannot be given. This is because an individual dose of Valcyte required for these patients is less than the 450 mg tablet strength. Thus, Valcyte should not be used in these patients (see Special dosage instructions and Warnings and Precautions).

Patients with hepatic impairment

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

Preclinical safety

Carcinogenicity

Valganciclovir, like ganciclovir, is a potential carcinogen. This is consistent with the positive mouse carcinogenicity study with ganciclovir.

Mutagenicity

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

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 medicines (see Warnings and Precautions).

Based upon animal studies where aspermatogenesis was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

Teratogenicity

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 to apply to both medicines (see Warnings and Precautions).

Data obtained using an *ex vivo* human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion.

Pharmaceutical Particulars

Special Remarks

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 Warnings and 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 sterile water or plain water if sterile water is not available.

Disposal of unused/expired medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Stability

Store below 30 °C.

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

Packs

Valcyte is packed in plastic bottles of 60 tablets.

Medicine Classification

Prescription Medicine

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Date of Preparation

31 May 2011