

VALGANCICLOVIR VIATRIS

1. Product Name

Valganciclovir Viatris 450 mg film-coated tablet.

2. Qualitative and Quantitative Composition

Each film-coated tablet contains 496.3 mg of valganciclovir hydrochloride equivalent to 450 mg of valganciclovir.

Excipient with known effect: Crospovidone

Allergen Declaration: Sulfites

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

A pink film-coated, oval, biconvex, beveled edge tablet debossed with “M” on one side of the tablet and “V45” on the other side.

4. Clinical Particulars

4.1 *Therapeutic indications*

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

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

4.2 *Dose and method of administration*

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

Dose

Valganciclovir Viatris is rapidly and extensively metabolised to ganciclovir after oral dosing. Oral valganciclovir 900 mg twice daily is therapeutically equivalent to intravenous ganciclovir 5 mg/kg twice daily.

The dosage and administration of Valganciclovir Viatris tablets as described below should be closely followed (see section 4.4).

Treatment of cytomegalovirus (CMV) retinitis

Adult patients

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is 900 mg (two 450 mg tablets) twice a day for 21 days and whenever possible, taken with food. Prolonged induction treatment may increase the risk of bone marrow toxicity (see section 4.4).

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) once daily and, whenever possible, taken with food. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance.

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

Paediatric population

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

Prevention of CMV disease in solid organ transplantation

Adult patients

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

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

Wherever possible, the tablets should be taken with food.

Special dosage instructions

Elderly patients

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, valganciclovir should be administered to elderly patients with special consideration of their renal status (see Table 1 below) (see section 5.2).

Patients with renal impairment

Adult patients

Serum creatinine or creatinine clearance levels should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in the Table 1 below (see sections 4.4 and 5.2).

Table 1. Dosage adjustment for creatinine clearance levels

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 x male value

Patients undergoing haemodialysis

For patients on haemodialysis (CrCl < 10 mL/min) a dose recommendation cannot be given. Thus, Valganciclovir Viatris should not be used in these patients (see sections 4.4 and 5.2).

Patients with hepatic impairment

The safety and efficacy of valganciclovir have not been established in patients with hepatic impairment (see section 5.2).

Paediatric patients

See sections 4.8 and 5.1 for information on paediatric use.

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

See section 4.4 before initiation of therapy.

Severe leukopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with valganciclovir (and ganciclovir). Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/ μ L or the platelet count is less than 25,000/ μ L or the haemoglobin is less than 8 g/100mL (see section 4.3, 4.4 and 4.8).

If there is significant deterioration of blood cell counts during therapy with valganciclovir, treatment with haematopoietic growth factors and/or dose interruption should be considered (see section 4.4).

Method of administration

Valganciclovir Viatris is administered orally, and whenever possible, should be taken with food (see section 5.1 and 5.2).

Precautions should be taken before handling or administering the medicinal product.

The tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see section 4.4). 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 unavailable.

4.3 Contraindications

Valganciclovir Viatris is contraindicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any of the excipients listed in section 6.1.

Valganciclovir Viatris is contraindicated during breast-feeding (see section 4.6).

Valganciclovir Viatris should not be administered if the absolute neutrophil count is less than 500 cells/ μ L, the platelet count is less than 25,000/ μ L, or the haemoglobin is less than 8 g/dL.

4.4 Special warnings and precautions for use

CMV Diagnosis

The diagnosis of CMV retinitis should be made by indirect ophthalmoscopy. 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.

Cross hypersensitivity

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

Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception

In animal studies ganciclovir was found to be mutagenic, clastogenic, aspermatogenic, teratogenic, carcinogenic and to impair fertility. Valganciclovir should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see section 5.3). Prior to initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus and to use contraceptive measures (see section 4.6). Based on clinical and nonclinical studies, valganciclovir may cause temporary or permanent inhibition of spermatogenesis in males (see section 4.2, 5.3 and 6.6). Women of child-bearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy (see sections 4.6, 4.8 and 5.3). Valganciclovir is indicated in those patients as outlined in section 4.1, where the potential benefits to the patient outweighs the risks stated herein.

Valganciclovir has the potential to cause carcinogenicity and reproductive toxicity in the long term.

Myelosuppression

Severe leukopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with valganciclovir (and ganciclovir) (see section 4.2 and 4.8). Concomitant administration of valganciclovir and other medicines that are known to be myelosuppressive or associated with renal impairment may result in added toxicity (see section 4.5)

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. (. It is recommended that complete blood counts and platelet counts be monitored in all patients frequently during therapy; especially in patients whom ganciclovir or other nucleoside analogues have previously resulted in leucopenia, or in whom neutrophil counts are less than 1000 cells/ μ L at the beginning of treatment.

Valganciclovir should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or are receiving myelosuppressive medicines or irradiation. Cytopenia may occur at any time during treatment and may increase with continued dosing. In patients with severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, treatment with haematopoietic growth factors and/or the interruption of therapy is recommended. Cell counts usually begin to recover within 3 to 7 days of discontinuing medication. Colony-stimulating factors have been shown to increase neutrophil counts in patients receiving ganciclovir for treatment of CMV retinitis. When extending prophylaxis beyond 100 days the possible risk of developing leukopenia and neutropenia should be taken into account (see sections 4.2, 4.8 and 5.1).

Difference in bioavailability with oral ganciclovir

The bioavailability of ganciclovir after a single dose of 900 mg valganciclovir is approximately 60%, compared with approximately 6% after administration of 1000 mg oral ganciclovir (as capsules). Excessive exposure to ganciclovir may be associated with life-threatening adverse reactions. Therefore, careful adherence to the dose recommendations is advised when instituting therapy, when switching from induction to maintenance therapy and in patients who may switch from oral ganciclovir to valganciclovir as Valganciclovir Viartis 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 Valganciclovir Viatriis tablets (see sections 4.2 and 4.9).

Renal impairment

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see sections 4.2 and 5.2).

Increased serum creatinine levels have been observed in trials evaluating valganciclovir. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see section 4.2). Valganciclovir Viatriis should not be used in patients on haemodialysis (see sections 4.2 and 5.2).

Hepatic impairment

The safety and efficacy of valganciclovir have not been established in patients with hepatic impairment (see section 5.2).

Elderly patients

The pharmacokinetic profiles of valganciclovir in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of valganciclovir.

Clinical studies of valganciclovir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other therapy. Valganciclovir is known to be substantially excreted by the kidney, and the risk of toxic reactions to this medicine may be greater in patients with impaired renal function. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored, and dosage adjustments should be made accordingly (see section 4.2 and 4.4).

Transplant patients

The controlled clinical study using valganciclovir for the prophylactic treatment of CMV disease in transplantation, as detailed in section 5.1, did not include lung and intestinal transplant patients. Therefore, experience in these transplant patients is limited.

4.5 Interaction with other medicines and other forms of interaction

In-vivo drug interaction studies with Valganciclovir Viatriis have not been performed. Since valganciclovir is extensively and rapidly metabolised to ganciclovir, drug interactions associated with ganciclovir will be expected for valganciclovir.

Drug interactions with ganciclovir

Pharmacokinetic interactions

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.

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both IV and oral). At ganciclovir oral doses of 3 g/day and 6 g/day, an increase in the AUC of

didanosine ranging from 84% to 124% has been observed, and likewise at IV doses of 5 mg/kg/day and 10 mg/kg/day, and increase in the AUC of didanosine ranging from 38% to 67% has been observed confirming a pharmacokinetic interaction during the concomitant administration of these medicines. There was no significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis).

Other antiretrovirals

Cytochrome P450 isoenzymes play no role in ganciclovir pharmacokinetics. As a consequence, pharmacokinetic interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors are not anticipated.

Pharmacodynamic interactions

Imipenem-cilastatin

Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly and a pharmacodynamic interaction between these two medicines cannot be discounted. Valganciclovir and imipenem-cilastatin should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4).

Zidovudine

Both zidovudine and valganciclovir have the potential to cause neutropenia and anaemia. A pharmacodynamic interaction may occur during concomitant administration of these medicines. Some patients may not tolerate concomitant therapy at full dosage.

Potential drug interactions

Toxicity may be enhanced when ganciclovir/valganciclovir is co-administered with other medicines 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), hydroxyurea and pegylated interferons/ribavirin. Therefore, these medicines should only be considered for concomitant use with valganciclovir if the potential benefits outweigh the potential risks. Patients treated with any of those medicines in conjunction with valganciclovir should be closely monitored for signs of added toxicity.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

As a result of the potential for reproductive toxicity and teratogenicity, women of childbearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Male patients must be advised to practice barrier contraception during and for at least 90 days following treatment with valganciclovir unless it is certain that the female partner is not at risk of pregnancy (see sections 4.4 and 5.3).

Pregnancy

The safety of valganciclovir for use in pregnant women has not been established. Its active metabolite, ganciclovir, readily diffuses across the human placenta. Valganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. In addition, the effect on the future fertility of boys is unknown. There are no adequate and well-controlled studies in pregnant women.

Valganciclovir Viartis should not be used in pregnancy unless the therapeutic benefit for the mother outweighs the potential risk of teratogenic damage to the foetus.

The safe use of valganciclovir during labour has not been established

Breastfeeding

It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Human data are not available but animal data indicate that ganciclovir is excreted in the milk of lactating rats. Therefore, valganciclovir should not be given to breastfeeding mothers or breastfeeding must be discontinued during treatment with valganciclovir (see sections 4.3 and 5.3). The minimum time interval before breastfeeding can safely be resumed after the last dose of valganciclovir is unknown.

Fertility

In animal studies, ganciclovir was found to impair fertility. In a clinical study, renal transplant patients receiving valganciclovir for CMV prophylaxis for up to 200 days were compared to an untreated control group. Spermatogenesis was inhibited during treatment with valganciclovir. 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 valganciclovir treated patients, all patients with normal sperm density (n=7) and 8/13 patients with low sperm density at baseline, had normal density approximately six months 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. Due to limitations of this study, these results are not sufficient to establish recovery of spermatogenesis.

Reproductive toxicity studies have not been conducted with valganciclovir. Valganciclovir is rapidly and extensively converted to ganciclovir and therefore is expected to have similar reproductive toxicity effects as ganciclovir. Animal data indicate that the administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses. It is considered probable that in humans, valganciclovir at the recommended doses may cause temporary or permanent inhibition of spermatogenesis.

Ganciclovir caused decreased mating behaviour, decreased fertility, and an increased incidence of embryoletality in female mice following IV doses of 90 mg/kg/day (approximately 2.1 times the mean drug exposure to ganciclovir in humans following the maximum recommended dose of valganciclovir, 900 mg twice daily, based on AUC comparisons).

Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or IV administration of doses ranging from 0.2 to 10 mg/kg/day. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.02 to 0.1 times the AUC of ganciclovir in humans following the maximum recommended dose of valganciclovir. Valganciclovir caused similar effects on spermatogenesis in mice, rats and dogs. It is considered likely that valganciclovir could cause inhibition of human spermatogenesis.

Prior to initiation of ganciclovir treatment, patients should be advised of the potential risks to the foetus and to use contraceptive measures.

4.7 *Effects on ability to drive and use machines*

No studies on the effects on ability to drive and use machines have been performed.

Adverse reactions such as seizures, dizziness, and confusion have been reported with the use of valganciclovir and/or ganciclovir. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

4.8 *Undesirable effects*

Clinical Trials

Experience with Valganciclovir

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

Treatment of CMV Retinitis in AIDS

The safety profiles of valganciclovir and IV ganciclovir during 28 days of randomized study phase (21 days induction dose and 7 days maintenance dose) in 158 patients 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 IV ganciclovir arm (see Table 2).

Table 2. Percentage of patients with selected adverse events occurring during the randomized study phase

Adverse Event	Valganciclovir arm (n = 79)	IV ganciclovir arm (n = 79)
Diarrhoea	16%	10%
Oral Candidiasis	11%	6%
Headache	9%	5%
Fatigue	8%	4%
Nausea	8%	14%
Venous phlebitis and thrombophlebitis	-	6%

Based on two clinical trials (n = 370) where patients with CMV retinitis received valganciclovir at a dosage of 900 mg twice daily or once daily, corresponding to the induction or maintenance regimen, respectively, the adverse events with an incidence of $\geq 5\%$, regardless of seriousness and drug relationship is shown in Table 3. Approximately 65% of these patients received valganciclovir for more than nine months (maximum duration was 30 months).

The most frequently reported adverse reactions regardless of seriousness, that were considered related (remotely, possibly or probably) to valganciclovir by the investigator were neutropenia, anaemia, diarrhoea and nausea.

Prevention of CMV Disease in Transplantation

Table 3 also shows the adverse events (up to 28 days after study treatment) regardless of seriousness and drug relationship with an incidence of $\geq 5\%$ from a clinical trial, where solid organ transplant patients received valganciclovir or oral ganciclovir starting within 10 days post-transplantation until Day 100 post-transplant.

The most frequently reported adverse reactions, regardless of seriousness, that were considered related (remotely, possibly or probably) to valganciclovir by the investigator in solid organ transplant patients treated until Day 100 post-transplant were leukopenia, diarrhoea, nausea and neutropenia and were leukopenia, neutropenia, anaemia and diarrhoea in kidney transplant patients treated until Day 200 post-transplant.

Table 3. 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 Oral Transplant Patients Dosing until Day 100 Post-Transplant	
	Valganciclovir (n = 370) %	Valganciclovir (n = 244) %	Oral ganciclovir (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
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 Disorders			
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
Paresthesia	6	5	5
Tremors	2	28	25
Dizziness (excl. vertigo)	9	10	6
Skin and Subcutaneous Tissue Disorders			
Dermatitis (all types)	18	4	5
Night sweats	7	3	4
Pruritus	6	7	4
Acne	<1	4	6
Rash (all types)	9	<1	-

	Patients with CMV retinitis		Solid Oral Transplant Patients Dosing until Day 100 Post-Transplant	
	Valganciclovir	Valganciclovir	Valganciclovir	Oral ganciclovir
System organ class	(n = 370) %	(n = 244) %	(n = 244) %	(n = 126) %
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
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 and transplant 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 for valganciclovir from these three clinical trials (n = 934) with a frequency of less than 5% and which are not mentioned in the two tables above, are listed below:

Blood and lymphatic system disorders: pancytopenia, bone marrow depression, aplastic anaemia, febrile neutropenia

Renal and urinary disorders: decreased renal creatinine clearance

Infections and infestations: local and systemic infections and sepsis

Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia

Nervous system disorders: convulsion, psychotic disorder, hallucinations, confusion, agitation

General disorder and administration site conditions: valganciclovir hypersensitivity

Severe neutropenia (ANC < 500/ μ L) 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 valganciclovir did not change with the extension of prophylaxis up to 200 days in high risk kidney transplant patients. Leucopenia 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 IMPACT 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 \geq 5% of high risk kidney transplant patients treated with valganciclovir (IMPACT Study, Days 1 - 100)

System Organ Class	100-day arm (n = 164)	200-day arm (n = 156)
	<i>n (%)</i>	<i>n (%)</i>
Gastrointestinal Disorder		
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)

System Organ Class	100-day arm (n = 164)	200-day arm (n = 156)
	<i>n (%)</i>	<i>n (%)</i>
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)

System Organ Class	100-day arm (n = 164)	200-day arm (n = 156)
	<i>n (%)</i>	<i>n (%)</i>
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 \geq 5% of high risk kidney transplant patients treated with valganciclovir (IMPACT Study, Days 101 onwards)

System Organ Class	100-day arm (n = 164)	200-day arm (n = 156)
	<i>n (%)</i>	<i>n (%)</i>
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

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

Gastrointestinal disorders: cholangitis, dysphagia, eructation, oesophagitis, faecal incontinence, flatulence, gastritis, gastrointestinal disorder, gastrointestinal haemorrhage, mouth ulceration, pancreatitis, tongue disorder

General disorders and administration site conditions: asthenia, bacterial, fungal and viral infections, haemorrhage, malaise, mucous membrane disorder, photosensitivity reaction, rigors, sepsis, taste disturbance, decreased libido

Hepatobiliary disorders: hepatitis, jaundice

Skin and subcutaneous tissue disorders: acne, alopecia, exfoliative dermatitis, dry skin, increased sweating, urticaria

Nervous system disorders: abnormal dreams, amnesia, anxiety, ataxia, coma, dry mouth, emotional disturbance, hyperkinetic syndrome, hypertonia, myoclonic jerks, nervousness, somnolence, tremor

Psychiatric disorder: abnormal thinking

Musculoskeletal and connective tissue disorders: musculoskeletal pain, myasthenic syndrome

Renal and urinary disorders: haematuria present, impotence, renal failure, urinary frequency

Metabolic and nutritional disorders: increased blood alkaline phosphatase, increased blood creatine phosphokinase, decreased blood glucose, increased blood lactic dehydrogenase, decreased blood magnesium, diabetes mellitus, oedema, abnormal hepatic function, hypocalcaemia, hypokalaemia, hypoproteinaemia

Eye disorders: amblyopia, blindness, eye haemorrhage, eye pain, glaucoma, abnormal vision, vitreous disorder

Ear and labyrinth disorders: earache, deafness, tinnitus

Blood and lymphatic system disorders: eosinophilia, leucocytosis, lymphadenopathy, splenomegaly

Cardiac disorders: arrhythmia (including ventricular arrhythmia), deep thrombophlebitis, hypertension, hypotension, migraine, phlebitis, tachycardia, vasodilatation

Respiratory, thoracic and mediastinal disorders: pleural effusion, sinus congestion

Description of selected adverse reactions

Neutropenia

The risk of neutropenia is not predictable on the basis of the number of neutrophils before treatment. Neutropenia usually occurs during the first or second week of induction therapy. The cell count usually normalizes within 2 to 5 days after discontinuation of the drug or dose reduction (see section 4.4).

Thrombocytopenia

Patients with low baseline platelet counts (< 100,000/ μ L) 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 AIDS (see section 4.4). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Influence of treatment duration or indication on adverse reactions

Severe neutropenia (ANC <500/ μ L) is seen more frequently in CMV retinitis patients (14%) undergoing treatment with valganciclovir, intravenous or oral ganciclovir 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 valganciclovir 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.

Paediatric patients

Valganciclovir has been studied in 179 paediatric solid organ transplant patients who were at risk of developing CMV disease (aged 3 weeks to 16 years) and in 133 neonates with symptomatic congenital CMV disease (aged 2 to 31 days), with duration of ganciclovir exposure ranging from 2 to 200 days (see section 4.8).

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

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

Congenital CMV

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

Laboratory abnormalities

Laboratory abnormalities reported in adult CMV retinitis and solid organ transplant (SOT) patients receiving valganciclovir until Day 100 post-transplant are listed in Table 6. The evidence of laboratory abnormalities was comparable with the extension of prophylaxis up to 200 days in high risk kidney transplant patients.

Laboratory abnormalities reported in paediatric SOT patients are listed in Table 7. The incidence of severe neutropenia (ANC<500/ μ L) was higher in paediatric kidney patients treated until Day 200 as

compared to paediatric patients treated until Day 100 and as compared to adult kidney transplant patients treated until Day 100 or Day 200.

Table 6. Laboratory abnormalities in adult patients

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)			
< 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

Table 7. Laboratory abnormalities in paediatric solid organ transplant patients

Laboratory Abnormalities	Valganciclovir in Paediatric SOT Patients	
	Dosing until Day 100 Post-Transplant n = 63 %	Dosing until Day 200 Post-Transplant n = 56 %
Neutropenia (ANC/ microlitre)		
< 500	5	30
500 - < 750	8	7
750 - < 1000	5	11
Anaemia (haemoglobin g/dL)		
< 6.5	0	0
6.5 - < 8.0	14	5
8.0 - < 9.5	38	29
Thrombocytopenia (platelets/microlitre)		
< 25000	0	0
25000 - < 50000	10	0
50000 - < 100000	3	4
Serum creatinine (mg/dL)		
> 2.5	2	5

Laboratory Abnormalities	Valganciclovir in Paediatric SOT Patients	
	Dosing until Day 100 Post-Transplant <i>n</i> = 63 %	Dosing until Day 200 Post-Transplant <i>n</i> = 56 %
> 1.5 – 2.5	11	20

Post-marketing

As valganciclovir is rapidly and extensively converted into ganciclovir, any adverse events associated with ganciclovir might also occur with valganciclovir. 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:

- Anaphylaxis
- Decreased fertility in males
- Agranulocytosis
- Granulocytopenia

Adverse events that have been reported during the post-marketing period are consistent with those seen in clinical trials with valganciclovir and ganciclovir (see section 4.8).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Overdose experience with valganciclovir and intravenous ganciclovir

It is expected that an overdose of valganciclovir could possibly result in increased renal toxicity (see sections 4.4 and 4.2).

Overdoses with intravenous ganciclovir, some with fatal outcomes, have been reported from clinical trials and 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*: myelosuppression including pancytopenia, bone marrow failure, leukopenia, neutropenia, granulocytopenia.
- *Hepatotoxicity*: hepatitis, liver function disorder.
- *Renal toxicity*: worsening of haematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine.
- *Gastrointestinal toxicity*: abdominal pain, diarrhoea, vomiting.
- *Neurotoxicity*: generalised tremor, seizure.

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see section 5.2).

Treatment of overdose should consist of general supportive measures.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use – nucleosides and nucleotides excluding reverse transcriptase inhibitors. ATC code: J05A B14

Mechanism of action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir. After oral administration, valganciclovir is rapidly and extensively metabolised to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine and 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 (HBV).

In cytomegalovirus (CMV)-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. Triphosphate metabolism 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 14.32 µM (3.58 µg/mL)

Antiviral activity

The *in-vitro* anti-viral activity, measured as IC₅₀ against CMV is in the range of 0.08 µM (0.02 µg/mL) to 14.32 µM (3.58 µg/mL).

Pharmacodynamic effect

Valganciclovir allows systemic exposure of ganciclovir comparable to that achieved with recommended doses of intravenous (IV) ganciclovir, which has been shown to be efficacious in the treatment of CMV.

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

Clinical efficacy and safety

Adult patients

Treatment of CMV retinitis in AIDS

In a randomised, controlled study, 160 patients with AIDS and newly diagnosed CMV retinitis were randomised to receive treatment with either valganciclovir tablets (900 mg twice daily for 21 days, then 900 mg daily for 7 days) or with IV ganciclovir solution (5 mg/kg twice daily for 21 days, then 5 mg/kg daily for 7 days). Participants in the two treatment arms were comparable with respect to age, sex, weight, height and race. The mean age in the valganciclovir treatment arm was 39.6 years compared with 37.7 years in the ganciclovir arm. There was a higher proportion of males in each treatment group; 90% in the valganciclovir arm and 91% in the ganciclovir arm. The median CD4+ T-cell count at screening was 20.0 cells/µL for patients on the valganciclovir arm, and 26.0 cells/µL

for patients on the ganciclovir arm; and the median HIV viral load was 4.8 log₁₀ copies/mL in the valganciclovir arm and 4.9 log₁₀ copies/mL in the ganciclovir arm.

In the final analysis of CMV retinitis progression by week 4 based on masked assessment of fundus photographs, 146 of 160 patients were included (73 in the valganciclovir tablets group and 73 in the IV ganciclovir group). The proportion of patients with retinitis progression at week 4 was the same in both treatment groups: 0.099 for the valganciclovir treatment group and 0.1 for the ganciclovir treatment group. The difference in progression proportions (IV ganciclovir minus valganciclovir tablets) was 0.001, with a 95% confidence interval of -0.097 to 0.100.

After week 4, all patients in this study were allowed to continue to receive treatment with valganciclovir tablets given at the dosage of 900 mg once daily. The mean (median) time from randomisation to progression of CMV retinitis in the group receiving induction and maintenance treatment with valganciclovir tablets (n = 80) was 226 (160) days and in the group receiving induction treatment with IV ganciclovir and maintenance treatment with valganciclovir tablets (n = 80) was 219 (125) days.

Satisfactory induction was achieved at week 4 in 47/61 (77%) patients given ganciclovir and 46/64 (72%) patients given valganciclovir. Satisfactory induction was defined as no progression, no increase in lesion activity and a reduction in retinitis border activity. Response was reassessed at 6 weeks when 39/62 (63%) patients given ganciclovir and 39/56 (70%) patients given valganciclovir maintained a satisfactory response to induction therapy. Three (8%) patients in each group had active retinitis at the week 6 assessment.

Prevention of CMV disease in solid organ transplantation

A double-blind, double-dummy clinical active comparator study has been conducted in 372 heart, liver and kidney transplant patients at high-risk for CMV disease (Donor seropositive/Recipient seronegative [(D+/R-)]). The study was designed to test for noninferiority between the 2 treatment arms. Patients were randomised (2 valganciclovir: 1 oral ganciclovir) to receive either valganciclovir (900 mg once daily) or oral ganciclovir (1000 mg three times daily) starting within 10 days of transplantation until Day 100 post-transplant.

The primary analysis of the primary endpoint, the proportion of patients who developed CMV disease, including CMV syndrome and/or tissue invasive disease during the first 6 months post-transplant was 12.1% in the valganciclovir arm (n = 239) compared with 15.2% in the oral ganciclovir arm (n = 125) as assessed by a blinded Endpoint Committee. The study achieved its objective and it was concluded that valganciclovir was non-inferior to oral ganciclovir for the prevention of CMV disease in solid organ transplant patients.

The majority of cases of CMV disease 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. See table 8 for a summary

Table 8. Summary of CMV disease (as assessed by the Endpoint Committee) and acute graft rejection up to 6 months post-transplant (ITT population)

No. of Patients	Ganciclovir (n = 125)		Valganciclovir (n = 239)		Total (n = 364)		Weighted Difference in Proportions (95% CI)	
		(%)		(%)		(%)		
Patients with CMV disease	19	15.2	29	12.1	48	13.2	3.4%	-4.2%
								11.0%*

CMV Syndrome	13	10.4	12	5.0	25	6.9		
Tissue-invasive CMV	6	4.8	17	7.1	23	6.3		
Acute Graft Rejection	45	36.0	71	29.7	116	31.9		

* If the lower limit of the 95% CI is ≥ -0.05 , then valganciclovir is non-inferior to ganciclovir. As the lower limit of the 95% confidence interval (-0.042) was above the pre-specified non-inferiority value of -0.05, non-inferiority was achieved.

A population pharmacokinetics analysis was conducted using plasma samples taken from 160/245 patients in the valganciclovir arm and 82/127 patients in the oral ganciclovir arm, and from this analysis it was estimated that the median exposure to ganciclovir from valganciclovir was 1.74 times higher than seen with oral ganciclovir (AUC_{0-24h} 44.3 vs. 25.4 $\mu\text{g.h/mL}$).

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/ 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 valganciclovir tablets (900 mg once daily) within 10 days of transplantation either 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 9 below

Table 9. Percentage of kidney transplant patients with CMV disease¹, 12 month ITT population^A

	Valganciclovir 900 mg once daily 100 Days (n= 163)	Valganciclovir 900 mg once daily 200 Days (n = 155)	Between Treatment Group Difference
Patients with confirmed or assumed CMV disease ²	71 (43.6%) [35.8%; 51.5%]	36 (23.2%) [16.8%; 30.7%]	20.3% [9.9%; 30.8%]
Patients with confirmed CMV disease	60 (36.8%) [29.4%; 44.7%]	25 (16.1%) [10.7%; 22.9%]	20.7% [10.9%; 30.4%]

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 disease before this time point.

^A The results found up to 24 months were in line with the up to 12 month results; Confirmed or assumes CMV disease was 48.5% in the 100 days treatment arm versus 34.2% in the 200 days treatment arm; difference between the treatment groups was 14.3% [3.2%; 25.3%]

Significantly less high-risk kidney transplant patients developed CMV disease following CMV prophylaxis with valganciclovir until Day 200 post-transplant compared to patients who received CMV prophylaxis with valganciclovir until Day 100 post-transplant.

The graft survival rate as well as the incidence of biopsy proven acute rejection was similar in both treatment groups. 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. Up to 24 month post-transplant, four additional cases of graft loss were reported, all in the 100 days dosing group. 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. Up to 24 month post-transplant, one additional case had been reported in the 200 days dosing group.

No clinical trials have been conducted in patients following haematological or lung transplant.

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 and/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 are the most frequently reported ganciclovir resistant-associated substitutions. Viruses containing mutations in the UL97 gene are resistant to ganciclovir alone, whereas mutations in the UL54 gene are resistant to ganciclovir and may show cross-resistance to other antivirals that may target the viral polymerase. Amino acid substitutions in UL54 conferring cross-resistance to ganciclovir and cidofovir are generally located within the exonuclease domains and region V, however amino acid substitutions conferring cross-resistance to foscarnet are diverse, but concentrate at and between regions II (codon 696-742) and III (codon 805-845).

Treatment of CMV retinitis in AIDS

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% (3/137), 6.5% (8/123), 12.8% (13/101) and 15.3% (13/85) contain UL97 mutations after 3, 6, 12 and 18 months, respectively, of valganciclovir treatment (using the number of patients still on treatment at the assessment time as the denominator). Phenotypic resistance was not identified, but very few CMV culture isolates were available for analysis.

Prevention of CMV disease in transplantation

Active comparator study

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 127 patients randomised 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 5.1). 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.

Extending prophylaxis study from 100 to 200 days post-transplant

Genotypic analysis was performed on the UL54 and UL97 genes derived from virus extracted from 72 patients who met the resistance analysis criteria: patients who experienced a positive viral load (> 600 copies/mL) at the end of prophylaxis and/or patients who had confirmed CMV disease up to 12 months (52 weeks) post-transplant. Three patients in each treatment group had a known ganciclovir resistance mutation.

Paediatric patients

Prevention of CMV disease in transplantation

The pharmacokinetics and safety of valganciclovir powder for oral solution has been studied in five open-label, multi-centre clinical trials in paediatric solid organ transplant (SOT) patients.

Three of these studies assessed only the pharmacokinetics and safety of oral valganciclovir in SOT patients requiring anti-CMV prophylaxis ranging in age from 4 weeks to 16 years of age (see section 5.2).

One study enrolled 20 liver transplant patients with a median age of 2 years (6 months to 16 years) who received a single daily dose of valganciclovir on 2 consecutive days. A second study enrolled 26 kidney patients with a median age of 12 years (1 to 16 years) who received multiple doses of valganciclovir on 2 consecutive days. The third study enrolled 14 heart transplant patients with a median age of 13 weeks (3 weeks to 125 days) who received a single daily dose of valganciclovir on 2 consecutive days. The other two studies assessed the development of CMV disease, as a measure of efficacy, following prophylaxis of valganciclovir for up to 100 days and 200 days post-transplant using a paediatric dosing algorithm.

One solid organ transplant study enrolled 63 paediatric kidney, liver or heart patients with a median age of 9 years (4 months to 16 years) who received daily doses of valganciclovir for up to 100 days. There was no CMV event reported during the study that would fulfil the definition of CMV disease. CMV events were reported in 7 patients during the study of which 3 did not require adjustment to study medicine or were not treated and, therefore, were not considered clinically significant (see section 4.8 and 5.2). The second study in solid organ transplant enrolled 57 paediatric kidney patients with a median age of 12 years (1 to 16 years) who received daily doses of valganciclovir for up to 200 days. There was no CMV event reported during the study that would fulfil the definition of CMV disease. While 4 patients reported CMV events, one could not be confirmed by the central laboratory and of the 3 remaining events one did not require treatment and, therefore, was not considered clinically significant (see section 4.8).

Congenital CMV

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

Efficacy was evaluated using relevant endpoints such as hearing outcomes, neurodevelopmental outcomes and correlations of CMV blood viral load with ganciclovir plasma concentrations and hearing (see section 4.8).

5.2 Pharmacokinetic properties

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

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

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.

Absorption

Valganciclovir is a prodrug of ganciclovir. It is well absorbed from the gastrointestinal tract and rapidly and extensively metabolised in the intestinal wall and liver to ganciclovir. Systemic exposure to valganciclovir is transient and low. The bioavailability of ganciclovir from oral dosing of valganciclovir is approximately 60% across all the patient populations studies and the resultant exposure to ganciclovir is similar to that after its intravenous administration (see below). For comparison, the bioavailability of ganciclovir after administration of 1000 mg oral ganciclovir (as capsules) is 6 – 8%.

Valganciclovir in HIV positive, CMV positive patients

Systemic exposure of HIV positive, CMV positive patients after twice daily administration of ganciclovir and valganciclovir for one week is:

Table 10.

Parameter	Ganciclovir (5 mg/kg, intravenous) <i>n</i> = 18	Valganciclovir (900 mg, by mouth) <i>n</i> = 25	
		Ganciclovir	Valganciclovir
AUC _(0–12h) (µg.h/ml)	2806 ± 9.0	32.8 ± 10.1	0.37 ± 0.22
C _{max} (µg/ml)	10.4 ± 4.9	6.7 ± 2.1	0.18 ± 0.06

The efficacy of ganciclovir in increasing the time-to-progression of CMV retinitis has been shown to correlate with systemic exposure (AUC).

Valganciclovir in solid organ transplant patients

Steady state systemic exposure of solid organ transplant patients to ganciclovir after daily administration of ganciclovir and valganciclovir is:

Table 11.

Parameter	Ganciclovir (1000 mg, three times daily) <i>n</i> = 82	Valganciclovir (900 mg, once daily) <i>n</i> = 161
		Ganciclovir
AUC _(0–24h) (µg.h/ml)	28.0 ± 10.9	46.3 ± 15.2
C _{max} (µg/ml)	1.4 ± 0.5	5.3 ± 1.5

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

Food effect

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 valganciclovir be administered with food (see section 4.2).

Distribution

Because of rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. The steady state volume of distribution (V_d) of ganciclovir after intravenous administration was 0.680 ± 0.161 L/kg (n=114). 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% to 2% over ganciclovir concentrations of 0.5 and 51 µg/mL.

Biotransformation

Valganciclovir is rapidly and extensively metabolised to ganciclovir; no other metabolites have been detected. Ganciclovir itself is not metabolised to a significant extent.

Elimination

Following dosing with oral valganciclovir, the drug is rapidly hydrolysed to ganciclovir. Ganciclovir is eliminated from the systemic circulation by glomerular filtration and active tubular secretion.

In patients with normal renal function greater than 90% of IV administered ganciclovir was recovered un-metabolized in the urine within 24 hours. In patients with normal renal function the post-peak plasma concentrations of ganciclovir after administration of valganciclovir decline with a half-life ranging from 0.4 h to 2-0 h. In these patients, ganciclovir concentrations decline with a half-life ranging from 3.5 to 4.5 hours similarly to that observed after direct IV administration of ganciclovir.

Pharmacokinetics in special populations

Elderly

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 4.2).

Patients with renal impairment

The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir was evaluated in 24 otherwise healthy individuals with renal impairment without HIV and/or CMV infections.

Table 12. Pharmacokinetic parameters of ganciclovir from a single oral dose of 900 mg valganciclovir tablets in patients with various degrees of renal impairment

Estimated Creatinine Clearance (mL/min)	n	Apparent Clearance (mL/min) Mean ± SD	AUC_{last} (µg·h/mL) Mean ± SD	Half-life (hours) Mean ± SD
51 - 70	6	249 ± 99	50.5 ± 23	4.85 ± 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	67.5 ± 34

Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see sections 4.2 and 4.4).

Patients undergoing haemodialysis

For patients receiving haemodialysis dose recommendations for valganciclovir 450 mg tablets cannot be given. This is because an individual dose of valganciclovir required for these patients is less than the 450 mg tablet strength. This valganciclovir tablets should not be used in these patients (see sections 4.2 and 4.4).

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 absolute bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed conditions, was approximately 60%. Ganciclovir AUC_{0-24h} was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant patients.

Patients with hepatic impairment

The safety and efficacy of valganciclovir tablets have not been studied in patients with hepatic impairment. Hepatic impairment should not affect the pharmacokinetics of ganciclovir since it is excreted renally and, therefore, no specific dose recommendation is made.

Patients with cystic fibrosis

In a phase I pharmacokinetic study in lung transplant recipients with or without cystic fibrosis (CF), 31 patients (16 CF/15 non-CF) received post-transplant prophylaxis with 900 mg/day valganciclovir. The study indicated that cystic fibrosis had no statistically significant influence on the overall average systemic exposure to ganciclovir in lung transplant recipients. Ganciclovir exposure in lung transplant recipients was comparable to that shown to be efficacious in the prevention of CMV disease in other solid organ transplant recipients.

Paediatric patients

Prevention of CMV disease in transplantation

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

The model indicated that clearance is influenced by body weight and creatinine clearance while the central and peripheral volumes of distribution were influenced by body weight (see section 4.2).

The mean ganciclovir C_{max} , AUC and half-life by age and organ type in studies using the paediatric dosing algorithm are listed in Table 13 and are consistent with estimates obtained in adult SOT patients.

Table 13. Summary of model-estimated mean (\pm SD) pharmacokinetics of ganciclovir in paediatric patients by age

Transplant Subgroups	PK Parameter	Age Group			
		Heart Transplant Recipients < 4 months of age		Solid Organ Transplant Patients 4 months to 16 years	
		< 4 mth ($n=14$)	4 mth \leq 2 years ($n=2$)	> 2 - < 12 years ($n=12$) [*]	\geq 12 years ($n=19$)

Kidney (n=33)	AUC _{0-24h} (µg.h/mL)	-	65.2 (16.6)	55.0 (11.9)	50.0 (11.6)
	C _{max} (µg/mL)	-	10.0 (0.04)	8.74 (2.49)	7.85 (2.10)
	t _{1/2} (h)	-	3.10 (0.59)	4.40 (1.41)	5.67 (1.06)
Liver (n=17)		-	4 mth ≤ 2 years (n=9)	> 2 - < 12 years (n=6)	≥ 12 years (n=2)
	AUC _{0-24h} (µg.h/mL)	-	69.4 (35.4)	58.4 (6.18)	35.6 (2.76)
	C _{max} (µg/mL)	-	11.7 (3.59)	9.35 (2.33)	5.55 (1.34)
	t _{1/2} (h)	-	2.72 (1.32)	3.61 (0.80)	4.50 (0.25)
Heart (n=26)		< 4 mth (n=14)	4 mth ≤ 2 years (n=6)	> 2 - < 12 years (n=2)	≥ 12 years (n=4)
	AUC _{0-24h} (µg.h/mL)	68.1 (19.8) **	56.3 (23.2)	60.0 (19.3)	61.2 (26.0)
	C _{max} (µg/mL)	10.5 (3.35)	8.22 (2.44)	12.5 (1.02)	9.50 (3.34)
	t _{1/2} (h)	2.00 (0.19)	3.60 (1.73)	2.62 (0.65)	5.05 (0.70)

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

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

Congenital CMV

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

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

The mean ganciclovir AUC_{0-12hr} after oral dose administration of valganciclovir was approximately 23.2 µg.h/mL (equivalent to 46.4 µg.h/mL in AUC_{0-24hr}) in the first study. Similar exposure was also observed in the second study.

5.3 Preclinical safety data

Valganciclovir is a pro-drug of ganciclovir and therefore effects observed with ganciclovir apply equally to valganciclovir. Toxicity of valganciclovir in pre-clinical safety studies was the same as that seen with ganciclovir and was induced at ganciclovir exposure levels comparable to, or lower than, those in humans given the induction dose.

These findings were gonadotoxicity (testicular cell loss) and nephrotoxicity (uraemia, cell degeneration), which were irreversible; myelotoxicity (anaemia, neutropenia, lymphocytopenia) and gastrointestinal toxicity (mucosal cell necrosis), which were reversible.

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

Further studies have shown ganciclovir to be teratogenic, embryotoxic, to inhibit spermatogenesis (i.e. impair male fertility) and to suppress female fertility.

Animal data indicate that ganciclovir is excreted in the milk of lactating rats.

Carcinogenicity

Ganciclovir was genotoxic and carcinogenic in animal studies. Valganciclovir should be considered a potential carcinogen in humans with the potential to cause cancers. No long-term carcinogenicity studies have been conducted with valganciclovir. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir.

Toxicity in mice, dogs and rats was primarily characterised by testicular atrophy. Male infertility occurred at doses of 2 mg/kg/day and above which was consistent with the infertility and testicular atrophy seen in toxicity studies with doses between 2 and 10 mg/kg/day. In females, a more complex range of effects were induced which were characterised by embryo-foetal abnormalities and embryo-foetal losses in mice and rabbits and in multi-dose studies, by toxic and eventually carcinogenic changes to the reproductive system in mice.

Ganciclovir was carcinogenic in the mouse after oral doses of 20 mg/kg/day for 18 months and 1000 mg/kg/day for 15 months. All ganciclovir-induced tumours were of haematopoietic epithelial or vascular origin. Epithelial tumours involved a wide variety of tissues, including the female reproductive organs, pancreas, gastrointestinal tract and skin, as well as rodent specific glands (perputial, clitoral and Harderian). Vascular tumours were observed in females, mainly in the reproductive organs, but also in the mesenteric lymph nodes and liver. No carcinogenic effects occurred at 1 mg/kg/day. Based on data on plasma drug concentrations, exposure of humans to ganciclovir would be similar to or greater than the exposure of mice in the above study at 1000 mg/kg/day. This potential is likely to be markedly greater in children, as cell division occurs more rapidly in children.

Genotoxicity

Valganciclovir increased mutations in mouse lymphoma cells and was clastogenic in the mouse micronucleus assay. Valganciclovir was not mutagenic in the Ames Salmonella assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes *in vitro*. Ganciclovir was clastogenic in the mouse micronucleus assay. Ganciclovir was not mutagenic in the Ames Salmonella assay.

Contraception in males and females

Valganciclovir is expected to have reproductive toxicity effects similar to ganciclovir. In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity.

Ganciclovir has been shown to be embryotoxic in rabbits and mice following IV administration, and teratogenic in rabbits. Foetal resorptions were present in at least 85% of rabbits at 60 mg/kg/day IV and mice at 108 mg/kg/day (2.7 times the mean drug exposure to ganciclovir in humans following the maximum recommended dose of valganciclovir, 900 mg twice daily, based on AUC comparisons). Effects observed in rabbits included: foetal growth retardation, embryoletality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were foetal toxicity and embryoletality.

Daily intravenous doses of 90 mg/kg administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach. The drug exposure in mice as estimated by the AUC was approximately 2.1 times the human AUC.

6. Pharmaceutical Particulars

6.1 *List of excipients*

Valganciclovir Viatris film coated tablets also contain

Tablet core

- microcrystalline cellulose
- crospovidone
- stearic acid

Tablet film coat

- hypromellose
- titanium dioxide
- macrogol
- iron oxide red
- polysorbate.

6.2 *Incompatibilities*

Not applicable

6.3 *Shelf life*

3 years

6.4 *Special precautions for storage*

Store at or below 25°C.

6.5 *Nature and contents of container*

HDPE bottle with a polypropylene cap and aluminium induction sealing wad.
Pack-size of 60 film-coated tablets.

6.6 *Special precautions for disposal and other handling*

Instructions for use, handling and disposal

Caution should be exercised in the handling of Valganciclovir Viatris tablets. Valganciclovir Viatris tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans and inhibits spermatogenesis, caution should be observed in handling broken or crushed tablets (see section 4.4). 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 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.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

02 April 2015

10. Date of Revision of the Text

16 October 2023

Summary table of changes

Section	Summary of new information
2	Updated excipient with known effect list and addition of allergen declaration
4.5	Minor editorial change