AUSTRALIAN PRODUCT INFORMATION

VALGANCICLOVIR VIATRIS

valganciclovir hydrochloride tablets

1 NAME OF THE MEDICINE

Valganciclovir hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VALGANCICLOVIR VIATRIS is available as film-coated tablets.

Each film-coated tablet contains 496.3 mg of valganciclovir HCl (corresponding to 450 mg valganciclovir) as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

VALGANCICLOVIR VIATRIS is available as 450 mg pink, film-coated, oval, biconvex, bevelled edge tablets 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 adult patients with acquired immunodeficiency syndrome (AIDS).

VALGANCICLOVIR VIATRIS is indicated for the prophylaxis of CMV infection and disease in adult and paediatric solid organ transplantation (SOT) patients who are at risk.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

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

Valganciclovir is rapidly and extensively converted to the active ingredient ganciclovir. The bioavailability of ganciclovir from valganciclovir is up to 10-fold higher than from oral ganciclovir, therefore the dosage and administration of VALGANCICLOVIR VIATRIS tablets as described below should be closely followed (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE AND 4.9 OVERDOSE).

Treatment of CMV Retinitis

Adult Patients

Induction Treatment

For patients with active CMV retinitis, the recommended dosage is 900 mg twice daily for 21 days with food. Prolonged induction treatment may increase the risk of bone marrow toxicity (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Maintenance Treatment

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

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

Paediatric Patients
The safety and efficacy of valganciclovir in paediatric patients have not been established in adequate and well-controlled clinical studies.

Prevention of CMV Disease in Transplantation

Adult Patients
For kidney transplant patients, the recommended dose is 900 mg once daily with food, starting within 10 days of transplantation post-transplantation and continuing until 200 days post-transplantation [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials - IMPACT Study (Study NT18435)]**.**

For all other solid organ transplant patients, the recommended dose is 900 mg once daily with food, starting within 10 days post-transplantation and continuing until 100 days post-transplantation (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials - Study PV16000).

Paediatric Patients
In paediatric solid organ transplant patients, (paediatric heart transplant patients from 4 weeks and paediatric kidney transplant patients from 4 months (see Section 5.1 PHARMACODYNAMIC PROPERTIES, CLINICAL TRIALS), who are at risk of developing CMV disease, the recommended once daily dose of VALGANCICLOVIR VIATRIS is based on body surface area (BSA) and creatinine clearance (CrCl) derived from Schwartz formula (CrCLS), and is calculated using the equation below:

Paediatric Dose (mg) = 7 x BSA x CrClS (see Mostellar BSA formula and Schwartz Creatine Clearance formula below). If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m^2, then a maximum value of 150 mL/min/1.73m^2 should be used in the equation.

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

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

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

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

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

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

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

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, VALGANCICLOVIR VIATRIS tablets may be used if the calculated doses are within 10% of available tablet doses and the patient is able to swallow tablets. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.

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

Special Patient Groups

Renal Impairment

Adult Patients

Serum creatinine or estimated creatinine clearance levels should be monitored carefully. Dosage adjustment is required based on creatinine clearance as shown in the Table 1 below (see Sections 5.2 PHARMACOKINETIC PROPERTIES and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Table 1: VALGANCICLOVIR VIATRIS Tablets Dose for Renally Impaired Patients

CrCl (mL/min)	Induction Dose of tablets	Maintenance/ Prevention Dose of tablets	Induction Dose of oral powder for solution	Maintenance/ Prevention Dose of oral powder for solution
≥ 60	900 mg twice daily	900 mg once daily	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days	450 mg once daily	225 mg once daily
10 – 24	450 mg every 2 days	450 mg twice weekly	225 mg once daily	125 mg once daily
< 10	not recommended	not recommended	200 mg (3 times a week after dialysis)	100 mg (3 times a week after dialysis)

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

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

For females = 0.85 x male value

Elderly

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatic Impairment

The safety and efficacy of valganciclovir has not been established in patients with hepatic impairment (see Sections 5.2 PHARMACOKINETIC PROPERTIES and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Paediatric Patients

Dosing of paediatric solid organ transplant patients is individualized based on a patient's renal function and size (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

Patients with severe leukopenia, neutropenia, anaemia, thrombocytopenia and/or pancytopenia
Severe leucopenia, 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/µL or the platelet count is less than 25,000/µL or the haemoglobin is less than 8 g/100 mL (see SECTIONS 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE AND 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Method of Administration

VALGANCICLOVIR VIATRIS is administered orally, and should be taken with food (see Section 5.2 PHARMACOKINETIC PROPERTIES, ABSORPTION).

Note that tablets (450 mg) should not be used in place of the powder for oral solution as the formulations are not considered interchangeable (powder for oral solution is available from other brand/s).

4.3 CONTRAINDICATIONS

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

VALGANCICLOVIR VIATRIS should not be administered if the absolute neutrophil count is less than 500 cells/µL, the platelet count is less than 25 000/µL, or the haemoglobin is less than 8 g/dL.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical toxicities of valganciclovir, which is metabolised to ganciclovir, include leucopenia and thrombocytopenia. Concomitant administration of valganciclovir and other medicines that are known to be myelosuppressive or associated with renal impairment may result in added toxicity (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In animal studies ganciclovir was found to be mutagenic, clastogenic, aspermatogenic, teratogenic and carcinogenic and to impair fertility. Valganciclovir should therefore be considered a potential teratogen and carcinogen in humans with potential to cause birth defects and cancers. Prior to initiation of ganciclovir treatment, patients should be advised of the potential risks to the foetus and to use contraceptive measures (see sections 4.6 Fertility, pregnancy and lactation). Based on clinical and non-clinical studies, valganciclovir may cause temporary or permanent inhibition of spermatogenesis (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION, and 5.3 PRECLINICAL SAFETY DATA and Section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL). Valganciclovir is indicated in those patients as outlined under Section 4.1 THERAPEUTIC INDICATIONS where the potential benefits to the patient outweighs the risks stated herein.

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 valaciclovir, a cross-hypersensitivity reaction between these medicines is possible. Caution should therefore be used when prescribing

valganciclovir tablets to patients with known hypersensitivity to aciclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively).

Haematologic

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anaemia have been observed in patients treated with valganciclovir (and ganciclovir) (see Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 4.2 DOSE AND METHOD OF ADMINISTRATION).

Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µL; or platelet count is less than 25 000/µL; 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 with renal impairment and those patients in whom ganciclovir or other nucleoside analogues have previously resulted in leucopenia, or in whom neutrophil counts are less than 1000 cells/µL 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.

Use in Renal Impairment

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required.

Increased serum creatinine levels have been observed in trials evaluating valganciclovir tablets. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in Hepatic Impairment

The safety and efficacy of valganciclovir have not been established in patients with hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES, SPECIAL POPULATIONS).

Paediatric Use

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

The use of valganciclovir in children warrants extreme caution. Valganciclovir should be considered a potential carcinogen in humans. This potential to cause cancers is greater in infants and children than in adults. Valganciclovir is likely to cause temporary or permanent inhibition of spermatogenesis. This could result in permanent male infertility. Administration to children should be undertaken only after careful evaluation and only if, in the opinion of the physician, the potential benefits of treatment outweigh these considerable risks (see Sections 5.1 PHARMACODYNAMIC PROPERTIES, CLINICAL TRIALS; 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Use in the Elderly

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 Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, USE IN RENAL IMPAIRMENT AND 4.2 DOSE AND METHOD OF ADMINISTRATION).

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Valganciclovir is rapidly and extensively converted to ganciclovir; therefore interactions associated with ganciclovir are expected.

Imipenem-cilastatin

Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly and a pharmacodynamic interaction between these two drugs cannot be discounted. Valganciclovir should not be administered concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Clinically Significant Potential Medicine 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, hydroxycarbamide (hydroxyurea)) and anti-infective agents (e.g. trimethoprim/sulphonamides, dapsone, amphotericin B (amphotericin), flucytosine, pentamidine), hydroxycarbamide (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.

Zidovudine

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

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 administration of these drugs. There was no significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis).

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 concomitantly should be closely monitored for ganciclovir toxicity.

Paediatric Population

Interaction studies have only been performed in adults.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 embryolethality 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 the use of contraceptive measures.

Use in Pregnancy

Pregnancy Category: D

The safety of valganciclovir for use in pregnant women has not been established however, ganciclovir readily diffuses across the human placenta. Valganciclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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.

Contraception in Males and Females

Women of childbearing potential should be advised to use effective contraception during and for at least 30 days after treatment with valganciclovir because of the mutagenic and teratogenic potential of ganciclovir. Sexually active men should be advised to practice barrier contraception during, and for at least 90 days after cessation of treatment with valganciclovir, unless it is certain that the female partner is not at risk of pregnancy.

The safe use of valganciclovir during labour and delivery has not been established.

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, embryolethality, 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 embryolethality.

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.

Use in Lactation

Peri- and postnatal 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. Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats. Therefore, valganciclovir should not be given to breastfeeding mothers or breastfeeding should be discontinued. The minimum time interval before breastfeeding can safely be resumed after the last dose of valganciclovir is unknown.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Experience with valganciclovir

Valganciclovir, a prodrug of ganciclovir, 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 valganciclovir. All of the adverse events observed in clinical studies with valganciclovir have been previously observed with ganciclovir.

Adult Patients

Treatment of CMV Retinitis in AIDS

The safety profiles of valganciclovir and IV ganciclovir during 28 days of randomised 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 randomised 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 ≥ 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 events, 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 ≥ 5% from a clinical trial, where solid organ transplant patients received valganciclovir or oral ganciclovir starting within 10 days of 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, 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 ≥ 5% of Patients in either CMV Retinitis or Solid Organ Transplantation clinical trials treated with valganciclovir or ganciclovir

System organ class	Patients with CMV retinitis	Solid Organ 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)			
Respiratory, thoracic and mediastinal disorders			
Cough	16	6	8
Dyspnoea	9	11	10
Productive cough	5	2	2
Rhinorrhea	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			
Back pain	8	20	15
Arthralgia	6	7	7
Muscle cramps	2	6	11
Pain in limbs	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/µL) is seen more frequently in CMV retinitis patients (16%) undergoing treatment with valganciclovir than in solid organ transplant patients receiving valganciclovir (5%) or oral ganciclovir (3%) until Day 100 post-transplant or valganciclovir (10%) until Day 200 post-transplant. There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 post-or Day 200 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. Leukopenia was reported with a slightly higher incidence in the 200 days arm while the incidence of neutropenia, anemia 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 8 shows adverse events occurring after day 100 of the study when only patients in the 200 days arm were receiving valganciclovir (patients in the 100 day arm were receiving placebo).

Table 4: Adverse events occurring in ≥ 5% of high risk kidney transplant patients treated with valganciclovir (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)
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 Cough	 8 (5) 8 (5)	 6 (4) 3 (2)

Table 5: 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 Neutropenia	 7 (4) 5 (3)	 30 (19) 8 (5)
Gastrointestinal disorders Diarrhoea	 18 (11)	 15 (10)
Infections and infestations Urinary tract infection Cytomegalovirus infection Nasopharyngitis Upper respiratory tract infection Cytomegalovirus syndrome	 11 (7) 20 (12) 7 (4) 4 (2) 12 (7)	 11 (7) 1 (<1) 10 (6) 11 (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: abdominal distension, cholangitis, dyspepsia, dysphagia, eructation, oesophagitis, faecal incontinence, flatulence, gastritis, gastrointestinal disorder, gastrointestinal haemorrhage, mouth ulceration, pancreatitis, tongue disorder

General disorders and administration site conditions: ascites, asthenia, bacterial, fungal and viral infections, haemorrhage, malaise, mucous membrane disorder, pain, 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

Paediatric Patients

Valganciclovir has been studied in 179 paediatric solid organ transplant patients who are at risk of developing CMV disease (aged 3 weeks to 16 years) and in 133 neonates with symptomatic congenital CMV disease (aged 2 to 31 days), with duration of ganciclovir exposure ranging from 2 to 200 days (see Section 5.1 PHARMACODYNAMIC PROPERTIES, CLINICAL TRIALS).

Prevention of CMV disease in Solid Organ Transplant (SOT)

Table 5 shows the adverse events (up to 28 days after completion of study treatment) regardless of seriousness and relationship with an incidence of ≥10% from two clinical trials where solid organ transplant paediatric patients received valganciclovir starting within 10 days post-transplantation until Day 100 post- transplant and where kidney transplant paediatric patients received valganciclovir once daily starting within 10 days post transplantation until Day 200 post-transplant. The overall safety profile was similar in paediatric patients as compared to adults. However, the rates of certain adverse events, such as, but not limited to, upper respiratory tract infection, pyrexia, abdominal pain and dysuria, that maybe characteristic of the paediatric population, were reported in somewhat higher incidence in paediatrics than in 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.

Table 6: Overview of the common adverse events that occur on treatment in ≥10% of the total population in paediatric SOT patients

	Paediatric Solid Organ Transplant Patients			
	Valganciclovir 100 days N = 63		Valganciclovir 200 days N = 56	
System Organ Class	N	%	N	%
Infection and Infestations				
Urinary tract infection	4	6	19	34
Escherichia Coli urinary tract infection	-	-	7	13
Upper respiratory tract infection	14	22	19	34
Gastrointestinal disorders				
Diarrhoea	20	32	18	32
Constipation	7	11	3	5
Nausea	7	11	5	9
Abdominal pain	4	6	10	18
Vomiting	13	21	7	13
Blood and lymphatic system disorder				
Leucopenia	1	2	14	25
	Paediatric Solid Organ Transplant Patients			

	Valganciclovir 100 days N = 63		Valganciclovir 200 days N = 56	
System Organ Class	N	%	N	%
Anaemia	9	14	9	16
Neutropenia	8	13	13	23
General disorders and administration site conditions				
Pyrexia	15	24	9	16
Investigations				
Blood creatine increase	1	2	9	16
Renal and urinary disorders				
Haematuria	4	6	6	11
Dysuria	1	2	10	18
Nervous system disorders				
Tremor	2	3	10	18
Headache	4	6	12	21
Vascular disorders				
Hypertension	14	22	9	16
Immune system disorders				
Transplant rejection	6	10	3	5

Congenital CMV

The safety profile of valganciclovir and ganciclovir for up to 6 months of treatment was assessed in 133 neonates or infants with symptomatic congenital CMV infection aged from 2 days to 31 days in two studies. Although this data is limited, no safety issues have been identified and safety appears consistent with the known safety profile of valganciclovir/ganciclovir.

In the first study, the primary toxicity associated with ganciclovir was neutropenia with 9 out of 24 subjects (38%) developing Grade 3 or 4 neutropenia while on therapy. Only one subject had to permanently discontinue antiviral treatment, due to neutropenia. Most events were manageable with continuation of antiviral therapy in this study. Growth (head circumference, weight and height) of all neonates, who had growth measurements recorded, increased over time in this non-comparative study.

In the second 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 SOT patients receiving valganciclovir until Day 100 post-transplant are listed in Table 7 below. The incidence of laboratory abnormalities was comparable with the extension of prophylaxis up to 200 days in high risk kidney transplant patients.

Laboratory abnormalities reported in paediatric SOT patients are listed in Table 8. The incidence of severe neutropenia (ANC<500/µL) 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 7: 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/µL)			
< 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/µL)			
< 25000	3	0	2
25000 - < 50000	5	1	3
50000 - < 100000	21	18	21
Serum creatinine (mg/dL)			
> 2.5	2	14	21
> 1.5 – 2.5	11	45	47

Table 8: Laboratory abnormalities in paediatric SOT transplant patients

Laboratories abnormalities	Valganciclovir in Paediatric SOT patients	
	Dosing until Day 100 Post-Transplant N=63	Dosing until Day 200 Post-Transplant N=56
	%	%
Neutropenia (ANC/µL)		
<500	5	30
500 - <700	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/µL)		
<25000	0	0
25000 - <50000	10	0
50000 - <100000	3	4
Serum creatinine (mg/dL)		
> 2.5	2	5
>1.5 – 2.5	11	20

Post-Marketing Experience

Experience with Ganciclovir and valganciclovir

As valganciclovir is rapidly and extensively converted to 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 Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) AND 5.1 PHARMACODYNAMIC PROPERTIES, CLINICAL TRIALS).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose experience with valganciclovir tablets

It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE AND 4.2 DOSE AND METHOD OF ADMINISTRATION).

Overdose Experience with Intravenous Ganciclovir

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

- *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, renal failure, and 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.

Treatment of overdose should consist of general supportive measures.

For information on the management of over dosage, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitors, ATC code: J05A B14.

Mechanism of Action

Valganciclovir is an L-valyl ester salt (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 type 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus.

In cytomegalovirus (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 CMV-infected cells (half-life 18 hours) and HSV-infected cells (half-life between 6 and 24 hours) after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase, and (b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, further viral DNA elongation. Typical anti-viral IC_{50} against CMV *in vitro* is in the range 0.08 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 (Study WV15376). CMV shedding was decreased in urine from 46% (32/69) of patients at study entry to 7% (4/55) of patients following four weeks of valganciclovir treatment.

Viral Resistance

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

Adult Patients

Treatment of CMV Retinitis in AIDS:

Genotypic analysis of CMV in polymorphonuclear leucocytes (PMNL) isolates from 148 patients 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:
Resistance was studied by genotypic analysis of CMV in PMNL samples collected i) on Day 100 (end of study drug prophylaxis) and ii) in cases of suspected CMV disease up to 6 months after transplantation. From the 245 patients randomised to receive valganciclovir, 198 Day 100 samples were available for testing and no ganciclovir resistance mutations were observed. This compares with 2 ganciclovir resistance mutations detected in the 103 samples tested (1.9%) for patients in the oral ganciclovir comparator arm.

Of the 245 patients randomised to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 127 patients randomised on the ganciclovir comparator arm, samples from the 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 PHARMACODYNAMIC PROPERTIES, Clinical Trials). 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.

Clinical Trials

Adult Patients

Study WV15376: 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 $\log_{10}$ copies/mL in the valganciclovir arm and 4.9 $\log_{10}$ 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.

Study PV16000: 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 non-inferiority 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. For a summary of PV16000 see Table 9 below.

Table 9: 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 (PV16000)	**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.

For study PV16000 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 ($AUC_{0\text{-}24h}$ 44.3 vs. 25.4 µg.h/mL).

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/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 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 10.

Table 10: Percentage of Kidney Transplant Patients with CMV Disease[1], 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 98.2% (160/163) for the 100-day dosing regimen and 98.1% (152/155) for the 200-day dosing regimen. The incidence of biopsy proven acute rejection at 12 months post-transplant was 17.2% (28/163) for the 100-day dosing regimen and 11.0% (17/155) for the 200- day dosing regimen.

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

Paediatric Patients

Prevention of CMV disease in transplantation

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

Three of these studies assessed only the pharmacokinetics and safety of oral valganciclovir on SOT patients aged from 4 weeks to 16 years of age who were requiring CMV prophylaxis (see Section 5.2 PHARMACOKINETIC PROPERTIES, SPECIAL POPULATIONS).

One study enrolled 20 liver transplant patients with a median age of 2 years (6 months to 16 years) who received a single daily dose of valganciclovir on 2 consecutive days. A second study enrolled 26 kidney patients with a median age of 12 years (1 to 16 years) who received multiple doses of valganciclovir on 2 consecutive days. The third study enrolled 14 heart transplant patients with a median age of 13 weeks (4 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 the prophylaxis of valganciclovir for up to 100 days and 200 days post-transplant using the described paediatric dosing algorithm (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 disease reported during the study that would fulfill the definition of CMV disease. However, CMV events were reported in 7 patients during the study of which 3 did not require adjustment to the study drug or were not treated and, therefore, were not considered clinically significant (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.2 PHARMACOKINETIC PROPERTIES) 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 fulfill the definition of CMV disease. While 4 patients reported CMV events, one could not be confirmed by the central laboratory and of the 3 remaining events one did not require treatment and, therefore, was not considered clinically significant (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS**)**).

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 the oral absorption of valganciclovir and the renal excretion of ganciclovir.

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. $AUC_{0\text{-}24h}$ 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 is given with food mean ganciclovir $AUC_{0\text{-}24h}$ increased by 24% to 56% depending on the dose. When valganciclovir was given with food at a dose of 875 mg, increases were seen in both mean ganciclovir $AUC_{0\text{-}24h}$ (approximately 30%) and mean ganciclovir C_{max} values (approximately 14%). Therefore, it is recommended that valganciclovir be administered with food (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

For ganciclovir, average $AUC_{0\text{-}24h}$ has been shown to correlate with time to progression of CMV retinitis.

The bioavailability of ganciclovir from valganciclovir is comparable across all the patient populations studied (adult and paediatric). 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 and paediatric dosing algorithm (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Distribution

Due to the rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. Plasma protein binding of ganciclovir was 1% to 2%. The steady state volume of distribution of ganciclovir after IV administration was 0.680 ± 0.161 L/kg.

Metabolism

Valganciclovir is rapidly hydrolysed to ganciclovir; no other metabolites have been detected. Ganciclovir is not metabolized to a significant extent.

Excretion

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.

The terminal half-life ($t_{½}$) of ganciclovir following oral administration of valganciclovir to either healthy or HIV- and CMV-positive subjects was 4.18 ± 0.80 hours (*n* = 244), and that following administration of IV ganciclovir was 3.85 ± 0.74 hours (*n* = 87).

In patients undergoing haemodialysis, approximately half of the ganciclovir present at the start of a dialysis session is removed during dialysis. The mean intra-dialysis half-life and the mean inter-dialysis half-life was estimated to be 3.47 hours and 51.0 hours, respectively.

Pharmacokinetics in Special Populations

Patients with renal impairment

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

Table 11: Pharmacokinetics parameters of ganciclovir from a single oral dose or 900 mg valganciclovir tablets in patients with various degrees of renal impairment

Estimates Creatine Clearance (mL/min)	N	Apparent Clearance (mL/min) Mean ±SD	AUC_{0}-∞(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
Haemodialysis	6	177 ± 31		3.6 ± 0.6

Decreased renal function resulted in decreased clearance of ganciclovir from valganciclovir, and a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and **4**.2 DOSE AND METHOD OF ADMINISTRATION).

Patients undergoing haemodialysis

Ganciclovir is readily removable by haemodialysis. Data obtained during intermittent haemodialysis in patients dosed with valganciclovir showed estimated dialysis clearance as 138 mL/min ± 9.1% (N = 3) and intra-dialysis half-life estimated to 3.47 h (N = 6). 55% of ganciclovir was removed during a 3 hour dialysis session.

Haemodialysis reduces plasma concentrations of ganciclovir by about 42 to 55% following valganciclovir administration. Adult patients receiving haemodialysis (CrCl less than 10mL/min) cannot use valganciclovir

tablets because the daily dose of valganciclovir tablets required for these patients is less than 450mg (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Stable liver transplant patients

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

Hepatic impairment

No pharmacokinetic study has been conducted and no population PK data has been collected in patients with hepatic impairment undergoing valganciclovir therapy (see PRECAUTIONS, Hepatic Impairment and DOSAGE AND ADMINISTRATION, Hepatic Impairment Hepatic Impairment).

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 DOSE AND METHOD OF ADMINISTRATION).

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 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 DOSE AND METHOD OF ADMINISTRATION).

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 12 and are consistent with estimates obtained in adult solid organ transplant patients.

Table 12: Summary of model-estimated mean (±SD) pharmacokinetics of ganciclovir in paediatric patients by age

	PK Parameter	Age Group			
		Heart Transplant recipients **<4 months of ages**		**Solid Organ Transplant patients** **4 months to 16 years**	
		<4 months (n=14)	**4 months - ≤2 years (n=2)**	**> 2 - < 12 years (n=12)***	**≥ 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)
			4 months - ≤2 years (n=9)	**< 2 - < 12 years (n=6)**	**≥ 12 years (n=2)**
Liver **(n=17)**	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)
		<4 months (n=14)	**4 months - ≤2 years (n=6)**	**< 2 - < 12 years (n=2)**	**≥ 12 years (n=4)**
Heart **(n=26)**	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 $AUC_{0\text{-}12hr}$ after oral dose administration of valganciclovir was approximately 23.2 μg.h/mL (equivalent to 46.4 μg.h/mL in $AUC_{0\text{-}24hr}$) in the first study. Similar exposure was also observed in the second study.

5.3 PRECLINICAL SAFETY DATA

Ganciclovir was genotoxic and carcinogenic in animal studies.

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 (preputial, 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, crospovidone, stearic acid, hypromellose, titanium dioxide, macrogol 400, polysorbate 80 and iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

VALGANCICLOVIR VIATRIS tablets should be stored below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

VALGANCICLOVIR VIATRIS is suppled in HDPE Bottle packs of 60 tablets in a child resistant closure.

Australian Register of Therapeutic Goods (ARTG)

AUST R 218477 – VALGANCICLOVIR VIATRIS valganciclovir (as hydrochloride) 450 mg film-coated tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

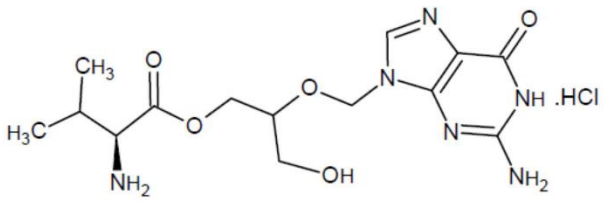
Caution should be exercised in the handling of VALGANCICLOVIR VIATRIS tablets. VALGANCICLOVIR VIATRIS tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans and inhibits spermatogenesis, caution should be observed in handling VALGANCICLOVIR VIATRIS tablets. Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with sterile water, or plain water if sterile water is unavailable.

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.

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



CAS Number

175865-59-5

The chemical name for valganciclovir hydrochloride is: L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride.

The molecular formula is $C_{14}H_{22}N_6O_5.HCl$ and the molecular weight is 390.83.

Valganciclovir hydrochloride (valganciclovir HCl) is the hydrochloride salt of the L-valyl ester of ganciclovir. Ganciclovir is a synthetic nucleoside analogue of guanine.

Valganciclovir HCl is a white to off-white crystalline powder.

Valganciclovir HCl is a polar hydrophilic compound with a solubility of 70 mg/mL in water at 25°C at a pH of 7.0 and an n-octanol/water partition coefficient of 0.0095 at pH 7.0. The pKa for valganciclovir HCl is 7.6.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

25/09/2015

10 DATE OF REVISION

05/05/2022

Summary Table of Changes

Section Changed	Summary of New Information
6.5	Add child resistant closure details to align with ARTG entry Update trade name to align with ARTG entry

VALGANCICLOVIR VIATRIS_pi\May22/00