NEW ZEALAND DATA SHEET

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.

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 pancytopenia

See section 4.4 before initiation of therapy.

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).

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).

4.4 Special warnings and precautions for use

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

Prior to initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies ganciclovir was found to be mutagenic, 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). Based on clinical and nonclinical studies, it is also considered likely that valganciclovir causes temporary or permanent inhibition of spermatogenesis. 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 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). Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/microlitre or the platelet count is less than 25,000/microlitre or the haemoglobin is less than 8 g/dL (see sections 4.2 and 4.8).

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

It is recommended that complete blood counts and platelet counts be monitored in all patients during therapy. Increased haematological monitoring may be warranted in patients with renal impairment and paediatrics, at a minimum each time the patient attends the transplant clinic.

In patients developing severe leukopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered (see section 4.2).

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 Viatris 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 Viatris 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).

Valganciclovir Viatris should not be used in patients on haemodialysis (see sections 4.2 and 5.2).

Use with other medicines

Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir. Valganciclovir should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section 4.5).

Patients treated with valganciclovir and (a) didanosine, (b) medicines that are known to be myelosuppressive (e.g. zidovudine), or (c) substances affecting renal function, should be closely monitored for signs of added toxicity (see section 4.5).

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

Drug interactions with valganciclovir

In-vivo drug interaction studies with Valganciclovir Viatris 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 intravenous ganciclovir. At intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38 to 67% has been observed confirming a pharmacokinetic interaction during the concomitant administration of these drugs. There was no significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis) (see section 4.4).

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

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

Zidovudine

Both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia. A pharmacodynamic interaction may occur during concomitant administration of these drugs. Some patients may not tolerate concomitant therapy at full dosage (see section 4.4).

Potential drug interactions

Toxicity may be enhanced when ganciclovir / valganciclovir is co-administered with other drugs known to be myelosuppressive or associated with renal impairment. This includes nucleoside (e.g. zidovudine, didanosine, stavudine) and nucleotide analogues (e.g. tenofovir, adefovir), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vinblastine, vincristine, hydroxyurea) and anti-infective agents (trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these drugs should only be considered for concomitant use with valganciclovir if the potential benefits outweigh the potential risks (see section 4.4).

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. Based on its pharmacological

mechanism of action and reproductive toxicity observed in animal studies with ganciclovir (see section 5.3) there is a theoretical risk of teratogenicity in humans.

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

Breast-feeding

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. Animal data indicate that ganciclovir is excreted in the milk of lactating rats. Therefore, breast-feeding must be discontinued during treatment with valganciclovir (see sections 4.3 and 5.3).

Fertility

A small clinical study with renal transplant patients receiving valganciclovir for CMV prophylaxis for up to 200 days demonstrated an impact of valganciclovir on spermatogenesis, with decreased sperm density and motility measured after treatment completion. This effect appears to be reversible and approximately six months after valganciclovir discontinuation, mean sperm density and motility recovered to levels comparable to those observed in the untreated controls.

In animal studies, ganciclovir impaired fertility in male and female mice and has shown to inhibit spermatogenesis and induce testicular atrophy in mice, rates and dogs at doses considered clinically relevant.

Based on clinical and nonclinical studies, it is considered likely that ganciclovir (and valganciclovir) may cause temporary or permanent inhibition of human spermatogenesis (see sections 4.4 and 5.3).

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

Summary of safety profile

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. Therefore, adverse drug reactions reported with intravenous or oral ganciclovir or with valganciclovir are included in the table of adverse drug reactions below (see table below).

In patients treated with valganciclovir/ganciclovir the most serious and frequent adverse drug reactions are haematological reactions and include neutropenia, anaemia and thrombocytopenia (see section 4.4).

The frequencies presented in the table of adverse reactions are derived from a pooled population of patients (n=1704) receiving maintenance therapy with ganciclovir or valganciclovir. Exception is made for anaphylactic reaction, agranulocytosis and granulocytopenia, the frequencies of which are derived from post-marketing experience.

Adverse reactions are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

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

Table 2. Tabulated list of adverse drug reactions

ADR (MedDRA) System Organ Class	**Frequency Category**
Infections and infestations	
Candid infections including oral candidiasis	Very common
Upper respiratory tract infection	
Sepsis	Common
Influenza	
Urinary tract infection	
Cellulitis	
Blood and lymphatic disorders	
Neutropenia	Very common
Anaemia	
Thrombocytopenia	Common
Leukopenia	
Pancytopenia	
Bone marrow failure	Uncommon
Aplastic anaemia	Rare
Agranulocytosis*	
Granulocytopenia*	
Immune system disorders	
Hypersensitivity	Common
Anaphylactic reaction*	Rare
Metabolic and nutrition disorders	
Decreased appetite	Very common
Weight decreased	Common
Psychiatric disorders	
Depression	Common
Confusional state	
Anxiety	
Agitation	Uncommon
Psychotic disorder	
Thinking abnormal	
Hallucinations	
Nervous system disorders	
Headache	Very common

Insomnia	Common
Neuropathy peripheral	
Dizziness	
Paraesthesia	
Hypoaesthesia	
Convulsion	
Dysgeusia (taste disturbance)	
Tremor	Uncommon
Eye disorders	
Visual impairment	Common
Retinal detachment**	
Vitreous floaters	
Eye pain	
Conjunctivitis	
Macular oedema	
Ear and labyrinth disorders	
Ear pain	Common
Deafness	Uncommon
Cardiac disorders	
Arrhythmias	Uncommon
Vascular disorders	
Hypotension	Common
Respiratory, thoracic and mediastinal disorders	
Cough	Very common
Dyspnoea	
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea	
Vomiting	
Abdominal pain	
Dyspepsia	Common
Flatulence	
Abdominal pain upper	
Constipation	
Mouth ulceration	
Dysphagia	
Abdominal distention	
Pancreatitis	
Hepato-biliary disorders	
Blood alkaline phosphatase increased	Common
Hepatic function normal	
Aspartate aminotransferase increased	

Alanine aminotransferase increased	
Skin and subcutaneous tissues disorders	
Dermatitis	Very common
Night sweats	Common
Pruritis	
Rash	
Alopecia	
Dry skin	Uncommon
Urticaria	
Musculoskeletal and connective tissue disorders	
Back pain	Common
Myalgia	
Arthralgia	
Muscle spasms	
Renal and urinary disorders	
Renal impairment	Common
Creatinine clearance renal decreased	
Blood creatinine increased	
Renal failure	Uncommon
Haematuria	
Reproductive system and breast disorders	
Infertility male	Uncommon
General disorders and administration site conditions	
Pyrexia	Very common
Fatigue	
Pain	Common
Chills	
Malaise	
Asthenia	
Chest pain	Uncommon

** The frequencies of these adverse reactions are derived from post-marketing experience.*
*** Retinal detachment has only been reported in HIV patients treated for CMV retinitis*

Description of selected adverse reactions

Neutropenia

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

Thrombocytopenia

Patients with low baseline platelet counts (< 100,000/µL) have an increased risk of developing thrombocytopenia. Patients with iatrogenic immunosuppression due to treatment with immunosuppressive drugs are at greater risk of thrombocytopenia than patients with 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/μL) 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 3. 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 4. 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 3. 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 4. 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
> 1.5 – 2.5	11	20

Post-marketing

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, Table 2).

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).

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'-deoxyguanosineand 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 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.

Antiviral activity

The *in-vitro* anti-viral activity, measures as IC_{50} against CMV is in the range of 0.08 µM (0.02 µg/mL) to 14 µM (3.5 µg/mL).

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

Patients with newly diagnosed CMV retinitis were randomised in one study to induction therapy with either valganciclovir 900 mg twice daily or intravenous ganciclovir 5 mg/kg twice daily. The proportion of patients with photographic progression of CMV retinitis at week 4 was comparable in both treatment groups, 7/70 and 7/71 patients progressing in the intravenous ganciclovir and valganciclovir arms respectively.

Following induction treatment dosing, all patients in this study received maintenance treatment with valganciclovir given at the dose 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 was 226 (160) days and in the group receiving induction treatment with intravenous ganciclovir and maintenance treatment with valganciclovir was 219 (125) days.

Prevention of CMV disease in solid organ transplantation

A double-blind, double-dummy clinical active comparator study has been conducted in heart, liver and kidney transplant patients (lung and gastro-intestinal transplant patients were not included in the study) at high risk of CMV disease (D+/R-) who received 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 incidence of CMV disease (CMV syndrome + 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). The large majority of cases occurred following cessation of prophylaxis (post Day 100) with cases in the valganciclovir arm occurring on average later than those in the oral ganciclovir arm. The incidence of acute rejection in the first 6 months was 29.7% in patients randomised to valganciclovir compared with 36.0% in the oral ganciclovir arm, with the incidence of graft loss being equivalent, occurring in 0.8% of patients, in each arm.

A double-blind, placebo controlled study has been conducted in 326 kidney transplant patients at high risk of CMV disease (D+/R-) to assess the efficacy and safety of extending 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 5 below

Table 5. Percentage of kidney transplant patients with CMV disease[1], 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 98.1% (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.

Viral resistance

Viruses resistant to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or the viral polymerase gene (UL54). In clinical isolates, seven canonical UL97 substitutions, 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.

Treatment of CMV retinitis

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

Prevention of CMV disease in transplantation

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%.

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 birth to 16 years of age (see section 5.1). 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 drug or were not treated and, therefore, were not considered clinically significant (see section 4.8 and 5.1). 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 6.

Parameter	**Ganciclovir (5 mg/kg, intravenous) n = 18**	**Valganciclovir (900 mg, by mouth) n = 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 7.

Parameter	**Ganciclovir (1000 mg, three times daily) n = 82**	**Valganciclovir (900 mg, once daily) n = 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.

Table 8. 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	49.5 ± 22.4	4.85 ± 1.4
21 - 50	6	136 ± 64	91.9 ± 43.9	10.2 ± 4.4
11 - 20	6	45 ± 11	223 ± 46	21.8 ± 5.2
≤ 10	6	12.8 ± 8	366 ± 66	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 bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed conditions, was approximately 60%. Ganciclovir $AUC_{0\text{-}24h}$ was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant patients.

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.

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 9 and are consistent with estimates obtained in adult SOT patients.

Table 9. Summary of model-estimated mean (±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 ⩽ 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)
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.

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

Valganciclovir Viatris 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 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 May 2022

Summary table of changes

Section	Summary of new information
4.2	Equivalency of oral valganciclovir and intravenous ganciclovir. Changes to “whenever possible, take with food”. Included statement for Paediatric population. Re-arranged text. Additional statement for patients with severe leukopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia. Additional information under Method of administration for handling of product.
4.3	Contraindicated during breast-feeding.
4.4	Additional information reinforcing use of effective contraception, with cross-reference to sections 4.6, 4.8 and 5.3. Included paragraph on Difference in bioavailability with oral ganciclovir. Re-arranged text.
4.5	Included additional headings and re-arranged text. Addition of other antiretrovirals.
4.6	Re-arranged text. Breast-feeding must be discontinued during treatment.
4.8	Percentage column removed from tabulated list of adverse drug reactions.
5.1	Correction to figures in Table 5 Additional information on extending prophylaxis study from 100 to 200 days post-transplant.
5.2	Additional Tables 6 & 7 supporting valganciclovir in HIV positive, CMV positive patients; and solid organ transplant patients. Correction to figures in Table 8. Patients undergoing haemodialysis should not use valganciclovir.

	Additional information for stable liver transplant patients.
5.3	Section rewritten.