NEW ZEALAND DATA SHEET

VALGANCICLOVIR MYLAN

1. Product Name

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

Valganciclovir Mylan 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.

Standard dosage

Valganciclovir Mylan is administered orally and should be taken with food (see section 5.1).

Valganciclovir Mylan is rapidly and extensively converted into the active ingredient ganciclovir. The bioavailability of ganciclovir from valganciclovir is up to 10-fold higher than from oral ganciclovir.

The dosage and administration of Valganciclovir Mylan 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 CMV retinitis, the recommended dose is 900 mg (two 450 mg tablets) with food twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity (see 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) with food once daily. Patients whose retinitis worsens may repeat induction treatment.

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

Prevention of CMV disease in transplantation

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

Special dosage instructions

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 below (see sections 5.2 and 4.4).

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 Mylan should not be used in these patients (see sections 5.2 and 4.4).

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).

Hepatic impairment

The safety and efficacy of valganciclovir have not been established in patients with hepatic impairment (see sections 5.1 and 4.4)

Paediatric patients

See sections 4.8 and 5.1 for information on paediatric use.

4.3 Contraindications

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

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 acyclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively).

Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception

In animal studies ganciclovir was found to be mutagenic, 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 6.6). Prior to initiation of ganciclovir treatment, patients should be advised of the potential risks to the foetus and to use contraceptive measures (see section 4.6). Based on clinical and nonclinical studies, valganciclovir may cause temporary or permanent inhibition of spermatogenesis (see sections 5.3 and 4.8).

Myelosuppression

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.

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/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).

It is recommended that complete blood counts and platelet counts be monitored in all patients during therapy, particularly in patients with renal impairment and in neonates and infants.

In patients with severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, treatment with haematopoietic growth factors and/or the interruption of therapy is recommended (see section 4.8).

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

For patients on haemodialysis (CrCl < 10 mL/min) a dose recommendation cannot be given. Thus, valganciclovir should not be used in these patients (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).

Zidovudine and valganciclovir each have the potential to cause neutropenia and anaemia. Some patients may not tolerate concomitant therapy at full dosage (see section 4.5).

Didanosine plasma concentrations may increase during concomitant use with valganciclovir; therefore, patients should be closely monitored for didanosine toxicity (see section 4.5).

Concomitant use of other medicines that are known to be myelosuppressive or associated with renal impairment with valganciclovir may result in added toxicity (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

Valganciclovir is the pro-drug of 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. These medicines should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4).

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, hydroxyurea) and anti-infective agents (trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these medicines should be considered for concomitant use with valganciclovir only if the potential benefits outweigh the potential risks (see section 4.4).

Zidovudine

Both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia and 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).

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).

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.

4.6 Fertility, pregnancy and lactation

Fertility

In animal studies ganciclovir was found to impair fertility (see section 5.3). 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 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.

Pregnancy

Pregnancy category D

The safety of valganciclovir for use in human pregnancy has not been established. However, ganciclovir readily diffuses across the human placenta. The use of valganciclovir should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the foetus. Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity.

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

Breast-feeding

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

Contraception in males and females

Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment. Sexually active men are recommended to use condoms during and for at least 90 days after cessation of treatment with valganciclovir (see section 5.1).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trials

Valganciclovir is a prodrug of ganciclovir, which is rapidly converted to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir usage can therefore be expected to occur with valganciclovir. All of the adverse events observed in valganciclovir clinical studies have been previously observed with ganciclovir. Therefore, adverse drug reactions reported with intravenous or oral ganciclovir (no longer available) or with valganciclovir are included in the table of adverse reactions (see Table 1).

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

The frequencies presented in the table of adverse reactions are derived from a pooled population of patients (n=1704) receiving maintenance therapy with ganciclovir (GAN 1697, GAN 1653, 2304, GAN 1774, GAN 2226, AVI 034, GAN 041) or valganciclovir (WV1537, WV15705). Exception is made for anaphylactic reaction, agranulocytosis and granulocytopenia the frequencies of which are derived from post-marketing experience.

Frequencies are presented as percentages and as CIOMS frequency categories defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

The overall safety profile of ganciclovir/valganciclovir is consistent in HIV and transplant populations except that retinal detachment has only been reported in patients with CMV retinitis. However, there are some differences in the frequency of certain reactions. Valganciclovir is associated with a higher

risk of 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 1. Frequency of ganciclovir/valganciclovir ADRs reported in HIV patients receiving maintenance therapy (n=1704)

ADR (MedDRA) System Organ Class	**Percentage**	**Frequency Category**
Infections and infestations		
Candid infections including oral candidiasis	22.42%	Very common
Upper respiratory tract infection	16.26%	
Sepsis	6.92%	Common
Influenza	3.23%	
Urinary tract infection	2.35%	
Cellulitis	1.47%	
Blood and lymphatic disorders		
Neutropenia	26.12%	Very common
Anaemia	19.89%	
Thrombocytopenia	7.34%	Common
Leucopenia	3.93%	
Pancytopenia	1.06%	
Bone marrow failure	0.29%	Uncommon
Aplastic anaemia	0.06%	Rare
Agranulocytosis*	0.02%	
Granulocytopenia*	0.02%	
Immune system disorders		
Hypersensitivity	1.12%	Common
Anaphylactic reaction*	0.02%	Rare
Metabolic and nutrition disorders		
Decreased appetite	12.09%	Very common
Weight decreased	6.46%	Common
Psychiatric disorders		
Depression	6.69%	Common
Confusional state	2.99%	
Anxiety	2.64%	
Agitation	0.59%	Uncommon
Psychotic disorder	0.23%	
Thinking abnormal	0.18%	
Hallucinations	0.18%	
Nervous system disorders		
Headache	17.37%	Very common
Insomnia	7.22%	Common
Neuropathy peripheral	6.16%	

ADR (MedDRA) System Organ Class	Percentage	Frequency Category
Dizziness	5.52%	
Paraesthesia	3.58%	
Hypoaesthesia	2.58%	
Convulsion	2.29%	
Dysgeusia (taste disturbance)	1.35%	
Tremor	0.88%	Uncommon
Eye disorders		
Visual impairment	7.10%	Common
Retinal detachment**	5.93%	
Vitreous floaters	3.99%	
Eye pain	2.99%	
Conjunctivitis	1.58%	
Macular oedema	1.06%	
Ear and labyrinth disorders		
Ear pain	1.17%	Common
Deafness	0.65%	Uncommon
Cardiac disorders		
Cardiac arrhythmias	0.47%	Uncommon
Vascular disorders		
Hypotension	2.05%	Common
Respiratory, thoracic and mediastinal disorders		
Cough	18.31%	Very common
Dyspnoea	11.80%	
Gastrointestinal disorders		
Diarrhoea	34.27%	Very common
Nausea	26.35%	
Vomiting	14.85%	
Abdominal pain	10.97%	
Dyspepsia	4.81%	Common
Flatulence	4.58%	
Abdominal pain upper	4.58%	
Constipation	3.70%	
Mouth ulceration	3.17%	
Dysphagia	2.93%	
Abdominal distention	2.41%	
Pancreatitis	1.64%	
Hepatobiliary disorders		
Blood alkaline phosphatase increased	3.58%	Common
Hepatic function normal	3.23%	
Aspartate aminotransferase increased	1.88%	

ADR (MedDRA) System Organ Class	Percentage	Frequency Category
Alanine aminotransferase increased	1.23%	
Skin and subcutaneous tissues disorders		
Dermatitis	11.80%	Very common
Night sweats	7.92%	Common
Pruritis	4.58%	
Rash	2.52%	
Alopecia	1.29%	
Dry skin	0.94%	Uncommon
Urticaria	0.70%	
Musculoskeletal and connective tissue disorders		
Back pain	4.46%	Common
Myalgia	3.52%	
Arthralgia	3.35%	
Muscle spasms	2.99%	
Renal and urinary disorders		
Renal impairment	2.52%	Common
Creatinine clearance renal decreased	2.35%	
Blood creatinine increased	1.88%	
Renal failure	0.76%	Uncommon
Haematuria	0.70%	
Reproductive system and breast disorders		
Infertility male	0.23%	Uncommon
General disorders and administration site conditions		
Pyrexia	33.51%	Very common
Fatigue	18.96%	
Pain	5.81%	Common
Chills	5.40%	
Malaise	2.11%	
Asthenia	2.00%	
Chest pain	0.88%	Uncommon

** The frequencies of these adverse reactions are derived from post-marketing experience.*
*** Retinal detachment has only been reported in AIDS 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 /mL) 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 (16%) undergoing treatment with valganciclovir than in solid organ transplant patients receiving valganciclovir or oral ganciclovir. In patients receiving valganciclovir or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia was 5% and 3% respectively, whilst in patients receiving valganciclovir until Day 200 post-transplant the incidence of severe neutropenia was 10%.

There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 or Day 200 post-transplant with both valganciclovir and oral ganciclovir when compared to CMV retinitis patients. However, impaired renal function is a feature more frequent in solid organ transplantation patients.

The overall safety profile of 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 2. 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 3. 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 2. 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 3. 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

Laboratory Abnormalities	Valganciclovir in Paediatric SOT Patients	
	Dosing until Day 100 Post-Transplant *n* = 63 %	**Dosing until Day 200 Post-Transplant *n* = 56 %**
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 1).

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 also 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. 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, leucopenia, 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: J05AB14

Mechanism of action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir, which after oral administration is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of herpes viruses *in vitro* and *in vivo.* Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. This has been shown to occur in HSV-and HCMV-infected cells with half-lives of 18 and between 6 and 24 hours respectively after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase, and (b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited further viral DNA elongation. Typical anti-viral IC_{50} against CMV *in vitro* is in the range 0.08 µM (0.02 µg/mL) to 14 µM (3.5 µg/mL).

The clinical antiviral effect of 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

Clinical studies of valganciclovir have been conducted in patients with AIDS and CMV retinitis. Valganciclovir has shown comparable efficacy for induction treatment of CMV retinitis to intravenous ganciclovir.

Patients with newly diagnosed CMV retinitis were randomised in one study to induction therapy with either valganciclovir or intravenous ganciclovir. The proportion of patients with progression of CMV retinitis at week 4 was the same in both treatment groups.

Following induction treatment dosing, patients in this study received maintenance treatment with valganciclovir given at the dose of 900 mg daily. The mean (median) time from randomisation to progression of CMV retinitis in the group receiving induction and maintenance treatment with valganciclovir was 226 (160) days and in the group receiving induction treatment with intravenous ganciclovir and maintenance treatment with valganciclovir was 219 (125) days.

Valganciclovir allows systemic exposure of ganciclovir similar to that achieved with recommended doses of intravenous ganciclovir, which has been shown to be efficacious in the treatment of CMV retinitis. Ganciclovir AUC has been shown to correlate with time to progression of CMV retinitis.

Study: Prevention of CMV disease in solid organ transplantation

A double-blind, double-dummy clinical active comparator study has been conducted in heart, liver and kidney transplant patients at high risk of CMV disease (D+/R-) who received either 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), as adjudicated by an independent Endpoint Committee, 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.

IMPACT Study: 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 4.

Table 4. 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 disease before this time point.

The graft survival rate at 12 months post-transplant was 98.1% (160/163) for the 100-day dosing regimen and 98.2% (152/155) for the 200-day dosing regimen. The incidence of biopsy proven acute rejection at 12 months post-transplant was 17.2% (28/163) for the 100-day dosing regimen and 11.0% (17/155) for the 200-day dosing regimen.

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).

Viral resistance

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

Adult patients

Treatment of CMV retinitis

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

Prevention of CMV disease in transplantation

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

Of the 245 patients randomised to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 125 patients on the ganciclovir comparator arm, samples from 29 patients with suspected CMV disease were tested, from which 2 resistance mutations were observed, giving an incidence of resistance of 6.9%.

Resistance was evaluated in a study that extended valganciclovir CMV prophylaxis from 100 days to 200 days post-transplant in adult kidney transplant patients at high risk for CMV disease (D+/R-) (see section 5.1). Five subjects from the 100 day group and four subjects from the 200 day group meeting the resistance analysis criteria had known ganciclovir resistance-associated amino acid substitutions detected. In six subjects, the following resistance associated amino acid substitutions were detected within pUL97: 100 day group: A440V, M460V, C592G; 200 day group: M460V, C603W. In three subjects, the following resistance-associated amino acid substitutions were

detected within pUL54: 100 day group: E315D, 200 day group: E315D, P522S. Overall, the detection of known ganciclovir resistance-associated amino acid substitutions was observed more frequently in patients during prophylaxis therapy than after the completion of prophylaxis therapy (during therapy: 5/12 [42%] versus after therapy: 4/58 [7%]). The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

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.

Absorption

Valganciclovir is a prodrug of ganciclovir, which is well absorbed from the gastrointestinal tract and rapidly metabolised in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir is approximately 60%. Systemic exposure to valganciclovir is transient and low, AUC_{24h} and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir in the dose range 450 to 2625 mg was demonstrated only under fed conditions. When valganciclovir was given with food at the recommended dose of 900 mg, increases were seen in both mean ganciclovir AUC_{24h} (approximately 30%) and mean ganciclovir C_{max} values (approximately 14%). Therefore, it is recommended that 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 of ganciclovir after intravenous administration was 0.680 ± 0.161 L/kg. For IV ganciclovir, the volume of distribution is correlated with body weight with values for the steady state volume of distribution ranging from 0.54 • 0.87 L/kg. Ganciclovir penetrates the cerebrospinal fluid. Binding to plasma proteins was 1% to 2% over ganciclovir concentrations of 0.5 and 51 µg/mL.

Metabolism

Valganciclovir is rapidly hydrolysed 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

Geriatric population

No investigations on valganciclovir or ganciclovir pharmacokinetics in adults older than 65 years of age have been undertaken. However, as valganciclovir is a pro-drug of ganciclovir and because ganciclovir is mainly renally excreted and since renal clearance decreases with age, a decrease in

ganciclovir total body clearance and a prolongation of ganciclovir half-life can be anticipated in elderly (see section 4.2).

Patients with renal impairment

The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir were evaluated in 24 otherwise healthy individuals with renal impairment.

Tablet 5. Pharmacokinetic parameters of ganciclovir from a single oral dose of 900 mg valganciclovir tablets in patients with various degrees of renal impairment

Estimated Creatinine Clearance (mL/min)	N	Apparent Clearance (ml/min) Mean ± SD	AUC_{last} (µg·h/mL) Mean ± SD	Half-life (hours) Mean ± SD
51 - 70	6	249 ± 99	50.5 ± 23	4.9 ± 1.4
21 - 50	6	136 ± 64	100 ± 54	10.2 ± 4.4
11 - 20	6	45 ± 11	252 ± 64	21.8 ± 5.2
≤ 10	6	12.8 ± 8	407 ± 83	68.1 ± 35

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

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.

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 estimates obtained in other patient populations. Ganciclovir $AUC_{0\text{-}24h}$ was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant recipients.

Patients with hepatic impairment

No pharmacokinetic study has been conducted and no population PK data was collected in patients with hepatic impairment undergoing valganciclovir therapy.

Patients with cystic fibrosis

In a phase I pharmacokinetic study, steady state systemic exposure to ganciclovir was assessed in lung transplant recipients with or without cystic fibrosis (N=31) who were receiving 900 mg/day of valganciclovir as part of their post-transplant prophylaxis. 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 5 and are consistent with estimates obtained in adult SOT patients.

Table 6. 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 $AUC_{0\text{-}12hr}$ 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

Carcinogenicity

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

Genotoxicity

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

Impairment of fertility

Ganciclovir causes impaired fertility and teratogenicity in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. The same reprotoxicity warning is seen as applying to both medicines (see section 4.4).

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

Reproductive toxicity

Ganciclovir causes teratogenicity in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. The same reprotoxicity warning is seen to apply to both medicines (see section 4.4).

6. Pharmaceutical Particulars

6.1 List of excipients

Valganciclovir Mylan film coated tablets also contain

Tablet core

- microcrystalline cellulose
- crospovidone
- stearic acid

Tablet film coat

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

Valganciclovir Mylan film coated tablets are lactose and gluten free.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 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 Mylan 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

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9. Date of First Approval

02 April 2015

10. Date of Revision of the Text

4 February 2019

Summary table of changes

Section	Summary of new information
All	Revise to SPC format
4.2	Reworded dosage for maintenance and prevention of CMV retinitis. Revised information for special population groups.
4.3	The contraindication to the use of valganciclovir in patients with

	hypersensitivity to aciclovir or valaciclovir has been changed to a warning and moved to section 4.4
4.4	Addition of sub-heading 'Cross hypersensitivity' and movement of information from section 4.3 to this sub-heading. Update to information under heading, Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception. Update to information under heading, Myelosuppression.
4.5	Section reformatted, with update to information under headings Potential medicine interactions, Zidovudine, Didanosine. Removed specific information for Mycophenolate mofetil, Zalcitabine, Stavudine, Trimethoprim and Ciclosporin as they are included under Potential medicine interactions.
4.6	Addition of clinical study information under the sub- heading, Fertility. Reworded section on Pregnancy.
4.7	Update to terms in this section
4.8	Additional information included under Clinical trials and Laboratory abnormalities. Tables of ADRs combined and reformatted
4.9	Editorial changes to this section
5.1	Pharmacotherapeutic group and ATC code included. Additional information regarding Paediatric patients and Resistance in adult patients.
5.2	Editorial changes. Addition of Tables 5 and 6. Additional information under heading Pharmacokinetics in special populations and Paediatric patients.
5.3	Editorial changes