NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Cymevene ® 500 mg powder for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of ganciclovir (as ganciclovir sodium).

After reconstitution with 10 mL of water for injections, each mL provides 50 mg of ganciclovir.

Cymevene is available as the sterile lyophilised powder containing ganciclovir sodium 543 mg equivalent to ganciclovir 500 mg and sodium 43 mg (2 mEq).

Excipients with known effect: approximately 43 mg (2 mEq) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for infusion)

White to off-white solid cake.

Ganciclovir, when formulated as monosodium salt in the intravenous (IV) dosage form, is a white to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cymevene (ganciclovir) administered as the IV infusion is indicated for the palliative treatment of confirmed sight-threatening cytomegalovirus (CMV) disease in AIDS and other severely immunocompromised individuals. It is indicated for the treatment of confirmed CMV pneumonitis in bone marrow transplant patients. It is also indicated for the prophylaxis of CMV infection and disease following bone marrow and solid organ transplantation in patients at risk of CMV disease.

NOTE: Cymevene (ganciclovir) is not indicated for congenital or neonatal CMV disease; nor for the treatment of CMV infection in non-immunocompromised individuals.

4.2 Dose and method of administration

General

Cymevene must be reconstituted and diluted under the supervision of a healthcare professional and administered as an intravenous infusion (see section 4.2).

Caution: Cymevene must only be administered by IV infusion over 1 hour, preferably via a plastic cannula, into a vein with adequate blood flow (intramuscular or subcutaneous injection may result in severe tissue irritation due to the high pH (~11) of ganciclovir

solutions). Do not administer by rapid or bolus IV injection because the resulting excessive plasma levels may increase the toxicity of Cymevene. (see section 4.2).

The recommended dosage, frequency or infusion rates should not be exceeded.

Because of individual patient variations in the clinical response of CMV disease and the sensitivity to the myelosuppressive effects of Cymevene, the treatment of each patient with Cymevene should be individualised on a case-by-case basis. Changes in dose should be based on regular clinical evaluations as well as by regular haematologic monitoring.

Standard dosage for Treatment of CMV Disease

Dosage for patients with normal renal function
Induction Treatment
Cymevene 5 mg/kg given as an IV infusion over 1 hour every 12 hours (10 mg/kg/day) for 14 to 21 days

Maintenance Treatment
For immunocompromised patients at risk of relapse maintenance therapy may be given.

The recommended dose is Cymevene 6 mg/kg given over 1 hour, once daily, 5 days per week, or 5 mg/kg once daily 7 days per week.

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

Treatment of Disease Progression
Any patient in whom the disease progresses, either while on maintenance treatment or because treatment with Cymevene was withdrawn, may be re-treated using the IV induction treatment regimen. The frequency and duration of response in such patients has not been adequately established.

Indefinite treatment may be required in patients with AIDS, but even with continued maintenance treatment, patients may have progression of CMV disease.

Standard dosage for the Prevention of CMV Disease in Transplant Recipients for Patients with Normal Renal Function
The duration of treatment with Cymevene solution in transplant recipients is based on the risk of CMV disease and should be determined on an individual basis.

Liver Transplantation
The recommended initial dosage of Cymevene solution is 5 mg/kg infused at a constant rate over 1 hour every 12 hours (10 mg/kg/day) for 7 to 14 days, followed by 5 mg/kg once daily 7 days a week or 6 mg/kg once daily 5 days a week for up to 100 days post-transplant.

Heart Transplantation
The recommended initial dosage of Cymevene solution is 5 mg/kg infused at a constant rate over 1 hour every 12 hours (10 mg/kg/day) for 14 days, followed by 6 mg/kg once daily 5 days a week for up to 100 days post-transplant.

In a controlled clinical trial in heart allograft recipients, the onset of newly diagnosed CMV disease occurred after treatment with IV Cymevene was stopped at day 28 post-transplant,

suggesting that continued dosing may be necessary to prevent late occurrence of CMV disease in this patient population.

Bone Marrow Transplantation
The recommended initial dosage of Cymevene solution is 5 mg/kg infused at a constant rate over 1 hour every 12 hours (10 mg/kg/day) for 7 days, followed by 5 mg/kg once daily 7 days a week for up to 100 to 120 days post-transplant.

In controlled clinical trials in bone marrow allograft recipients, CMV disease occurred in several patients who discontinued treatment with Cymevene solution prematurely.

Other Transplantations
The recommended initial dosage of Cymevene solution is 5 mg/kg infused at a constant rate over 1 hour every 12 hours (10 mg/kg/day) for 7 to 14 days, followed by 5 mg/kg once daily 7 days a week or 6 mg/kg once daily on 5 days a week.

Special Dosage Instructions
Renal Impairment
For patients with impaired renal function, the IV dose of Cymevene should be modified as shown in the table below.

The following recommended dosages in renal impairment are not based on experience in patients with AIDS.

Table 1: Cymevene dosing for renally impaired patients

Creatinine Clearance	**Serum Creatinine**	**Cymevene Induction Dose**	**Dosing Interval**	**Cymevene Maintenance Dose**	**Dosing Interval**
(mL/min)	(micromol/L)	(mg/kg)	(hours)	(mg/kg)	(hours)
≥ 70	< 125	5.0	12	5.0	24
50 - 69	125 - 175	2.5	12	2.5	24
25 - 49	176 - 350	2.5	24	1.25	24

Creatinine Clearance	Serum Creatinine	Cymevene Induction Dose	Dosing Interval	Cymevene Maintenance Dose	Dosing Interval
10 - 24	> 350	1.25	24	0.625	24
< 10	> 350 (and on haemodialysis)	1.25	3 times per week, following haemodialysis	0.625	3 times per week following haemodialysis

To calculate an estimated creatinine clearance:

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

For females = 0.85 x male value

Hepatic impairment
The safety and efficacy of Cymevene have not been studied in patients with hepatic impairment (see section 5.2).

Elderly
No studies on the efficacy or safety of Cymevene have been conducted specifically in elderly patients. Since elderly individuals may have reduced renal function, Cymevene should be administered to the elderly patients with care and with special consideration of their renal status (see section 4.2).

Paediatric population
Safety and efficacy of ganciclovir in paediatrics have not been established, including use for the treatment of congenital or neonatal CMV infections. The use of Cymevene in children warrants extreme caution due to the potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should outweigh the risks. Method of Administration

Based on patient weight the appropriate calculated dose volume should be removed from the vial (Cymevene concentration 50 mg/mL) and added to an acceptable infusion fluid (typically 100 mL) for delivery over the course of one hour. Infusion concentrations greater than 10 mg/mL are not recommended. The following infusion fluids are compatible with Cymevene: normal saline, glucose 5% in water, Ringer's Injection, Ringer-Lactate Solution for Injection.

For instructions on reconstitution and dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

Cymevene is contraindicated in pregnant women, nursing mothers, and in patients who are hypersensitive to ganciclovir, valganciclovir or to any of the excipients.

Cymevene should not be administered to patients if the absolute neutrophil count falls below 0.5 x 109/L (500 cells/µL) or platelet count below 2.5 x 1010/L (25,000/µL) or the haemoglobin is less than 80 g/L (8 g/dL).

The safety and efficacy of Cymevene have not been evaluated for prophylaxis of CMV disease in donor negative/receptor negative (D-/R-) transplant patients, or in populations other than those stated under Therapeutic Indications, section 4.1.

4.4 Special warnings and precautions for use

General

The main clinical toxicities of ganciclovir include leucopenia, anaemia and thrombocytopenia.

Cymevene is only indicated in those patients as outlined under Therapeutic Indications in section 4.1 where the potential benefits to the patient outweigh the risks stated herein. It is recommended that complete blood counts and platelet counts be monitored during therapy.

The diagnosis of CMV retinitis should be made by indirect ophthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis included candidiasis, toxoplasmosis, histoplasmosis, retinal scars, cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason it is essential that the diagnosis of CMV be established by an ophthalmologist familiar with the presentation of these conditions. The diagnosis of CMV retinitis may be supported by culture of CMV in the urine, blood, throat, or other sites, but a negative culture does not rule out CMV retinitis.

HIV+ Patients with CMV Retinitis: Ganciclovir is not a cure for CMV retinitis, and immunocompromised patients may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4 to 6 weeks while being treated with Cymevene. Some patients will require more frequent follow-up.

Cross hypersensitivity

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

Mutagenicity, teratogenicity, fertility and contraception

In animal studies ganciclovir was found to be mutagenic, teratogenic, carcinogenic and to impair fertility. Cymevene should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. . Prior to initiation of ganciclovir treatment, patients should be advised of the potential risks to the foetus and to use contraceptive measures. Based on clinical and nonclinical studies, Cymevene may cause temporary or permanent inhibition of spermatogenesis in males (see sections 4.6, 4.8 and 5.3).

Ganciclovir caused point mutations and chromosomal damage in mammalian cells *in vitro* and *in vivo*. Ganciclovir was clastogenic in the mouse micronucleus assay. Ganciclovir was not mutagenic in the Ames Salmonella assay.

Myelosuppression

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with Cymevene (see sections 4.2 and 4.8).

Cymevene should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or are receiving myelosuppressive medicines or irradiation. Cytopenia may occur at any time during treatment and may increase with continued dosing. Cell counts usually begin to recover within 3 to 7 days of discontinuing the medicine. Colony-stimulating factors have been shown to increase neutrophil counts in patients receiving ganciclovir for treatment of CMV retinitis.

Neutropenia: Patients receiving ganciclovir have manifested neutropenia (neutrophil count < 1×10^9/L). Data from treatment with IV Cymevene indicates neutropenia typically occurs during the first or second week of induction therapy and prior to administration of a total cumulative dose of 200 mg/kg, but may occur at any time during treatment. With IV therapy neutropenia has occurred in up to 40% of patients. Evidence of recovery of cell counts usually occurs within 3 to 7 days after either discontinuing the medicine or decreasing the dosage. The risk of neutropenia may not necessarily be predicted from pre-treatment cell counts. Cymevene should not be administered if the absolute neutrophil count is below 0.5×10^9/L.

Thrombocytopenia (platelet count < 5.0×10^{10}/L) has been observed in patients treated with ganciclovir. Data from studies of IV Cymevene indicates that patients with initial platelet counts < 1.0×10^{11}/L appear to be at increased risk of this toxicity. Cymevene should not be initiated if the absolute platelet count is < 2.5×10^{10}/L.

Anaemia (haemoglobin < 95 g/L) has been observed in patients treated with ganciclovir. Cymevene should not be administered if the haemoglobin is < 80 g/L.

Bone Marrow Transplantation

Cymevene should not be administered to bone marrow transplant patients in the early post-transplant phase, but withheld until early signs of haemopoetic recovery are evident, usually at about three weeks post-transplantation.

Intravenous Administration

In clinical studies with Cymevene, the maximum dose studied has been 6 mg/kg given by IV infusion over a period of one hour. It is likely that larger doses, or more rapid infusions, could result in increased toxicity, and therefore, it is recommended that the dosage regimen be strictly adhered to.

Administration of Cymevene by IV infusion should be accompanied by adequate hydration, since ganciclovir is excreted by the kidneys and normal clearance depends upon adequate renal function. If renal function is impaired, dosage adjustments based on serum creatinine/creatinine clearance, are required (see **section** 4.2).

Cymevene solutions have a high pH (range 9 to 11) and may cause phlebitis and/or pain at the site of IV infusion. Care must be taken to infuse Cymevene solutions only into veins with adequate blood flow to afford rapid dilution and distribution.

Use in Patients with Renal Impairment

Cymevene should be used with caution in patients renal impairment. Both the plasma half-life of ganciclovir as well as peak plasma levels are increased in patients with elevated serum creatinine levels. In a very small number of patients who were undergoing dialysis, ganciclovir plasma levels were reduced by approximately 50% following haemodialysis.

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see section 4.2). Serum creatinine/creatinine clearance should be monitored at least once every two weeks.

Paediatric Use

A higher risk of hematological cytopenias in neonates and infants warrants careful monitoring of blood counts in these age groups. Monitoring of liver function abnormalities, renal function and gastrointestinal fluid loss is also recommended in paediatric patients. The use of ganciclovir in paediatric patients warrants caution due to the probability of long-term carcinogenicity and reproductive toxicity. Administration to children should be undertaken only after careful evaluation and only if, in the opinion of the physician, the potential benefits of treatment outweigh these considerable risks. Cymevene is not indicated for the treatment of congenital or neonatal CMV infection.

Effect on Laboratory Tests

Due to the frequency of neutropenia, leucopenia, anaemia or thrombocytopenia observed in patients receiving Cymevene, it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leucopenia, or in whom neutrophil counts are $< 1.0 \times 10^9$/L at the beginning of treatment. In patients with severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered. Because dosing with Cymevene should be modified in patients with renal impairment, patients should have serum creatinine or creatinine clearance values followed carefully.

Excipients

Cymevene contains 2 mmol (43 mg) sodium per 500mg dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Probenecid

Probenecid given with oral ganciclovir resulted in statistically decreased renal clearance of ganciclovir by 20% leading to statistically significant increased exposure (40%). These changes were consistent with a mechanism of interaction involving competition for renal tubular excretion. Therefore, patients taking probenecid and Cymevene should be closely monitored for ganciclovir toxicity.

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with IV ganciclovir. At IV doses of 5 and 10 mg/kg/day ganciclovir, an increase in AUC of

didanosine ranging from 38 to 67% was observed confirming a pharmacokinetic interaction during the concomitant administration of these drugs. Patients should be monitored closely for didanosine toxicity, including pancreatitis (see section 4.8).

Imipenem-cilastatin
Seizures have been reported in patients receiving 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 risks (see section 4.4).

Zidovudine
Both zidovudine and ganciclovir can cause neutropenia and anaemia and a pharmacodynamic interaction may occur during concomitant administration of these drugs. Some patients receiving these medicines concomitantly are at an increased risk of developing these conditions and may not tolerate concomitant therapy at full dosage. Regular haematological monitoring should be performed and dose adjustment may be required.

Potential Drug Interactions
Toxicity may be enhanced when ganciclovir 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 (e.g. trimethroprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these medicines should only be considered for concomitant use with ganciclovir if the potential benefits outweigh the potential risks.

4.6 Fertility, pregnancy and lactation

Pregnancy
Use in Pregnancy - Category D

In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity (see sections 4.4 and 5.3). The safety of Cymevene in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. The use of Cymevene should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the foetus.

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

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

Ganciclovir has been shown to be embryotoxic in rabbits and mice following IV administration, and teratogenic in rabbits (see section 5.3).

Breast-feeding

It is not known if Cymevene is excreted in human milk but animal data indicates that ganciclovir is excreted in the milk of lactating rats. Since many medicines are, and because of the potential for serious adverse reactions from ganciclovir in nursing infants, Cymevene should not be given to breastfeeding mothers. Alternatively, mothers should be instructed to discontinue nursing if they are receiving Cymevene. The minimum time interval before breastfeeding can safely be resumed after the last dose of Cymevene is unknown.

Contraception in males and females

Women of reproductive potential should be advised to use an effective method of contraception during and 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 Cymevene unless it is certain that the female partner is not at risk of pregnancy (see sections 4.4 and 5.3).

Fertility

In animal studies ganciclovir was found to impair fertility. In a clinical study renal transplant patients receiving Valcyte (which is a pro-drug of Cymevene) for CMV prophylaxis for up to 200 days were compared to an untreated control group. Spermatogenesis was inhibited during treatment with Valcyte. 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 Valcyte treated patients, all patients with normal sperm density (n=7) and 8/13 patients with low sperm density at baseline, recovered to normal counts 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.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Based on the adverse reaction profile, ganciclovir may have a minor influence on the ability to drive and use machines. Adverse reactions, for example convulsions, dizziness, and confusion may occur in patients taking Cymevene. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

4.8 Undesirable effects

Valganciclovir is a pro-drug of ganciclovir, and adverse reactions associated with valganciclovir can be expected to occur with ganciclovir. Therefore, adverse drug reactions reported with IV or oral ganciclovir (no longer available) or with valganciclovir are included in the table of adverse reactions (see Table 2).

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

The frequencies presented in the table of adverse reactions are derived from a pooled population of HIV-infected patients (n=1704) receiving maintenance therapy with ganciclovir (GAN1697, GAN1653, GAN2304, GAN1774, GAN2226, AVI034, GAN041) or valganciclovir (WV1537, WV15705). Exception is made for agranulocytosis, granulocytopenia and anaphylactic reaction; 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 HIV patients with CMV retinitis. However, there are some differences in the frequency of certain reactions. Intravenous ganciclovir is associated with a lower risk of diarrhea compared to oral valganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC <500µL) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction is reported more frequently in organ transplant recipients.

Paediatric population

Based on the cumulative experience, including valganciclovir pediatric studies, the overall safety profile of ganciclovir in the pediatric population appears similar to the safety profile established in adults. There is a higher risk of hematological cytopenias in neonates and infants (see section 4.4)

Table 2 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:		
Candida 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
Anemia	19.89%	
Thrombocytopenia	7.34%	Common
Leucopenia	3.93%	
Pancytopenia	1.06%	
Bone marrow failure	0.29%	Uncommon

ADR -(MedDRA) System Organ Class	Percentage	Frequency Category
Aplastic anemia	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%	
Dizziness	5.52%	
Paraesthesia	3.58%	
Hypoaesthesia	2.58%	
Seizures	2.29%	

ADR -(MedDRA) System Organ Class	Percentage	Frequency Category
Dysgeusia (taste disturbance)	1.35%	
Tremor	0.88%	Uncommon
Eye disorders:		
Retinal detachment**	8.04%	Common
Visual impairment	7.57%	
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*:*		
Arrhythmia	0.47%	Uncommon
Vascular disorders*:*		
Hypotension	2.05%	Common
Respiratory, thoracic and mediastinal disorders:		
Cough	18.31%	Very common
Dyspnoea	11.80%	
Gastrointestinal disorders:		
Diarrhea	34.27%	Very common
Nausea	26.53%	
Vomiting	14.67%	
Abdominal pain	10.97%	
Constipation	8.39%	Common

ADR -(MedDRA) System Organ Class	Percentage	Frequency Category
Dyspepsia	4.81%	
Flatulence	4.69%	
Abdominal pain upper	4.58%	
Mouth ulceration	3.17%	
Dysphagia	2.93%	
Abdominal distention	2.29%	
Pancreatitis	1.64%	
Hepato-biliary disorders:		
Blood alkaline phosphatase increased	3.58%	Common
Hepatic function abnormal	3.23%	
Aspartate aminotransferase increased	1.88%	
Alanine aminotransferase increased	1.23%	
Skin and subcutaneous tissues disorders:		
Dermatitis	11.80%	Very common
Night sweats	7.92%	Common
Pruritus	4.58%	
Rash	2.52%	
Alopecia	1.29%	
Dry skin	0.94%	Uncommon
Urticaria	0.70%	
Musculo-skeletal and connective tissue disorders:		
Back pain	4.46%	Common
Myalgia	3.52%	
Arthralgia	3.35%	
Muscle spasms	2.99%	

ADR -(MedDRA) System Organ Class	Percentage	Frequency Category
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
Hematuria	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%	
Injection site reaction	6.98%	Common
Pain	5.81%	
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 studies in AIDS patients treated with Cymevene 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.

Laboratory Abnormalities

Laboratory abnormalities in HIV infected patients

Laboratory abnormalities reported from three clinical trials in HIV infected patients receiving intravenous ganciclovir as maintenance treatment for CMV retinitis are listed below in Table 3. One hundred seventy-nine patients were eligible for the laboratory abnormality analysis.

Table 3 Laboratory abnormalities

Laboratory abnormalities	**N=179**
Neutropenia (ANC /mm^3)	
<500	25.1 %
500 – <750	14.3 %
750 – <1000	26.3 %
Anemia (hemoglobin g/dL)	
<6.5	4.6 %
6.5 – <8.0	16.0 %
8.0 – <9.5	25.7 %
Thrombocytopenia (platelets/mm^3)	
<25000	2.9 %
25000 – <50000	5.1 %
50000 – <100000	22.9 %
Serum creatinine (mg/dL)	
>2.5	1.7 %
>1.5 – 2.5	13.9 %

Post-marketing Experience

Safety reports from the post-marketing setting are consistent with safety data from clinical trials with ganciclovir and valganciclovir (see 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

Toxic manifestations seen in animals given very high single IV doses of Cymevene (500 mg/kg) included emesis, hypersalivation, anorexia, bloody diarrhoea, inactivity, cytopenia, elevated liver function test results, elevated serum urea, testicular atrophy, and death.

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

- Haematological toxicity: myelosuppression including pancytopenia, bone marrow failure, leucopenia, neutropenia, granulocytopenia.

- Hepatotoxicity: hepatitis, liver function disorder.

- Renal toxicity: worsening of haematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine.

- Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting.

- Neurotoxicity: generalised tremor, convulsion.

In patients who have received an overdose of Cymevene, dialysis and hydration may be of benefit in reducing drug plasma levels. The use of haematopoietic growth factors should be considered.

Treatment of overdose should consist of general supportive measures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766) (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anitviral for systemic use, direct acting antivirals, nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: J05AB06.

Mechanism of Action

Ganciclovir is a synthetic nucleoside analogue of 2-deoxyguanosine that inhibits replication of herpes viruses both *in vitro* and *in vivo*. Sensitive human viruses include cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), herpes virus type -6, -7 and -8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella zoster virus (VZV) and hepatitis B virus. Ganciclovir was less potent against HHV-7 and HHV-8 than HHV-6. *In vitro,* synergy has been demonstrated between ganciclovir and foscarnet against CMV and herpes simplex virus Types 1 and 2 and between ganciclovir and beta-interferon against herpes simplex virus Type 2. Ganciclovir has been shown to be active against HCMV in human clinical studies.

A virus-encoded protein kinase homologue, encoded by the CMV gene UL97, has been demonstrated to control phosphorylation of ganciclovir in human CMV-infected cells. The product of the UL97 gene, along with cellular kinases which are induced upon CMV infection, appear to be responsible for phosphorylation of ganciclovir to its active triphosphate. It has been shown that there is as much as a 100-fold greater concentration of ganciclovir-triphosphate in CMV-infected cells than in uninfected cells, indicating a preferential phosphorylation of ganciclovir in virus-infected cells. *In vitro*, ganciclovir-triphosphate is catabolised slowly, with 60% to 70% of the original level remaining in the infected cells 18 hours after removal of ganciclovir from the extracellular medium. The antiviral activity of ganciclovir-triphosphate is believed to be the result of inhibition of viral DNA synthesis by two known modes: (1) competitive inhibition of viral DNA polymerases (2) direct incorporation into viral DNA, resulting in eventual termination of viral DNA elongation. The cellular DNA polymerase alpha is also inhibited, but at a higher concentration than that required for inhibition of viral DNA polymerase. The median concentration of ganciclovir that inhibits CMV replication (IC_{50}) *in vitro* (laboratory strains or clinical isolates) has ranged from 0.08 to 14 µM (0.02 to 3.5 mcg/mL). Ganciclovir inhibits mammalian cell proliferation (TD_{50}) *in vitro* at higher concentrations ranging from 40 to >1000 µM (10 to >250 mcg/mL). Ganciclovir has been shown to be more toxic in proliferating cells than in confluent, contact-inhibited cells (toxicity of 27 µM GCV in confluent MRC-5 cells = 0%, where as in proliferating MRC-5 cells = 26 - 44%). Bone marrow-derived colony-forming cells are more sensitive (TD_{50} 2.7 - 12 µM; 0.68 - 3 mcg/mL). The relationship of *in vitro* sensitivity of CMV to ganciclovir and clinical response has not been established.

Clinical efficacy and safety

Viral Resistance

Viruses resistant to ganciclovir can arise after chronic dosing with ganciclovir or 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).

The possibility of viral resistance should be considered in patients who repeatedly achieve a poor clinical response or experience continuous viral excretion during treatment.

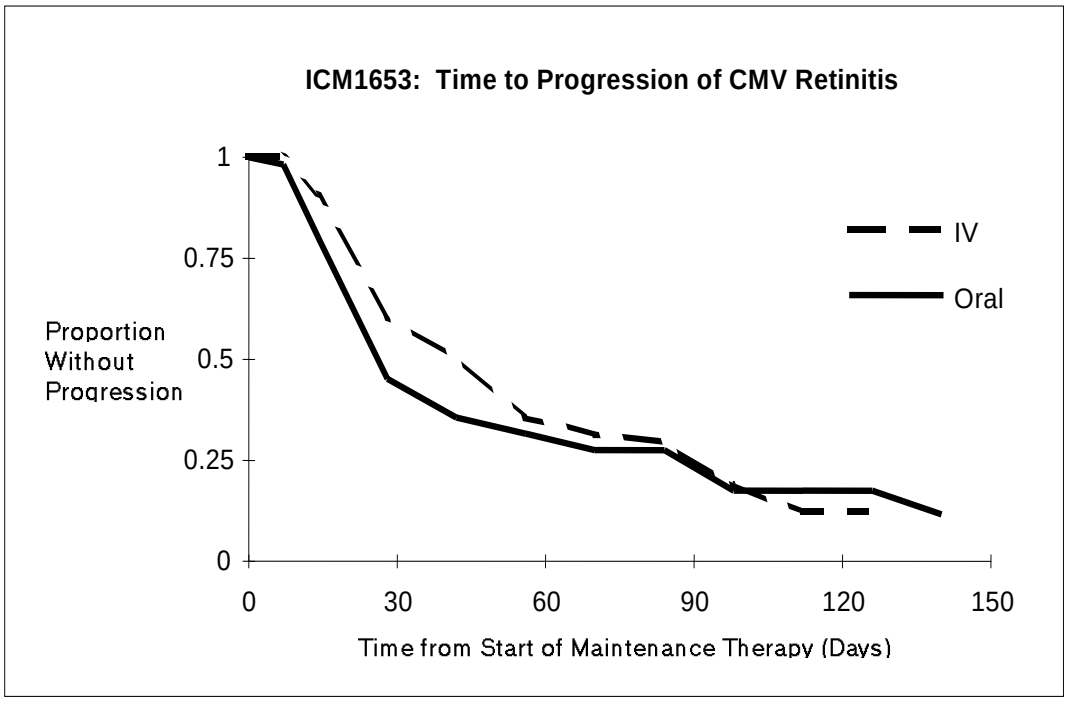
CMV Retinitis

The diagnosis of CMV retinitis should be made by indirect ophthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis included candidiasis, toxoplasmosis, histoplasmosis, retinal scars, cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason it is essential that the diagnosis of CMV be established by an ophthalmologist familiar with the presentation of these conditions. The diagnosis of CMV retinitis may be supported by culture of CMV in the urine, blood, throat, or other sites, but a negative culture does not rule out CMV retinitis.

Patients enrolled in the three controlled Cymevene IV/oral maintenance studies were 22 to 62 years of age with median baseline CD_4 counts of 7.0 to 10.0 (range 0 to 320); the majority of patients were male (93 to 99%) and Caucasian (81 to 88%). Mean observation times for the three studies were from 42.5 to 47.0 days. The results of one of these studies is presented below (see ICM 1653).

ICM 1653: In this randomised, open label, parallel group trial, conducted between March 1991 and November 1992, patients with AIDS and newly diagnosed CMV retinitis received a 3-week induction course of Cymevene solution, 5 mg/kg bd for 14 days followed by 5 mg/kg once daily for one additional week. Following the 21-day IV induction course, patients with stable CMV retinitis were randomised to receive 20 weeks of maintenance induction treatment with either Cymevene solution, 5 mg/kg once daily or Cymevene capsules 500 mg six times daily. The study showed that mean (95% CI) times to progression of CMV retinitis, as assessed by masked reading of fundus photographs was 57 days (44, 70) for patients on oral therapy compared to 62 days (50, 73) for patients on IV therapy. The difference (95% CI) in the mean time to progression between the oral and intravenous therapies (oral-IV) was -5 days (-22, 12). See Figure 1 for comparison of the proportion of patients remaining free of progression over time.

Figure 1



Prophylaxis of CMV Disease in Heart and Bone Marrow Transplantation

ICM 1496: In a randomised, double blind, placebo-controlled study of the prophylaxis of tissue-invasive CMV in heart transplant patients who had asymptomatic infection or were receiving CMV seropositive organs, 149 patients aged 13 to 68 were enrolled (placebo $n = 73$ and ganciclovir $n = 76$) with the primary efficacy measure being CMV illness (defined as biopsy-proven CMV disease, CMV retinitis and/or CMV syndrome). Patients received placebo or ganciclovir 5 mg/kg every 12 hours for 14 days followed by 6 mg/kg once daily 5 days per week for 2 weeks (until day 25) whereupon CMV prophylaxis was discontinued and patients monitored until day 120 post-transplant. Doses were modified for renal function.

Thirty-one of 73 placebo vs. 12 of 76 ganciclovir patients developed CMV illness (42.5 vs. 15.8%, p = 0.0004). Additionally, the time from transplant to CMV illness was significantly longer in the ganciclovir group (p = 0.0001). A sustained antiviral effect was demonstrated by a significant difference in the incidence of positive CMV cultures at day 15 post-transplant (16.4 vs. 2.7%, p = 0.005) and continuing through days 29 and 60 (43.1 vs. 4.5%, p < 0.001; 56.4 vs. 19%, p < 0.001). The incidence of adverse events was similar in the two arms.

Table 4: CMV illness within 120 days post-transplant by Donor/Recipient (D/R) CMV serological status

Donor (D) /Recipient (R) CMV status	Ganciclovir % (*n*)	Placebo % (*n*)
CMV disease		
D+/R-	35.0 (7)	29.4 (5)
D+/R+	8.9 (5)	46.4 (26)
Total	15.8 (12)	42.5 (31)

ICM 1689: In a randomised, double blind, placebo-controlled study of the prophylaxis of tissue-invasive CMV in bone marrow transplant patients with asymptomatic infection, 72 patients aged 3 to 56 were enrolled (placebo n = 35, ganciclovir n = 37), with the primary efficacy endpoint being progression to life-threatening, biopsy-confirmed, tissue-invasive disease. Patients received placebo or ganciclovir 5 mg/kg twice daily for 7 days, followed by 5 mg/kg once daily until day 100 post-transplant (adjusted for renal function). The study was terminated after a planned interim analysis of 58 patients demonstrated a statistically significant decrease in CMV disease in the ganciclovir group. At day 100, 15 of 35 placebo patients vs. 1 of 37 ganciclovir patients had developed CMV disease (42.9 vs. 2.7%, p = 0.00005). Additionally, there was a significant reduction in deaths from any cause in the ganciclovir arm (37.1 vs. 10.8%, p = 0.0096); none of the deaths in patients treated with ganciclovir occurred during the period in which the medicine was given. The time from transplant to CMV-related deaths was also significantly longer in the ganciclovir group (p = 0.0048). The significant difference in the incidence of CMV disease was maintained at 6 months after transplant, after prophylaxis had been ceased (42.9 vs. 16.2%, p = 0.013). The overall incidence of adverse events was similar, however more patients in the ganciclovir arm experienced absolute neutrophil counts below 1 x 10^9/L, often requiring dose modification.

<u>Oral Cymevene for Prophylaxis of CMV Disease in Liver Transplantation</u>

In a multicentre, double-blind, randomised, placebo-controlled study of the efficacy and safety of ganciclovir capsules 3 g/day in the prevention of CMV disease in liver transplantation, prophylaxis was initiated within 10 days of transplantation in 304 patients and continued through week 14 after transplantation. The primary efficacy parameter was the prevention of CMV disease. The patients were also assessed for the incidence of CMV infection, other herpes virus infections, opportunistic infections, graft rejection and/or loss and patient survival. CMV disease was defined as one of the following: CMV syndrome (spiking fever with no response to antibiotics, malaise and/or fall in neutrophil counts over three consecutive daily measurements and with other causes excluded); CMV hepatitis, gastroenteritis, oesophagitis or colitis (confirmed by biopsy and other criteria); CMV pneumonia (confirmed with lavage and other criteria); CMV retinitis (by dilated fundus

examination); or CMV encephalitis (by examination of cerebrospinal fluid). CMV infection was defined as one or more of the following: (1) CMV antigen detected in leukocytes; (2) a positive CMV culture obtained from any site in the body; and/or (3) seroconversion demonstrated by the appearance of IgG or IgM antibodies in a patient previously known to be seronegative.

In all, 19.5% of the placebo group vs. 4.8% of the ganciclovir group developed CMV disease ($p < 0.001$) and 9.8% vs. 0.7% developed tissue-invasive CMV disease by the 6-month timepoint. These reductions were observed irrespective of the recipient's gender, age, immunosuppression as well as whether the patient received antilymphocyte antibodies for induction of immunosuppression and/or the treatment of rejection. The time from transplant to first CMV infection was significantly increased in the ganciclovir group; 48.8% of the placebo vs. 11.4% of the ganciclovir group had developed infection by day 98 post-transplant. Severe adverse events were reported equally in the two groups. 97% of patients in the placebo arm and 94% in the ganciclovir arm maintained absolute neutrophil counts ≥ 1 x 10^9/L.

Table 5: Summary of Kaplan Meier estimates and absolute incidences of study endpoints

Endpoint	**Ganciclovir** **1000 mg q8h p.o.** ***n* = 150** **%**	**Placebo** ***n* = 154** **%**	**p-value**
CMV Disease	**4.8**	**19.5**	**< 0.001**
Syndrome	4.1	12.4	0.008
Hepatitis	0.7	7.2	0.004
Gastroenteritis, oesophagitis or colitis	0.0	2.0	NS
Lung involvement (pneumonia)	0.0	2.6	0.046
CMV tissue invasive disease	**0.7**	**9.8**	**< 0.001**
CMV infection	**24.5**	**51.5**	**< 0.001**
Herpes simplex infections	**3.5**	**23.5**	**< 0.001**
Other opportunistic infections*	**3.3**	**5.8**	**NS**
Death (all causes)	**3.4**	**5.8**	**NS**

* absolute incidence – all other figures are Kaplan-Meier six month estimates

Table 6: CMV disease according to Donor/Recipient (D/R) CMV serological status

Donor (D) /Recipient (R) CMV status (6-month Kaplan-Meier Estimates)	**Ganciclovir** **% (no. of patients with an event/no. at risk)**		**Placebo** **% (no. of patients with an event/no. at risk)**		**p-value**
CMV disease					
D+/R-	14.8	(3/21)	44	(11/25)	0.019
D+/R+	2.7	(2/76)	19.5	(15/77)	< 0.001
D-/R+	3.9	(2/52)	7.9	(4/51)	NS
CMV tissue invasive disease					
D+/R-	0	(0/21)	24.7	(6/25)	0.016
D+/R+	0	(0/76)	9.1	(7/77)	0.007
D-/R+	1.9	(1/52)	4.0	(2/51)	NS

5.2 Pharmacokinetic properties

The pharmacokinetics of IV Cymevene are based on limited studies in immunodeficient adult patients with serious cytomegalovirus infection who were also receiving other medicines.

The pharmacokinetics of IV ganciclovir is linear over the range of 1.6 - 5.0 mg/kg. The systemic exposure ($AUC_{0-\infty}$) following a single dose of IV ganciclovir (5 mg/kg, 1 h infusion) in adult liver transplant patients was on average 50.6 µg.h/mL (CV% 40).In this patient population peak plasma concentration (C_{max}) was on average 12.2 µg/mL (CV% 24).

Absorption

Not applicable.

Distribution

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 to 0.87 L/kg. Ganciclovir penetrates the cerebrospinal fluid, and diffuses across the placenta. Binding to plasma proteins was 1% to 2% over ganciclovir concentrations of 0.5 and 51 mcg/mL. Therefore, medicine interactions involving binding site displacement are not expected.

Biotransformation

Ganciclovir is not metabolised to a significant extent.

Elimination

Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. In patients with normal renal function, greater than 90%of IV administered ganciclovir was recovered unmetabolised in the urine within 24

hours. Administration of a dose of 5 mg/kg IV ganciclovir as a 1 h infusion in 22 patients with normal renal function demonstrated that, the plasma half life ($t_{1/2}$) of ganciclovir averaged 2.9 ± 1.3 h and systemic clearance (Cliv) averaged 3.64 ± 1.86 mL/min/kg. In this patient population, greater than 90% of ganciclovir is recovered unmetabolised, in urine. Therefore, one would expect the renal status of patients to influence the kinetics of ganciclovir.

Pharmacokinetics in Special Populations

Paediatric population

The pharmacokinetics of IV ganciclovir were investigated across two studies in paediatric liver (N=18) and renal (N=25) transplant patients aged 3 months to 16 years and evaluated using a population pharmacokinetic model. The mean total clearance was 5.4 L/hr (90 mL/min) for a child with a creatinine clearance of 70.4 mL/min. The steady state volume of distribution and peripheral volume of distribution were on average 20 and 15 L, respectively. CrCL was identified as statistically significant covariate for ganciclovir clearance and height of the patient as statistically significant covariate for ganciclovir clearance, steady state volume and peripheral volume of distribution. Neither age, gender, nor types of organ transplant were significant covariates in these populations. Table 7 gives the estimated pharmacokinetic parameters by age group.

Table 7 Pharmacokinetic parameters in renal and liver solid organ transplant patients expressed as medians (minimum-maximum)

	< 6 years	**6 to <12 years**	**≥12 to <16 years**
	n=17	n=9	n=17
CL(L/h)	4.23 (2.11-7.92)	4.03 (1.88-7.8)	7.53 (2.89-16.8)
Vcent (L)	1.83 (0.45-5.05)	6.48 (3.34-9.95)	12.1 (3.6-18.4)
Vperiph (L)	5.81 (2.9-11.5)	16.4 (11.3-20.1)	27 (10.6-39.3)
Vss (L)	8.06 (3.35-16.6)	22.1 (14.6-30.1)	37.9 (16.5-57.2)

Pharmacokinetics of IV ganciclovir given according to the dosing regimen approved for adults (5 mg/kg IV infusion administered over 1 hour) were studied in a small group of infants and children with normal renal function, aged 9 months to 12 years(n=10, average 3.1 years). Exposure as measured by mean AUC_{∞} on Days 1 (n=10) and AUC_{0-12} on Day 14 (n=7) were 19.4 ± 7.1 and 24.1 ± 14.6 µg.h/mL with corresponding C_{max} values of 7.59 ± 3.21 and 8.31 ± 4.9 µg/mL (Days 1 and 14) respectively. A trend towards lower exposures in younger paediatric patients was observed with body weight based dosing used in this study. In paediatric patients up to 5 years the average values for $AUC_{0-\infty}$ on Day 1 (n=7) and AUC_{0-12h} on Day 14 (n=4) were 17.7±5.5 and 17.1±7.5 µg.h/mL.

The ganciclovir IV dosing regimen based on BSA and renal function (3x BSA x CrCLS) is derived from the paediatric dosing algorithm with valganciclovir, the oral pro-drug of ganciclovir. Pharmacokinetic simulations have confirmed that both dosing regimens provide similar ganciclovir exposures in the paediatric population from birth to 16 years.

Table 8 Simulated* ganciclovir AUC0-24h (µg. h/mL) for paediatric patients treated with ganciclovir dose (mg) of 3x BSA x CrCLS given as 1 hour infusion

	< 4 months	≥ 4 months to ≤ 2 years	> 2 to < 6 years	≥ 6 to < 12 years	≥ 12 to ≤ 16 years	All Patients
No. patients simulated	781	384	86	96	126	1473
Median	55.6	56.9	54.4	51.3	51.4	55.4
Mean	57.1	58.0	55.1	52.6	51.8	56.4
Min	24.9	24.3	16.5	23.9	22.6	16.5
Max	124.1	133.0	105.7	115.2	94.1	133.0
Patients AUC < 40 µg • h/mL	89 (11%)	38 (10%)	13 (15%)	23 (24%)	28 (22%)	191 (13%)
Patients AUC 40–60 µg • h/mL	398 (51%)	195 (51%)	44 (51%)	41 (43%)	63 (50%)	741 (50%)
Patients AUC > 60 µg • h/mL	294 (38%)	151 (39%)	29 (34%)	32 (33%)	35 (28%)	541 (37%)

AUC=area under the plasma concentration-time curve; BSA=body surface area;

CrCL=creatinine clearance; max=maximum; min=minimum.

*Simulations were performed using a validated pediatric population PK model and demographic data from pediatric patients receiving valganciclovir or ganciclovir treatment in clinical studies (n=1473 data records).

The pharmacokinetics were also studied in 3 children with impaired renal function administered IV ganciclovir (1.25 mg/kg). The study showed these patients to have a Cmax of 3.66 mcg/mL, AUC 34.75 mcg.h/mL and $t_{1/2}$ of 7.87 h.

Elderly

No ganciclovir pharmacokinetic studies have been conducted in adults older than 65 years of age. However, because ganciclovir is mainly renally excreted and since renal clearance decreases with age a decrease in ganciclovir total body clearance and prolongation of ganciclovir elimination half-life can be anticipated in the elderly (see section 4.2).

Patients with renal impairment

The total body clearance of ganciclovir is linearly correlated with creatinine clearance. In patients with mild, moderate, and severe renal impairment, mean systemic clearances of 2.1, 1.0 and 0.3 mL/min/kg were observed. Patients with renal impairment show an increased elimination half-life. In patients with severe renal impairment elimination half-life was increased by 10-fold (see section 4.2).

As the major excretion pathway for ganciclovir is renal (glomerular filtration and active tubular secretion), the dosage of the medicine must be reduced according to serum creatinine/ creatinine clearance (see section 4.2).

Patients with renal impairment undergoing haemodialysis
Plasma concentrations of ganciclovir are reduced by about 50% during a 4 hour hemodialysis session (see section 4.9).During intermittent haemodialysis, estimates for the clearance of ganciclovir ranged from 42 to 92 mL/min, resulting in intra-dialytic half-lives of 3.3 to 4.5 hours. Estimates of ganciclovir clearance for continuous dialysis were lower (4.0 to 29.6 mL/min) but resulted in greater removal of ganciclovir over a dose interval. For intermittent haemodialysis, the fraction of ganciclovir removed in a single dialysis session varied from 50% to 63%.

Hepatic impairment
No pharmacokinetic study has been conducted and no population PK data were collected in patients with hepatic impairment undergoing ganciclovir therapy. Hepatic impairment is not anticipated to affect the pharmacokinetics of ganciclovir since ganciclovir is excreted renally.

Oral ganciclovir
The pharmacokinetics of ganciclovir following oral administration of Cymevene capsules have been evaluated in 500 immunocompromised adults. When administered orally ganciclovir exhibits linear kinetics up to a total daily dose of 4 g/day. When single doses of Cymevene capsules ranging from 500 mg to 2000 mg were administered to HIV-positive patients under fasting conditions, mean absolute bioavailability was 5.6% and 2.6% with the 500 mg dose and 2000 mg dose respectively. Absolute bioavailability of a single 1000 mg dose administered under fasted conditions in transplant patients was 7.2%. Following oral administration of a single 1000 mg dose of ^{14}C-radiolabelled ganciclovir, 86% of administered ganciclovir was recovered in the faeces as unchanged drug, and 5% was recovered in the urine. No metabolite accounted for more than 1% to 2% of the radioactivity recovered in urine or faeces indicating that orally administered ganciclovir is excreted essentially unchanged.

A meal immediately prior to dosing with Cymevene capsules, 1000 mg every 8 hours, increased the mean steady state area under the serum concentration versus time curve (AUC) of ganciclovir by approximately 20%. Multiple dose pharmacokinetic studies were conducted using Cymevene capsules. At a dose of 1000 mg administered three times daily with food the mean steady state peak concentration of ganciclovir was 0.98 mcg/mL and the mean steady state morning trough concentration was 0.20 mcg/mL. The steady state AUC_{0-24} for this regimen was 13.0 mcg·hr/mL compared with 26.0 mcg·hr/mL for a single ganciclovir IV solution dose of 5 mg/kg (the standard maintenance regimen for treatment of CMV retinitis). The mean plasma $t_{1/2}$ was 5.03 hours. The absolute bioavailability of multiple dose regimens of ganciclovir administered orally in doses of 3000 mg to 6000 mg daily in fed patients was approximately 6%.

5.3 Preclinical safety data

In animal studies ganciclovir was found to be mutagenic, teratogenic, and carcinogenic (see section 4.4). Cymevene should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see section 4.2 and 4.4) It is also considered likely that Cymevene causes temporary or permanent inhibition of spermatogenesis (see **section** 4.4 and 4.8).

Carcinogenicity
In an 18-month study, ganciclovir was carcinogenic in the mouse after oral doses of 20 mg/kg/day and 1000 mg/kg/day. All ganciclovir-induced tumours were of epithelial or vascular origin, except for histiocytic sarcoma of the liver. Epithelial tumours involved a wide variety of tissues. No carcinogenic effects occurred at 1 mg/kg/day. Based on data on plasma drug concentrations, exposure of humans to ganciclovir would be greater than exposure of mice in the above study at 20 mg/kg. Thus, Cymevene should be considered a potential carcinogen in humans.

Genotoxicity
Ganciclovir caused point mutations and chromosomal damage in mammalian cells *in vitro* and *in vivo*. Ganciclovir was clastogenic in the mouse micronucleus assay. Ganciclovir was not mutagenic in the Ames Salmonella assay.

Impairment of fertility
Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility in males. These effects were reversible at lower doses but irreversible at higher doses. Animal data also indicate that suppression of fertility in females may occur.

Female mice exhibited decreased fertility, decreased mating behaviour and increased embryolethality after daily IV doses of 90 mg/kg. Daily IV doses of up to 20 mg/kg did not impair female fertility but doses as low as 5 mg/kg caused reduction in the birth weights of pups; higher doses were associated with hypoplasia of testes and seminal vesicles in male pups.

In male mice, fertility was decreased after daily IV doses of 2 mg/kg. These effects were reversible after daily IV doses of 2 mg/kg, but were irreversible or incompletely reversible after daily IV doses of 10 mg/kg. Ganciclovir has also caused hypospermatogenesis in dogs after daily IV doses of $\geq$ 0.4 mg/kg.

Reproductive toxicity
Ganciclovir has been shown to be embryotoxic in rabbits and mice following IV administration, and teratogenic in rabbits. Foetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day, respectively (doses approximately equivalent to the recommended human dose – calculated on the basis of body surface area).

Daily IV doses of ganciclovir of 90 mg/kg administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in month-old offspring, as well as pathologic changes in the nonglandular region of the stomach. The drug exposure in mice as estimated by the AUC was approximately 1.6x the human AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with medicinal products except those mentioned in section 6.6.

Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), since these are incompatible with Cymevene sterile powder and may cause precipitation.

6.3 Shelf life

3 years

Cymevene vials should be administered within 24 hours of reconstitution to reduce microbiological hazard. If required, it may be diluted with the infusion solutions named above and held at 2 – 8 °C for 24 hours after reconstitution (do not freeze).

Cymevene vials are for one dose in one patient only. Discard any remaining contents of the vial.

6.4 Special precautions for storage

Cymevene freeze-dried powder for IV infusion should be stored below 30 °C.

For storage conditions after reconstitution and after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Cymevene for IV infusion is available in 10 mL clear glass vials containing sterile freeze-dried ganciclovir sodium 543 mg equivalent to ganciclovir 500 mg. Each carton contains 5 vials.

6.6 Special precautions for disposal and other handling

Caution should be exercised in the handling and preparation of Cymevene products in a manner similar to that for cytotoxic medicines since Cymevene is considered a potential teratogen and carcinogen in humans.

Avoid ingestion, inhalation, or direct contact with the skin and mucous membranes with either Cymevene solution or powder. It is advised that latex gloves and safety glasses be used to handle the preparation of Cymevene solution.

If ganciclovir contacts the skin or mucous membranes, wash thoroughly with soap and water for at least 15 minutes. For eye exposure rinse thoroughly with plain water. Cymevene IV solutions are alkaline (pH approximately 11).

Method of Preparation of Intravenous Solution

Each 10 mL clear glass vial contains the equivalent of 500 mg of the ganciclovir free base. The contents of the vial should be prepared for administration as follows (see section 4.1):

1. The freeze-dried powder should be reconstituted by injecting 10 mL of sterile water for injection into the vial.

Do not use bacteriostatic water for injection containing para-hydroxybenzoates, since these are incompatible with Cymevene sterile powder and may cause precipitation.

2. The vial should be shaken to dissolve the medicine.

3. Reconstituted solution should be inspected for particulate matter prior to proceeding with admixture preparation.

Administration of Infusion Solution
Based on patient weight the appropriate calculated dose volume should be removed from the vial (Cymevene concentration 50 mg/mL) and added to an acceptable infusion fluid (typically 100 mL) for delivery over the course of one hour. Infusion concentrations greater than 10 mg/mL are not recommended. The following infusion fluids are compatible with Cymevene: normal saline, glucose 5% in water, Ringer's Injection, Ringer-Lactate Solution for Injection.

Cymevene should not be mixed with other IV products.

For storage conditions of diluted solution for infusion, see section 6.3.

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. MEDICINE SCHEDULE

Prescription only medicine

8. SPONSOR

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060

Telephone: 09 377 3336

9. DATE OF FIRST APPROVAL

21 June 1990

10. DATE OF REVISION OF THE TEXT

5 December 2018

Summary of Changes Table

Section Changed	Summary of new information
8	New sponsor details