AUSTRALIAN PRODUCT INFORMATION
Cymevene® (ganciclovir)

1. NAME OF THE MEDICINE
Ganciclovir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Cymevene vial contains 500 mg of ganciclovir (as ganciclovir sodium 543 mg equivalent to ganciclovir 500 mg and sodium 43 mg (2 mEq). ganciclovir sodium).

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

There are no excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM
Sterile lyophilised powder for intravenous infusion

Ganciclovir, when formulated as monosodium salt in the intravenous (IV) dosage form, is a white to off-white lyophilised powder. The lyophilised powder has an aqueous solubility of greater than 50 mg/mL at 25 °C. At physiological pH, ganciclovir sodium exists as the un-ionized form.

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
Dose

Reconstituted Cymevene sterile powder is for IV administration only.

Intravenous Administration

Cymevene must be reconstituted and diluted under the supervision of a healthcare professional and administered as an intravenous infusion (see section 6.6 Special precautions for disposal and other handling).

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.

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 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.

5 mg/kg given as an IV infusion over one hour, once daily on 7 days per week. or 6 mg/kg given once daily on 5 days per week.

The duration of maintenance therapy 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 Prevention of CMV Disease in Transplant Recipients
Dosage 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 table below.

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

Table 1: Cymevene dosing for patients with renal impairment receiving mg/kg dosing

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
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

As dosage modifications are recommended in patients with renal impairment, serum creatinine or estimated creatinine clearance levels should be monitored carefully.

To calculate an estimated creatinine clearance:

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

$$\text{For females} = 0.85 \times \text{male value}$$

Hepatic Impairment

The safety and efficacy of Cymevene has not been studied in patients with hepatic impairment (see section 4.8 Adverse Effects (Undesirable Effects)).

Reduction of Dosage

Severe neutropenia (absolute neutrophil count < 0.5×10^9/L) or thrombocytopenia (platelets < 2.5×10^{10}/L) requires a dose interruption until some evidence of marrow recovery is observed (absolute neutrophil count > 0.75×10^9/L, platelets > 5×10^{10}/L).

Dose reductions should also be considered for anaemia and leukopenia.

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 (see section 5.3 Preclinical Safety Data).

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 and when wiping the outer surface of the bottle/cap and the table after reconstitution.

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 Administration

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 sections 4.2 Dose and Method of Administration and 6.6 Special Precautions for Disposal and Other Handling):

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.

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.

Compounding centres
1. which are licensed by the Australian Therapeutic Goods Administration to reconstitute and/or further dilute cytotoxic medicines, and
2. have validated aseptic procedures and regular monitoring of aseptic technique

may apply a shelf-life of 15 days at 2 – 8 °C (refrigerate, do not freeze) to Cymevene infusions reconstituted with water and further diluted with 0.9% sodium chloride or glucose (dextrose) 5%. These further diluted solutions have been shown to be chemically stable for this period. The extended shelf-life does not apply to reconstituted injections diluted with Ringer's Injection and Ringer-Lactate Solution for Injection.

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 10^9/L (500 cells/µL) or platelet count below 2.5 x 10^{10}/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 section 4.1 Therapeutic Indications.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The main clinical toxicities of ganciclovir include leucopenia, anaemia and thrombocytopenia.

In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic, 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 (see section 4.2 Dosage and method of administration and 5.3 Preclinical safety data). 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 section 4.6 Fertility, pregnancy and lactation and 4.8 Adverse effects (Undesirable effects)).

Cymevene is only indicated in those patients as outlined under section 4.1 Therapeutic Indications, 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 acyclovir 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).

Haematologic

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anaemia have been observed in patients treated with Cymevene. It is recommended that complete blood counts including platelet counts be monitored in all patients during therapy, particularly in patients with renal impairment (see sections 4.4 Special Warnings and Precautions for Use, section 4.8 Adverse Effects (Undesirable Effects) and 4.2 Dose and Method of Administration).

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.

Cymevene should not be administered to patients if the absolute neutrophil count falls below 0.5×10^9/L (500 cells/µL) or platelet count below 2.5×10^{10}/L (25,000/µL) or the haemoglobin is less than 80 g/L (8 g/dL) (see section 4.3 Contraindications).

Neutropenia. Patients receiving ganciclovir have manifested neutropenia (neutrophil count $< 1 \times 10^9$/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. Thrombocytopenia (platelet count $< 5.0 \times 10^{10}$/L) has been observed in patients treated with ganciclovir. Data from studies of IV Cymevene indicates that patients with initial platelet counts $< 1.0 \times 10^{11}$/L appear to be at increased risk of this toxicity. Cymevene should not be initiated if the absolute platelet count is $< 2.5 \times 10^{10}$/L.

Anaemia. 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 Dose and Method of Administration).

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.

Renal Impairment

Cymevene should be used with caution in patients with 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 Dose and method of administration- Renal impairment). Serum creatinine/creatinine clearance should be monitored at least once every two weeks.

Paediatric Use

Safety and efficacy of Cymevene in paediatrics has not been established. There has been very limited clinical experience in treating life- or sight-threatening cytomegalovirus disease with Cymevene in patients under the age of 12 years.

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

The use of ganciclovir in paediatric patients warrants extreme 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.

Use in the 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 4.4 Special Warnings and Precautions for Use and 4.2 Dose and Method of Administration, Special dosage instructions, Renal Impairment**)**.

Effects 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 and particularly in patients with renal impairment. In patients with severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose

interruption is recommended. Because dosing with Cymevene should be modified in patients with renal impairment, patients should have serum creatinine or creatinine clearance values followed carefully.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Imipenem-cilastatin

Generalised 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 benefit outweighs the risk (see section 4.4 Special Warnings and Precautions for Use).

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.

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. Consequently, patients should be monitored closely for didanosine toxicity, including pancreatitis (see section 4.8 Adverse effects (Undesirable effects)). If didanosine is given two hours prior to ganciclovir a 23% decrease in the AUC of ganciclovir occurs. There is no effect on the AUC of ganciclovir if the two medicines are given at the same time.

Probenecid

At an oral dose of 1 g of Cymevene every 8 hours (n = 11), ganciclovir AUC_{0-8} increased 40% (95% CI: 6 - 85%) in the presence of probenecid, 500 mg every 6 hours. The increase in AUC_{0-8} was accompanied by a decrease in renal clearance of ganciclovir by 20%. 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. Consideration should also be given to other such medicines which inhibit renal tubular secretion, as these medicines may reduce renal clearance of Cymevene and thereby increase the plasma half-life of Cymevene.

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. cyclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vinblastine, vincristine, hydroxyurea) and anti-infective agents (e.g. trimethroprim/sulfonamides, dapsone, amphotericin B, flucytosine, pentamidine), hydroxyurea and pegylated interferons/ribavirin. Therefore, these medicines should only be considered for concomitant use with ganciclovir if the potential benefits outweigh the potential risks.

No dose adjustment is required in case of Stavudine, Trimethoprim and Cyclosporin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

In animal studies ganciclovir was found to impair fertility. In a clinical study renal transplant patients receiving 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 approximately six months after treatment cessation. In the control group, all patients with normal sperm density (n=6) and 2/4 patients with low sperm density at baseline, had normal density at the end of follow-up.

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.

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. Due to limitations of this study, these results are not sufficient to establish recovery of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur. No human data are available in this regard but it is considered probable that such effects will occur in humans.

Although clinical data have not been obtained to support these animal findings, it is considered likely that Cymevene in the recommended doses will result in temporary or permanent inhibition of spermatogenesis in men. Permanent suppression of fertility in women may occur.

Because of the mutagenic potential of ganciclovir, women of reproductive potential should be advised to use an effective method of contraception during and for at least 30 days after treatment. Sexually active men should be advised to use condoms during and for at least 90 days following treatment with Cymevene unless it is certain that the female partner is not at risk of pregnancy (see section 4.4 Special Warnings and Precautions for Use).

Use in Pregnancy - Category D

Cymevene may be teratogenic and/or embryotoxic at the dose levels recommended for human use. There have been no studies of Cymevene in pregnant women. The safety of Cymevene in pregnant women has not been established. Cymevene should not be given to pregnant women as there is a high likelihood of damage to the developing foetus (see section 4.3 Contraindications).

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 µg/mL and occurred by passive diffusion.

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

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.

Use in Lactation

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 (see section 4.3 Contraindications). 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.

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. Adverse reactions, for example seizures, dizziness, ataxia, 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

Experience with intravenous ganciclovir

HIV-infected patients

The safety of IV ganciclovir in AIDS patients was studied in several clinical trials. The pooled safety information of the use of IV ganciclovir in six clinical trials is displayed below in comparison to the control arm (oral placebo plus intravitreal ganciclovir implant) of one of these studies. Clinical adverse events, which occurred in more than 2% of patients taking ganciclovir intravenously, regardless of causal relationship or seriousness, but which occurred in a higher frequency in the IV ganciclovir arm compared to the control arm, are summarised in Table 2.

Injection site reactions occurred more frequently in patients taking IV ganciclovir than in the control group.

Table 2: Percentage of HIV-infected patients with adverse events occurring at a frequency of equal to or greater than 2% of all patients

Body system Adverse event	**Intravenous ganciclovir** *n* = 412	**Control** *n* =119
Haemic and lymphatic system		
Neutropenia	25.7%	11.8%
Anaemia	19.7%	16.8%
Thrombocytopenia	6.6%	5.0%
Leucopenia	3.2%	0.8%
Lymphadenopathy	2.9%	1.7%
Gastrointestinal system		
Diarrhoea	26.5%	24.4%
Abdominal pain	9.0%	7.6%
Dysphagia	2.7%	1.7%
Oesophageal candidiasis	2.2%	1.7%
Body as a whole		
Pyrexia	35.9%	35.3%
Candida	10.4%	4.2%
Injection site infection	8.0%	0.8%
Sepsis	6.1%	3.4%
Sepsis secondary	5.8%	—
Anorexia	4.9%	—
Mycobacterium avium complex	4.9%	4.2%
Pain	4.6%	2.5%
Chest pain	4.4%	3.4%
Blood culture positive	3.2%	1.7%
Injection site inflammation	2.2%	—
Central and peripheral nervous system		
Hypoesthesia	3.2%	1.7%
Anxiety	2.4%	1.7%
Skin and appendages		
Pruritus	3.2%	2.5%

Body system Adverse event	**Intravenous ganciclovir** *n* = 412	**Control** *n* =119
Respiratory system		
Cough	16.0%	15.1%
Pneumocystis carinii pneumonia	7.3%	2.5%
Productive cough	3.6%	2.5%
Sinus congestion	3.4%	2.5%
Metabolic and nutritional disorders		
Blood alkaline phosphatase increased	4.4%	4.2%
Blood creatinine increased	3.2%	1.7%
Musculoskeletal system		
Arthralgia	2.4%	1.7%

The control (*n* = 119) group includes data from treatment of CMV retinitis and prevention of CMV disease in people with CMV seropositivity or culture positivity.

Transplant patients

Several clinical trials have investigated IV ganciclovir for the treatment or prevention of CMV disease in transplant patients.

Clinical adverse events, which occurred in equal to or more than 5% of patients taking IV ganciclovir in three pooled bone marrow studies, regardless of causal relationship or seriousness, are summarised in Table 3. Adverse events which occurred in a higher frequency in the placebo/observational control arm compared to the IV ganciclovir arm have not been included in Table 3 below.

Table 3: Percentage of patients with adverse event occurring at a frequency of equal to or greater than 5% of all patients

Body system Adverse event	**Bone marrow transplant patients** (ICM 1308, 1570 and 1689)	
	Intravenous ganciclovir (*n* = 122)	**Placebo/observational control** (*n* = 120)
Haemic and lymphatic system		
Pancytopenia	31%	25%
Leucopenia	20%	7%
Body as a whole		
Headache	15%	13%
Mucous membrane disorder	14%	13%
Pyrexia	11%	8%
Rigors	7%	4%
Sepsis	7%	2%
Anorexia	7%	5%
Face oedema	5%	2%
Gastrointestinal system		
Diarrhoea	24%	23%
Nausea	20%	19%
Dyspepsia	8%	6%
Abdominal distension	8%	6%
Metabolic and nutritional disorders		
Blood creatinine increased	16%	13%
Hepatic function abnormal	11%	10%
Blood magnesium decreased	11%	10%
Hypocalcemia	9%	8%
Hypokalemia	9%	8%
Central and peripheral nervous system		
Tremor	8%	7%
Confusion	5%	3%
Skin and appendages		
Dermatitis exfoliative	10%	9%
Respiratory system		
Rhinitis	9%	5%
Dyspnea	6%	4%
Cardiovascular system		
Tachycardia	16%	15%

Body system Adverse event	**Bone marrow transplant patients** (ICM 1308, 1570 and 1689)	
	Intravenous ganciclovir (*n* = 122)	**Placebo/observational control** (*n* = 120)
Hypotension	11%	7%
Urogenital system		
Haematuria present	16%	13%
Special senses		
Eye haemorrhage	5%	3%
Musculoskeletal system		
Myalgia	5%	3%

Clinical adverse events which occurred in equal to or more than 5% of patients taking IV ganciclovir in a placebo controlled heart transplant study, regardless of causal relationship or seriousness, but which occurred in a higher frequency in the IV ganciclovir arm (*n* = 76) compared to the placebo arm (*n* = 73) are listed below.

- Body as a whole: headache (18%), infection (18%)
- Metabolic and nutritional disorders: oedema (9%)
- Central and peripheral nervous system: confusion (5%), peripheral neuropathy (7%)
- Respiratory system: pleural effusion (5%)
- Cardiovascular system: hypertension (20%)
- Urogenital system: renal impairment (14%), renal failure (12%)

Paediatric population

Based on the cumulative experience, including valganciclovir paediatric studies, the overall safety profile of ganciclovir in the paediatric population appears similar to the safety profile established in adults. There is a higher risk of haematological cytopenias in neonates and infants (see section 4.4 Special warnings and precautions for use- Paediatric use).

Other experience with intravenous and oral ganciclovir

Other adverse events that were thought to be "probably" or "possibly" related to treatment with orally administered or intravenously administered Cymevene in clinical studies in either patients with AIDS or transplant recipients are listed below. These events all occurred with a frequency of less than 1%:

Body as a Whole: cellulitis, enlarged abdomen, chest pain, chills, drug level increased, malaise, abscess, back pain, oedema, face oedema, injection site abscess, injection site oedema, injection site haemorrhage, injection site phlebitis, laboratory test abnormality, photosensitivity reaction, neck pain, neck rigidity, chills and fever.

Digestive System: eructation, mouth ulceration, constipation, dysphagia, faecal incontinence, haemorrhage, hepatitis, melaena, tongue disorder, aphthous stomatitis, gastritis.

Haemic and Lymphatic System: hypochromic anaemia, pancytopenia, eosinophilia, marrow failure, splenomegaly.

Respiratory System: dyspnoea, cough increased.

Central Nervous System: somnolence, dizziness, paraesthesia, abnormal thoughts or dreams, anxiety, euphoria, insomnia, abnormal gait, ataxia, confusion, dry mouth, hypaesthesia, manic reaction, agitation, amnesia, coma, depression, hypertonia, libido decreased, nervousness, psychosis, seizures, tremor trismus, emotional lability, hyperkinesia.

Skin and Appendages: sweating, acne, maculopapular rash, dry skin, fixed eruption, herpes simplex, skin discolouration, urticarial, vesiculobullous rash.

Special Senses: abnormal vision, taste perversion, vitreous disorder, eye pain, amblyopia, blindness, conjunctivitis, deafness, retinal detachment, glaucoma, retinitis, photophobia, tinnitus.

Metabolic and Nutritional Disorders: hypokalaemia increases in creatinine, alkaline phosphatase, SGPT, SGOT, creatinine phosphokinase and lactic dehydrogenase.

Cardiovascular System: arrhythmia, hypertension, hypotension, deep thrombophlebitis, migraine, vasodilatation.

Urogenital System: breast pain, haematuria increased serum urea, kidney failure, decreased creatinine clearance, abnormal kidney function, urinary frequency, urinary tract infection, impotence.

Musculoskeletal System: myasthenia, myalgia, bone pain.

Laboratory Abnormalities: decreased blood sugar.

NOTE: The following adverse events reported in patients receiving ganciclovir potentially may be fatal: pancreatitis, sepsis, multiple organ failure.

In addition, the following adverse events were reported in at least one of the various clinical trials of Cymevene capsules for the prevention of CMV in HIV positive patients, and/or transplant patients. The incidence was usually less than 2% or within 2% incidence of that reported for the placebo arm. These include weight loss, cholestatic jaundice, neuropathy, hyperglycaemia, leg cramps, amnesia, arthralgia, oesophagitis, myoclonus.

Post-marketing Data

<u>The Following are Post-marketing Events Not Listed Above</u>

Listed below are adverse events reported spontaneously since the marketing introduction of Cymevene sterile powder and oral capsules that had not been reported during clinical trials. These events may have occurred as part of an underlying disease process. These voluntary reports include the following:

Body as a Whole: *rare* dysaesthesia *very rare* allergic reaction, Stevens-Johnson syndrome, anaphylactic reaction, congenital anomaly, rhabdomyolysis.

Digestive System: *very rare* perforated intestine, intestinal ulceration.

Hepatic System: *rare* hepatic failure.

Haemic and Lymphatic System: *very rare* haemolytic anaemia, *rare* agranulocytosis and granulocytopenia

Respiratory System: *very rare* bronchospasm, pulmonary fibrosis.

Central Nervous System: *rare* encephalopathy, hallucinations *very rare* dysphasia, myelopathy, extrapyramidal reaction, facial palsy, irritability.

Skin and Appendages: *very rare* exfoliative dermatitis.

Special Senses: *very rare* cataracts, loss of sense of smell, dry eyes.

Metabolic and Nutritional Disorders: *rare* acidosis *very rare* hyponatremia, elevated triglyceride levels.

Cardiovascular System: *rare* cardiac arrest *very rare* stroke, intracranial hypertension, vasculitis, peripheral ischaemia, ventricular tachycardia, cardiac conduction abnormality, Torsades de Pointes.

Urogenital System: *very rare* infertility, testicular hypotrophy.

Musculoskeletal System: *very rare* arthritis.

Laboratory Abnormalities: *very rare* syndrome of inappropriate antidiuretic hormone secretion.

Laboratory abnormalities in HIV-infected patients

Laboratory abnormalities reported from three clinical trials in HIV-infected patients receiving IV ganciclovir as maintenance treatment for CMV retinitis are listed below in Table 4. One hundred seventy-nine patients were eligible for the laboratory abnormality analysis.

Table 4 Laboratory abnormalities in HIV-infected patients

Laboratory abnormalities	***n* = 179**
Neutropenia (absolute neutrophil count/mm^3)	
< 500	25.1%
500 – < 750	14.3%
750 – < 1000	26.3%
Anaemia (haemoglobin 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%

Reporting of suspected adverse reactions

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

4.9 OVERDOSE

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, leukopenia, 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, seizure.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antivirals 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 µg/mL). Ganciclovir inhibits mammalian cell proliferation (TD_{50}) *in vitro* at higher concentrations ranging from 40 to >1000 µM (10 to >250 µg/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 µg/mL). The relationship of *in vitro* sensitivity of CMV to ganciclovir and clinical response has not been established.

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 demonstrate poor clinical response or experience continuous viral excretion during treatment.

Emergence of viral resistance was reported in humans with AIDS and CMV retinitis and was associated with clinical failure of ganciclovir treatment. The number of patients with resistant isolates increased with

duration of ganciclovir exposure, and was estimated to occur in 3% to 26% of patients after 3 to 9 months of treatment, respectively, and occurred with equal frequency in patients treated with IV and oral medicines.

Clinical trials

Intravenous Cymevene in CMV Retinitis

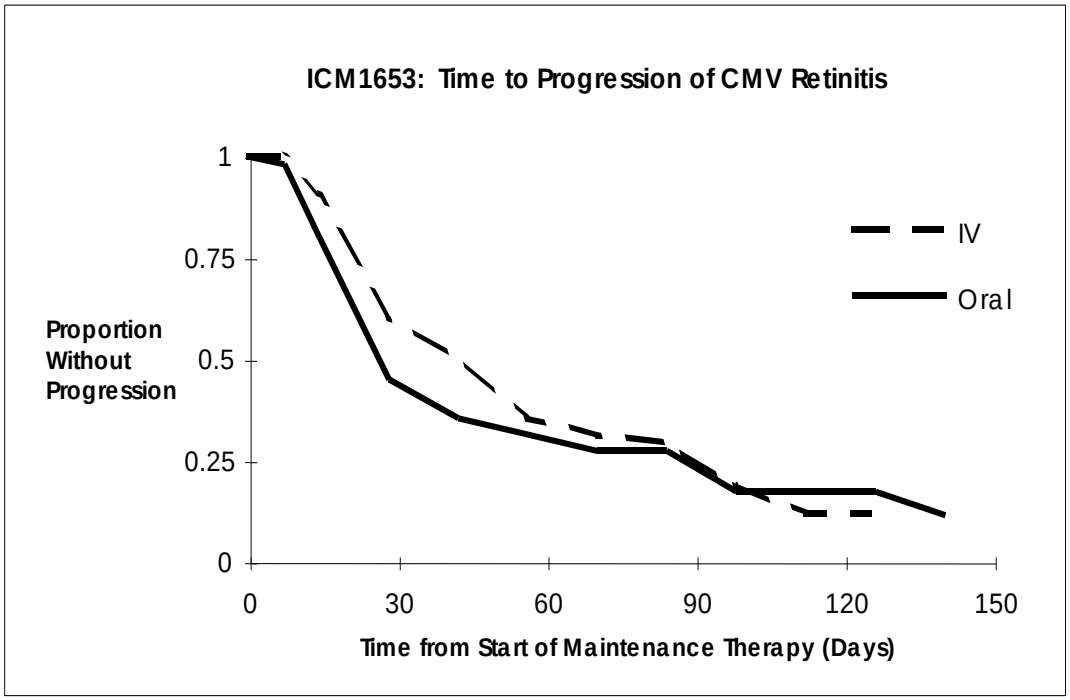
The diagnosis of CMV retinitis should be made by indirect ophthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis included candidiasis, toxoplasmosis, histoplasmosis, retinal scars, cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason 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 meantime 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



Intravenous Cymevene for 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 5: 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.

Oral Cymevene for Prophylaxis of CMV Disease in Liver Transplantation

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 $\geq 1 \times 10^9$/L.

Table 6: 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 7 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 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). Whereas, following a dose of 5 mg/kg/day (n = 16) with IV ganciclovir the AUC_{0-24} and C_{max} were 26.0 ± 6.06 and 9.03 ± 1.42 µg/mL respectively. Most studies indicated that C_{min} of ganciclovir (plasma level at 11 h after start of infusion) averaged 0.56 µg/mL.

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 µg/mL. Therefore, medicine interactions involving binding site displacement are not expected.

Metabolism
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 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 (Cl_{iv}) averaged 3.64 ± 1.86 mL/min/kg. Dose-dependent kinetics of ganciclovir over the dose range 1.6 to 5.0 mg/kg were demonstrated in as much as AUC for ganciclovir increased in proportion to the increase in dose by the systemic clearance and plasma $t_{½}$ values were similar at all dose levels. 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.

Special Populations
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.

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 Dose and Method of Administration, Renal Impairment).

Haemodialysis
Plasma concentrations of ganciclovir are reduced by about 50%-60% during a 4 hour hemodialysis session (see section 4.9 Overdose).

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.

Paediatric patients
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 8 gives the estimated pharmacokinetic parameters by age group.

Table 8 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 (n=10) 1 and AUC0-12 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 AUC0-∞ on Day 1 (n=7) and AUC0-12h 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 9 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 C_{max} of 3.66 µg/mL, AUC 34.75 µg.h/mL and $t_{1/2}$ of 7.87 h.

Elderly patients

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.

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 µg/mL and the mean steady state morning trough concentration was 0.20 µg/mL. The steady state $AUC_{0\text{-}24}$ for this regimen was 13.0 µg·hr/mL compared with 26.0 µg·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

Carconogenicity

In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic. Cymevene should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. It is also considered likely that Cymevene causes temporary or permanent inhibition of spermatogenesis (see sections 4.6 Fertility, Pregancy and Lactation and section 4.8 Adverse Effects (Undesirable Effects)).

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.

Genotoxity

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None.

6.2 INCOMPATIBILITIES

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.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials

Store below 30 °C.

Reconstituted vials

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.

Compounding centres

1. which are licensed by the Australian Therapeutic Goods Administration to reconstitute and/or further dilute cytotoxic medicines, and
2. have validated aseptic procedures and regular monitoring of aseptic technique

may apply a shelf-life of 15 days at 2 – 8 °C (refrigerate, do not freeze) to Cymevene infusions reconstituted with water and further diluted with 0.9% sodium chloride or glucose (dextrose) 5%. These further diluted solutions have been shown to be chemically stable for this period. The extended shelf-life does not apply to reconstituted injections diluted with Ringer's Injection and Ringer-Lactate Solution for Injection.

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

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.

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

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

Ganciclovir is a synthetic nucleoside analogue of guanine. Its chemical name is 9-(1,3-dihydroxy-2-propoxymethyl) guanine. Ganciclovir has also been referred to as DHPG. Ganciclovir has a molecular formula of $C_9H_{13}N_5O_4$ and a molecular weight of 255.2.

Ganciclovir is a polar hydrophilic compound with a solubility of 2.6 mg/mL in water at 25 ºC (Hydrated Phase II polymorph) and an n-octanol/water partition coefficient of 0.022. The solubility of ganciclovir is independent of the crystalline phase composition. Ganciclovir has two dissociation constants: $pKa_1 = 2.2$ and $pKa_2 = 9.4$.

CAS number

82410-32-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4. Prescription Only Medicine.

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

11 June 1991

10. DATE OF REVISION OF THE TEXT

09 October 2018

Summary table of changes

Section Changed	Summary of new information
All sections	New PI format and mandatory text
4.3	Use of ganciclovir in patients with hypersensitivity to aciclovir or valaciclovir has been changed to a warning and moved to section 4.4
4.4	The information on cross hypersensitivity has been moved to section 4.4, under the heading of Cross hypersensitivity New text under the heading Paediatric Use has been added to reflect the risk of haematological cytopenias
4.5	Deletion of information on Mycophenolate mofetil, stavudine, trimethoprim and cyclosporin as this information is reflected under the heading, Potential drug interactions
4.7	Information has been added. The term 'sedation' has been removed.
4.8	Information on paediatric population has been added
5.1	Information on Cross-Resistance has been removed Information in Pharmacokinetics section, Absorption, Distribution, Metabolism and Elimination has been updated Information under Special populations; Renal impairment, Haemodialysis and hepatic impairment has been updated. Paediatric patients section now includes information from the two paediatric studies WP16303 and WP16296. Elderly section has also been updated.