Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cymevene 500 mg powder for concentrate for solution for 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.

Excipient(s) 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 concentrate).

White to off-white solid cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cymevene is indicated in adults and adolescents ≥ 12 years of age for the:

- treatment of cytomegalovirus (CMV) disease in immunocompromised patients;
- prevention of CMV disease using pre-emptive therapy in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy).

Cymevene is also indicated from birth for the:

- prevention of CMV disease using universal prophylaxis in patients with drug-induced
- immunosuppression (for example following organ transplantation or cancer chemotherapy).

Consideration should be given to official guidance on the appropriate use of antiviral agents.

4.2 Posology and method of administration

Posology

Treatment of CMV disease

Adults and paediatric population ≥12 years of age with normal renal function:

- Induction treatment: 5 mg/kg given as an intravenous infusion over one hour, every 12 hours for 14 - 21 days.
- Maintenance treatment: For immunocompromised patients at risk of relapse maintenance therapy may be given. 5 mg/kg given as an intravenous infusion over one hour, once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration of maintenance treatment should be determined on an individual basis, local treatment guidelines should be consulted.
- Treatment of disease progression: Any patient, in whom CMV disease progresses, either while on maintenance treatment or because treatment with ganciclovir has been withdrawn, may be re-treated using the induction treatment regimen.

Paediatric population from birth to < 12 years of age:
Currently available paediatric data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Prevention of CMV disease using pre-emptive therapy
Adults and paediatric population ≥12 years of age with normal renal function:
Induction therapy: 5 mg/kg given as an intravenous infusion over one hour, every 12 hours for 7 – 14 days.
Maintenance therapy: 5 mg/kg given as an intravenous infusion over one hour, once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration of maintenance therapy is based on the risk of CMV disease, local treatment guidelines should be consulted.

Paediatric population from birth to < 12 years of age:
Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Prevention of CMV disease using universal prophylaxis
Adults and paediatric population >16 years of age:
5 mg/kg given as an intravenous infusion over one hour, once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration is based on the risk of CMV disease, local treatment guidelines should be consulted.

Paediatric population from birth to ≤ 16 years of age:
The recommended once daily dose of ganciclovir given as an intravenous infusion over one hour is based on Body Surface Area (BSA) using the Mostellar BSA formula and creatinine clearance derived from Schwartz formula (CrCLS), and is calculated using the equations below. The duration of universal prophylaxis is based on the risk of CMV disease and should be determined on an individual basis.

Paediatric dose (mg) = 3 x BSA x CrCLS (see Mostellar BSA formula and Schwartz Creatinine Clearance formula below).

If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m^2, then a maximum value of 150 mL/min/1.73m^2 should be used in the equation:

where k = 0.33 for patients <1 year of age with low birth weight, 0.45 for patients aged < 2 years, 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and 0.7 for boys aged 13 to 16 years. Refer to adult dosing for patients older than 16 years of age.
The k values provided are based on the Jaffe method of measuring serum creatinine, and may require correction when enzymatic methods are used.
It is recommended that serum creatinine levels, height and weight are reviewed regularly and the dose amended as appropriate.

Special dosage instructions

Renal impairment

Paediatric patients (from birth to ≤16 years of age) with renal impairment receiving a prophylactic dose of ganciclovir calculated using the 3 x BSA x CrCLS dosing algorithm do not require further dose modification because this dose is already adjusted for creatinine clearance.

For patients 12 years and older with renal impairment, treated on a mg/kg bodyweight basis for pre-emptive therapy and treatment of CMV disease, the mg/kg dose of ganciclovir should be modified according to creatinine clearance as shown in the table below (see sections 4.4 and 5.2).

Dose modifications for patients with renal impairment receiving mg/kg dosing:

CrCl	**Induction dose**	**Maintenance dose**
>70 mL/min	5.0 mg/kg q12h	5.0 mg/kg/day
50-69 mL/min	2.5 mg/kg q12h	2.5 mg/kg/day
25-49 mL/min	2.5 mg/kg/day	1.25 mg/kg/day
10-24 mL/min	1.25mg/kg/day	0.625 mg/kg/day
<10 mL/min	1.25 mg/kg 3x/wk after haemodialysis	0.625 mg/kg 3x/wk after haemodialysis

Estimated creatinine clearance can be calculated from serum creatinine using the following formulae:

For males: (140 – age [years]) x (body weight [kg])

(72) x (0.011 x serum creatinine [micromol/L])

For females: 0.85 x male value

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

Hepatic impairment

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

Severe leukopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia

See section 4.4 before initiation of treatment.

If the blood cell counts are significantly reduced during therapy with ganciclovir, treatment with haematopoietic growth factors and/or discontinuation of treatment should be considered (see sections 4.4 and 4.8).

Elderly

No studies on the efficacy or safety of ganciclovir in the elderly have been conducted. Since renal function decreases with age, ganciclovir should be administered to the elderly with special consideration for their renal status (see section 5.2).

Method of administration

Caution:
Ganciclovir must be administered by intravenous infusion over 1 hour at a concentration not exceeding 10 mg/mL. Do not administer by rapid or bolus intravenous injection because the resulting excessive plasma levels may increase the toxicity of ganciclovir.

Do not administer by intramuscular or subcutaneous injection because this may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions (see section 4.8).

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

Cymevene is a powder for solution for infusion. After reconstitution Cymevene is a colourless to slightly yellowish solution, practically free from visible particles.

The infusion should be given into a vein with adequate blood flow, preferably via a plastic cannula.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Precaution to be taken before handling or administering the medicinal product:

Since ganciclovir is considered a potential teratogen and carcinogen in humans, caution should be taken in its handling (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or valganciclovir or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Cross-hypersensitivity
Due to the similarity of the chemical structure of 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, carcinogenicity, fertility and contraception
Prior to initiation of ganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies ganciclovir was found to be mutagenic, teratogenic, carcinogenic and to impair fertility. Based on clinical and nonclinical studies it is considered likely that ganciclovir causes temporary or permanent inhibition of spermatogenesis (see sections 4.6, 4.8 and 5.3).
Ganciclovir should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. Therefore, women of childbearing potential must be advised to use effective contraception during treatment and for at least 30 days thereafter. Men must be advised to practice barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy (see sections 4.6, 4.8 and 5.3).

The use of ganciclovir warrants extreme caution, especially in the paediatric population due to the potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should be carefully considered in each case and should clearly outweigh the risks (see section 4.2). Refer to treatment guidelines.

Myelosuppression
Cymevene should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.
Severe leukopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia and bone marrow failure have been observed in patients treated with ganciclovir. Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/microliter or the platelet count is less than 25,000 cells/microliter or the haemoglobin is less than 8 g/dL (see sections 4.2 and 4.8).

It is recommended that complete blood counts including platelet counts be monitored during therapy. Increased haematological monitoring may be warranted in patients with renal impairment and in neonates and infants (see section 4.8). During the first 14 days of administration it is recommended that white blood cell count (preferably as a differential test) is conducted every second day; in patients with low baseline neutrophil levels (< 1,000 neutrophils/microliter), those who developed leukopenia during previous therapy with other myelotoxic substances, and those with renal impairment, this monitoring should be performed daily.

For patients with severe leukopenia, neutropenia, anaemia and/or thrombocytopenia it is recommended to consider the use of treatment with haematopoietic growth factors and/or the interruption of ganciclovir therapy (see sections 4.2 and 4.8).

Renal impairment

Patients with impaired renal function are at increased risk of toxicity (especially haematological toxicity). Dosage reduction is required (see sections 4.2 and 5.2).

Use with other medicines

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

Patients treated with ganciclovir and didanosine, medicines known to be myelosuppressive or affecting renal function, should be closely monitored for signs of added toxicity (see section 4.5).

Excipients

This medicinal product contains 43 mg sodium per 500 mg vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Probenecid

Probenecid given with oral ganciclovir resulted in statistically decreased renal clearance of ganciclovir and led to clinically significant increased exposure. Such an effect is also anticipated during concomitant administration of intravenous ganciclovir and probenecid. 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 ganciclovir. At intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38% to 67% has been observed. There was no clinically significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (see section 4.4).

Other antiretrovirals

Cytochrome P450 isoenzymes play no role in ganciclovir pharmacokinetics. Consequently, pharmacokinetic interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors are not anticipated.

Pharmacodynamic interactions

Imipenem-cilastatin

Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4).

Zidovudine

Both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia. A pharmacodynamic interaction may occur during concomitant administration of these drugs. Some patients may not tolerate concomitant therapy at full dosage (see section4.4).

Other potential drug interactions

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

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Fertility

A small clinical study with renal transplant patients receiving Valcyte for CMV prophylaxis for up to 200 days demonstrated an impact of valganciclovir/ganciclovir on spermatogenesis, with decreased sperm density and motility measured after treatment completion. This effect appears to be reversible and approximately six months after Valcyte discontinuation, mean sperm density and motility recovered to levels comparable to those observed in the untreated controls.
In animal studies, ganciclovir impaired fertility in male and female mice and has shown to inhibit spermatogenesis and induce testicular atrophy in mice, rats and dogs at doses considered clinically relevant.
Based on clinical and nonclinical studies, it is considered likely that ganciclovir may cause temporary or permanent inhibition of human spermatogenesis (see sections 4.4 and 5.3).

Pregnancy

The safety of ganciclovir for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity (see sections 4.4 and

5.3). Therefore, ganciclovir should not be used in pregnant women unless the clinical need for treatment of the woman outweighs the potential teratogenic risk to the foetus.

Contraception in males and females

As a result of the potential for reproductive toxicity and teratogenicity, women of childbearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Male patients must be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir unless it is certain that the female partner is not at risk of pregnancy (see sections 4.4 and 5.3).

Breastfeeding

It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breastfed infant cannot be excluded. Animal data indicate that ganciclovir is excreted in the milk of lactating rats. Therefore, breastfeeding must be discontinued during treatment with ganciclovir (see section 4.3).

4.7 Effects on ability to drive and use machines

Ganciclovir may have a major influence on the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Valganciclovir is a pro-drug of ganciclovir, and adverse reactions associated with valganciclovir can be expected to occur with ganciclovir. Oral ganciclovir is no longer available but adverse reactions reported with its use can also be expected to occur in patients receiving intravenous ganciclovir. Therefore, adverse drug reactions reported with intravenous or oral ganciclovir or with valganciclovir are included in the table of adverse reactions.

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

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 or valganciclovir. Exception is made for agranulocytosis, granulocytopenia and anaphylactic reaction; the frequencies of which are derived from post-marketing experience. Adverse reactions are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

The overall safety profile of ganciclovir/valganciclovir is consistent in HIV and transplant populations except that retinal detachment has only been reported in 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 diarrhoea compared to oral valganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC <500/microliter) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

Tabulated list of adverse reactions

ADR (MedDRA) System Organ Class	**Frequency Category**
Infections and infestations:	
Candida infections including oral candidiasis.	Very common
Upper respiratory tract infection	
Sepsis	Common
Influenza	
Urinary tract infection	
Cellulitis	
Blood and lymphatic disorders:	

Neutropenia	Very common
Anaemia	
Thrombocytopenia	Common
Leukopenia	
Pancytopenia	
Bone marrow failure	Uncommon
Aplastic anaemia	Rare
Agranulocytosis*	
Granulocytopenia*	
Immune system disorders:	
Hypersensitivity	Common
Anaphylactic reaction*	Rare
Metabolic and nutrition disorders:	
Decreased appetite	Very common
Weight decreased	Common
Psychiatric disorders:	
Depression	Common
Confusional state	
Anxiety	
Agitation	Uncommon
Psychotic disorder	
Thinking abnormal	
Hallucinations	
Nervous system disorders:	
Headache	Very common
Insomnia	Common
Neuropathy peripheral	
Dizziness	
Paraesthesia	
Hypoaesthesia	
Seizure	
Dysgeusia (taste disturbance)	
Tremor	Uncommon
Eye disorders:	
Visual impairment	Common
Retinal detachment	
Vitreous floaters	
Eye pain	
Conjunctivitis	
Macular oedema	
Ear and labyrinth disorders:	
Ear pain	Common
Deafness	Uncommon
Cardiac disorders:	
Arrhythmia	Uncommon
Vascular disorders:	
Hypotension	Common
Respiratory, thoracic and mediastinal disorders:	
Cough	Very common
Dyspnoea	
Gastrointestinal disorders:	
Diarrhoea	Very common
Nausea	
Vomiting	
Abdominal pain	
Dyspepsia	

Flatulence	Common
Abdominal pain upper	
Constipation	
Mouth ulceration	
Dysphagia	
Abdominal distention	
Pancreatitis	
Hepato-biliary disorders:	
Blood alkaline phosphatase increased	Common
Hepatic function abnormal	
Aspartate aminotransferase increased	
Alanine aminotransferase increased	
Skin and subcutaneous tissue disorders:	
Dermatitis	Very common
Night sweats	Common
Pruritus	
Rash	
Alopecia	
Dry skin	Uncommon
Urticaria	
Musculoskeletal and connective tissue disorders:	
Back pain	Common
Myalgia	
Arthralgia	
Muscle spasms	
Renal and urinary disorders:	
Renal impairment	Common
Creatinine clearance renal decreased	
Blood creatinine increased	
Renal failure	Uncommon
Haematuria	
Reproductive system and breast disorders:	
Infertility male	Uncommon
General disorders and administration site conditions:	
Pyrexia	Very common
Fatigue	
Injection site reaction	Common
Pain	
Chills	
Malaise	
Asthenia	
Chest pain	Uncommon

** The frequencies of these adverse reactions are derived from post-marketing experience, all other frequency categories are based on the frequency recorded in clinical trials.*

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 and following administration of a cumulative dose of ≤ 200 mg / kg. The cell count usually normalises within 2 to 5 days after discontinuation of the drug or dose reduction (see section 4.4).

Severe neutropenia

Severe neutropenia was reported more frequently in HIV patients (14%) receiving maintenance therapy with valganciclovir, oral or intravenous ganciclovir (n=1704) than in organ transplant patients receiving valganciclovir or oral ganciclovir. In patients receiving valganciclovir or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia was 5% and 3% respectively, whilst in patients receiving valganciclovir until Day 200 post-transplant the incidence of severe neutropenia was 10%.

Thrombocytopenia

Patients with low baseline platelet counts (< 100,000 / microliter) 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.

Seizures

Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir (see sections 4.4 and 4.5).

Retinal detachment

This adverse reaction has only been reported in studies in HIV patients treated with Cymevene for CMV retinitis.

Injection site reactions

Injection site reactions occur commonly in patients receiving ganciclovir. Cymevene should be administered as recommended in section 4.2 to reduce the risk of local tissue irritation.

Paediatric population

Formal safety studies with ganciclovir have not been conducted in children < 12 years of age but based on experience with valganciclovir, a pro-drug of ganciclovir, the overall safety profile of the active drug is similar in paediatric and adult patients. Neutropenia occurs more often in paediatric patients, but there is no correlation between neutropenia and infectious adverse reactions in the paediatric population. A higher risk of cytopenias in neonates and infants warrants the careful monitoring of blood counts in these age groups (see section 4.4).

Only limited data are available in neonates or infants with HIV/AIDS or symptomatic congenital CMV infection treated with valganciclovir or ganciclovir, however the safety profile appears to be consistent with the known safety profile of valganciclovir/ganciclovir.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms

Reports of overdoses with i.v. ganciclovir, some with fatal outcomes, have been received from clinical trials and during post-marketing experience. The majority of the reports were either not associated with any adverse reactions, or included one or more of the adverse reactions listed below:

- Haematological toxicity: myelosuppression including pancytopenia, bone marrow failure, leukopenia, neutropenia, granulocytopenia
- Hepatotoxicity: hepatitis, liver function disorder
- Renal toxicity: worsening of haematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine
- Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting
- Neurotoxicity: generalised tremor, seizure

Management

Ganciclovir is removed by haemodialysis, therefore haemodialysis may be of benefit in reducing drug exposure in patients who receive an overdose of ganciclovir (see section 5.2).

Additional information on special populations

Renal impairment: It is expected that an overdose of ganciclovir could result in increased renal toxicity in patients with renal impairment (see section 4.4).

Paediatric population

No specific information available

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 analogue of 2'-deoxyguanosine, which inhibits replication of herpes viruses both *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus 1 and 2 (HSV-1 and HSV-2), human herpesvirus 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella zoster virus (VZV), and hepatitis B virus. Clinical studies have been limited to evaluation of efficacy in patients with CMV infection.

In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by several cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. This has been shown to occur in HSV- and HCMV-infected cells, with half-lives of 18 and 6-24 hours, respectively, after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.
The virustatic activity of ganciclovir is a result of the inhibition of viral DNA synthesis by: (1) competitive inhibition of incorporation of deoxyguanosine triphosphate into DNA by DNA polymerase, and (2) incorporation of ganciclovir triphosphate into viral DNA, causing termination of, or very limited, viral DNA elongation.

Antiviral activity

The *in vitro* antiviral activity, measured as IC50 of ganciclovir against CMV, is in the range of 0.08 micromol/L (0.02 microgram/mL) to 14 micromol/L (3.57 microgram/mL).

Clinical efficacy and safety

Viral resistance

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

Viral resistance to ganciclovir can arise by selection of mutations in the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or the viral polymerase gene (UL54). Viruses containing mutations in the UL97 gene are resistant to ganciclovir alone, whereas viruses with mutations in the UL54 gene are resistant to ganciclovir but may show cross-resistance to other antivirals that also target viral polymerase.

Paediatric population
In a prospective study, 36 severely immunocompromised paediatric patients (6 months - 16 years of age) with HIV and CMV infection received intravenous ganciclovir at a dose of 5 mg/kg per day for 2 days followed by oral ganciclovir for a median of 32 weeks. Ganciclovir was effective with a toxicity profile similar to that seen in adults. Ganciclovir was associated with a decrease in the detection of CMV by culture or polymerase chain reaction. Neutropenia was the only severe adverse drug

reaction observed during the study and although none of the children required treatment cessation, 4 required granulocyte colony-stimulating factor (G-CSF) treatment to maintain absolute neutrophil counts > 400 cells/mm ^{3}.

In a retrospective study, 122 paediatric liver transplantation recipients (16 days – 18 years of age, median age 2.5 years) received a minimum of 14 days of intravenous ganciclovir 5 mg/kg twice a day followed by pre-emptive CMV PCR monitoring. Forty-three patients were considered high-risk for CMV and 79 were routine-risk. Asymptomatic CMV infection was detected by PCR in 34.4% of subjects and was more likely in high-risk than in routine-risk recipients (58.1% vs. 21.8%, p = 0.0001). Twelve subjects (9.8%) developed CMV disease (8 high-risk vs. 4 routine-risk, p = 0.03). Three subjects developed acute rejection within 6 months of detection of CMV, but CMV was preceded by rejection in 13 subjects. There were no deaths secondary to CMV. A total of 38.5% of subjects were spared antiviral medications beyond their initial postoperative prophylaxis. In a retrospective analysis, the safety and efficacy of ganciclovir was compared to valganciclovir in 92 paediatric kidney and/or liver transplant patients (7 months - 18 years of age, median age 9 years). All children received intravenous ganciclovir 5 mg/kg twice daily for 2 weeks following transplantation. Children treated before 2004 then received oral ganciclovir 30 mg/kg/dose up to 1 g/dose three times daily (n = 41), while children treated after 2004 received valganciclovir up to 900 mg once daily (n = 51). The overall incidence of CMV was 16% (15/92 patients). Time to onset of CMV infection was comparable in both groups.

In a randomised, controlled study, 100 neonates (≤ 1 month of age) with symptomatic congenital CMV disease with CNS involvement received 6 weeks of intravenous ganciclovir 6 mg/kg every 12 hours or no treatment. Of the 100 patients enrolled, 42 met all study criteria and had both baseline and 6-month follow up audiometric evaluations. Of these, 25 received ganciclovir and 17 received no treatment. Twenty-one of 25 ganciclovir recipients had improved hearing or maintained normal hearing from baseline to 6 months compared with 10/17 control patients (84% and 59%, respectively p = 0.06). None of the ganciclovir recipients had worsening hearing from baseline to 6 months, compared with 7 control patients (p < 0.01). By one year after baseline, 5/24 ganciclovir recipients and 13/19 control patients had worsening hearing (p < 0.01). In the course of the study, 29/46 ganciclovir-treated patients had neutropenia, compared with 9/43 control patients (p < 0.1). There were 9 deaths during the study, 3 in the ganciclovir group and 6 in the control group. No deaths were related to study medication.

In a Phase III, randomised, controlled study, 100 neonates (3-33 days of age, median age 12 days) with severe symptomatic congenital CMV with CNS involvement, received either intravenous ganciclovir 6 mg/kg twice daily for 6 weeks (n = 48) or no antiviral treatment (n = 52). Infants who received ganciclovir had improved neurodevelopmental outcomes at 6 and 12 months compared with those who did not receive antiviral treatment. Although ganciclovir recipients had fewer delays and more normal neurological outcomes, most were still behind what would be considered normal development at 6 weeks, 6 months, or 12 months of age. Safety was not assessed in this study.

A retrospective study investigated the effect of antiviral treatment on late-onset hearing loss in infants with congenital CMV infection (4-34 months of age, mean age 10.3 ± 7.8 months, median age 8 months). The study included 21 infants with normal hearing at birth who developed late-onset hearing loss. Antiviral treatment consisted of either:

- Intravenous ganciclovir 5 mg/kg daily for 6 weeks followed by oral valganciclovir 17 mg/kg twice daily for 6 weeks then daily until 1 year of age, or
- Oral valganciclovir 17 mg/kg twice daily for 12 weeks then daily for 9 months.

None of the children required a cochlear implant and hearing loss improved in 83% of ears affected by hearing loss at baseline. Neutropenia was the only side effect reported and it was not necessary to discontinue treatment in any patient.

5.2 Pharmacokinetic properties

The systemic exposure ($AUC_{0-\infty}$) reported following dosing with a single 1-hour IV infusion of 5 mg/kg ganciclovir in adult liver transplant patients was on average 50.6 microgram.h/mL (CV% 40). In this patient population peak plasma concentration (C_{max}) was on average 12.2 microgram/mL (CV% 24).

Distribution

The volume of distribution of intravenously administered ganciclovir is correlated to body weight. The steady state volume of distribution has a range of 0.54-0.87 L/kg. Plasma protein binding was 1%-2% over ganciclovir concentrations of 0.5 and 51 microgram/mL. Ganciclovir penetrates the cerebrospinal fluid, where concentrations observed reach 24%-67% of the plasma concentrations.

Biotransformation

Ganciclovir is not metabolised to a significant extent.

Elimination

Ganciclovir is predominantly eliminated by renal excretion via glomerular filtration and active tubular secretion of unchanged ganciclovir. In patients with normal renal function, more than 90% of the intravenously administered ganciclovir dose is recovered unchanged in the urine within 24 hours. The mean systemic clearance ranged from 2.64 ± 0.38 mL/min/kg (N = 15) to 4.52 ± 2.79 mL/min/kg (N = 6) and renal clearance ranged from 2.57 ± 0.69 mL/min/kg (N = 15) to 3.48 ± 0.68 mL/min/kg (N = 20), corresponding to 90%-101% of administered ganciclovir. Half-lives in subjects without renal impairment ranged from 2.73 ± 1.29 (N = 6) to 3.98 ± 1.78 hours (N = 8).

Linearity/non-linearity

Intravenous ganciclovir exhibits linear pharmacokinetics over the range of 1.6-5.0 mg/kg.

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 and 0.3 mL/min/kg were observed. Patients with renal impairment have an increased elimination half-life. In patients with severe renal impairment elimination half-life was increased by 10-fold (see section 4.2 for dose modifications required in patients with renal impairment).

Patients with renal impairment undergoing haemodialysis

Haemodialysis reduces plasma concentrations of ganciclovir by about 50% after intravenous administration during a 4-hour haemodialysis session.
During intermittent haemodialysis, estimates for the clearance of ganciclovir ranged from 42-92 mL/min, resulting in intra-dialytic half-lives of 3.3-4.5 hours. The fraction of ganciclovir removed during a single dialysis session varied from 50% to 63%. Estimates of ganciclovir clearance for continuous dialysis were lower (4.0-29.6 mL/min) but resulted in greater removal of ganciclovir over a dose interval.

Patients with hepatic impairment

The safety and efficacy of Cymevene have not been studied in patients with hepatic impairment. Hepatic impairment should not affect the pharmacokinetics of ganciclovir since it is excreted renally and, therefore, no specific dose recommendation is made (see section 4.2).

Paediatric population

The pharmacokinetics of IV ganciclovir (administered as 200 mg/m^2 dose) 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. Creatinine clearance (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. When CrCL and height were included in the model, the apparent differences in ganciclovir PK across various age groups was accounted for andneither age, gender, nor types of organ transplant were significant covariates in these populations. Table 1 gives the estimated pharmacokinetic parameters by age group.

Table 1 Pharmacokinetic parameters after ganciclovir IV given by BSA (200mg/m2) 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)
AUC_{0-24h} (microgram.h/mL)	24.3 (14.1-38.9)	40.4 (17.7-48.6)	37.6 (19.2-80.2)
Cmax (microgram/mL)	12.1 (9.17-15)	13.3 (4.73-15)	12.4 (4.57-30.8)

Furthermore, the pharmacokinetics of intravenous 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 and aged 9 months-12 years (n = 10, average 3.1 years). Exposure as measured by mean $AUC_{0-\infty}$ on Day 1 (n = 10) and AUC_{0-12} on Day 14 (n = 7) were 19.4 ± 7.1 and 24.1 ± 14.6 microgram.h/mL with corresponding C_{max} values of 7.59 ± 3.21 microgram/mL (Day 1) and 8.31 ± 4.9 microgram/mL (Day 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 of age 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 microgram.h/mL.

The ganciclovir IV dosing regimen based on BSA and renal function (3x BSA x CrCLS), derived from the paediatric dosing algorithm with valganciclovir, leads to similar ganciclovir exposures in the paediatric population from birth to 16 years of age (see Table 2).

Table 2 Simulated* Ganciclovir AUC_{0-24h} (microgram · h/mL) for paediatric patients treated with ganciclovir dose (mg) of 3xBSAxCrCLS 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	1,473
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 microgram · h/mL	89 (11%)	38 (10%)	13 (15%)	23 (24%)	28 (22%)	191 (13%)
Patients AUC 40-60 microgram · h/mL	398 (51%)	195 (51%)	44 (51%)	41 (43%)	63 (50%)	741 (50%)
Patients AUC > 60 microgram · 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 paediatric population PK model and demographic data from paediatric patients receiving valganciclovir or ganciclovir treatment in clinical studies (n = 1,473 data records)*						

Elderly

No studies have been conducted in adults older than 65 years of age (see section 4.2).

5.3 Preclinical safety data

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

Ganciclovir causes impaired fertility and teratogenicity in animals. Based upon animal studies where inhibition of spermatogenesis was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir causes inhibition of human spermatogenesis.

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 other medicinal products except those mentioned in section 6.6.. Do not use bacteriostatic water for injections containing parabens (para-hydroxybenzoates) since these are incompatible with Cymevene and may cause precipitation.

6.3 Shelf life

5 years

After reconstitution:
Chemical and physical in-use stability has been demonstrated for the reconstituted product for 12 hours at 25°C after dissolving with water for injections. Do not refrigerate or freeze.
From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2–8°C (do not freeze).
From a microbiological point of view, the Cymevene infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Single-dose glass vials of 10 mL with fluoro-resin laminated/siliconised rubber stopper and aluminum closure with flip-off cap.
Available in packs of 1 vial or 5 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Caution should be exercised in the handling of Cymevene.
Since Cymevene is considered a potential teratogen and carcinogen in humans, caution should be observed in its handling. Avoid inhalation or direct contact of the powder contained in the vials or direct contact of the reconstituted solution with the skin or mucous membranes. Cymevene solutions are alkaline (pH ~11). If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with plain water.

<u>Preparation of the reconstituted concentrate</u>

Aseptic technique should be used throughout to reconstitute lyophilised Cymevene.

1. The flip-off cap should be removed to expose the central portions of the rubber stopper. Draw 10 mL of water for injection into a syringe, then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial.
Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), since these are incompatible with Cymevene.

2.The vial should be gently swirled in order to ensure complete wetting of the product.

3. The vial should be gently rotated/ swirled for some minutes to obtain a clear reconstituted solution.

4. The reconstituted solution should be checked carefully to ensure that the product is in solution and practically free from visible particles prior to dilution with compatible solvent. Reconstituted solutions of Cymevene range in colour from colourless to light yellow.

For storage conditions of the reconstituted concentrate, see sections 6.3.

Preparation of final diluted solution for infusion

Based on patient weight the appropriate volume should be removed with a syringe from the vial and further diluted into an appropriate infusion solution. Add a volume of 100ml of diluent to the reconstituted solution. Infusion concentrations greater than 10mg/mL are not recommended.
Sodium chloride, dextrose 5%, Ringer's or lactated Ringer's solutions are determined chemically or physically compatible with Cymevene.

Cymevene should not be mixed with other intravenous products.

The diluted solution should then be infused intravenously over 1 hour as directed in section 4.2. Do not administer by intramuscular or subcutaneous injection because this may result in severe tissue irritation due to the high pH (~11) of ganciclovir solution.

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

Disposal

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Cheplapharm Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA2239/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 January 1990

Date of last renewal: 09 January 2010

10 DATE OF REVISION OF THE TEXT

May 2023