CYMEVENE® for Intravenous infusion

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Antiviral
ATC code: J05AB06

1.2 Type of Dosage Form

Powder for concentrate for solution for infusion.

1.3 Route of Administration

Intravenous (IV) infusion.

1.4 Sterile/Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: ganciclovir in the form of sodium salt
Each vial of Cymevene contains 543 mg of sterile, freeze-dried ganciclovir sodium equivalent to 500 mg ganciclovir as a white to off-white powder. Reconstitution with 10 mL of sterile Water for Injections BP gives a ganciclovir concentration of 50 mg/mL, pH 11. Further dilution in an appropriate intravenous solution must be performed before infusion (see *2.2 Dosage and Administration*, Method of Administration).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Cymevene is indicated for the treatment of life-threatening or sight-threatening cytomegalovirus (CMV) infections in immunocompromised individuals. These states include acquired immunodeficiency syndrome (AIDS), iatrogenic immunosuppression associated with organ transplantation, or chemotherapy for neoplasia.

Cymevene may also be used for the prevention of CMV disease, specifically in those patients receiving immunosuppressive therapy secondary to organ transplantation.

2.2 Dosage and Administration

Treatment of CMV Infection

Initial (Induction) Treatment. 5 mg/kg infused at a constant rate over 1 hour every 12 hours (10 mg/kg/day) for 14 to 21 days.
Long –term (Maintenance) treatment. For immunocompromised patients at risk of relapse of CMV retinitis a course of maintenance therapy may be given. Intravenous infusion of 6 mg/kg daily 5 days per week, or 5 mg/kg daily 7 days per week is recommended.

Treatment of Disease Progression. Indefinite treatment may be required in patients with AIDS, but event with continued maintenance treatment, patients may have progression of retinitis. Any patient in whom the retinitis progresses, either while on maintenance treatment or because treatment with Cymevene has been withdrawn, may re-treated using the induction treatment regimen.

Prevention of CMV Disease
Induction Regimen: 5 mg/kg infused every 12 hours (10 mg/kg/day) for 7 to 14 days.
Maintenance Regimen: Intravenous infusion of 6 mg/kg daily 5 days per week, or 5 mg/kg 7 days per week is recommended.

Method of Administration
Cymevene must be reconstituted and diluted under the supervision of a healthcare professional and administered as an intravenous infusion (see section 4.2 *Special Instructions for Use, Handling and Disposal*).

Cymevene must only be given by intravenous infusion, preferably via a plastic cannula, into a vein with adequate blood flow. Cymevene infusions must be given using a 5-micron (or smaller) in-line filter. Infusions are recommended to be given over at least one hour, since rapid intrevenous injections may increase the toxicity. Intramuscular or subcutaneous injection may result in severe tissue irritation due to the high pH of the solution.

Administration of Cymevene by intravenous infusion should be accompanied by adequate hydration.

Reconstitution of the vial: Caution should be exercised in the handling of Cymevene (*see Pharmaceutical Precautions*).

1. The contents of the vial should be reconstituted by the addition of 10 mL Water for Injections BP. Do not use bacteriostatic water for injection containing para-hydroxybenzoates, since these are incompatible with ganciclovir and may cause precipitation.
2. The vial should be shaken to dissolve the drug.
3. Reconstituted solution should be inspected for particulate matter; if there is any present, the drug should not be administered.
4. Due to the possibility of crystal formation, the contents of the reconstituted vial should be used immediately. It should not be refrigerated

Infusion solution preparation and administration
Based on patient weigh, the appropriate calculated dose volume should be removed from the vial (ganciclovir concentration 50 mg/mL) and added to 100 mL of a suitable infusion fluid for delivery, using a 5-micron (or smaller) in-line filter, over the course of one hour. Infusion concentrations greater than 10 mg/mL are not recommended. The following infusion fluids are compatible with ganciclovir: Sodium Chloride Intravenous Infusion BP (0.9% w/v); Glucose Intravenous Infusion BP (5% w/v); Compound Sodium Lactate Intravenous Infusion BP; Ringers's Solution for Injection.

Because non-bacteriostatic infusion fluid must be used with Cymevene, the infusion solution must be used within 24 hours of dilution to reduce the risk of bacterial contamination. The infusion solution should be refrigrated. Freezing is not recommended.

2.2.1 Special Dosage Instructions
Patients with renal impairment
For patients with renal insufficiency the inductions dose should be modified as follows:

Serum creatinine (micromole/L)	Dose (mg/kg)	Dosing interval (hours)
<124	5.0	12
125 – 225	2.5	12
226 – 398	2.5	24

>398	1.25	24

The optimal maintenance dose for patients with renal insufficiency is not known.
Patients undergoing dialysis should be given 1.25 mg/kg/24 hours. On days when dialysis is performed the dose should be given shortly after the dialysis session.

Geriatric patients
No studies on the efficacy or safety of Cymevene in geriatric patients have been conducted. Since geriatric individuals often have reduced renal function, Cymevene should be administered to geriatric patients with special consideration for their renal status (see information above located under head title Patients with renal impairment and section *3.2.5 Pharmacokinetics in Special Populations, Geriatric population*).

Pediatric patients
There has been limited clinical experience in treating patients under the age of 12 years. Reported adverse events were similar to those seen in adults.

Cymevene is not indicated for the treatment of congenital or neonatal CMV infections.

See also section *2.5.5 Paediatric Use*

Laboratory monitoring and dosage reductions
Because of individual patient sensitivity to the myelosuppressive effects of Cymevene regular clinical and haematological assessments are recommended. White blood cell and platelet counts should be performed every two days for the first 14 days of treatment. Patients with a history of marrow sensitivity to ganciclovir or other nucleoside analogues, or with white blood cell counts less than 1000 cells/µL at the beginning of treatment should be monitored daily. During maintenance treatment complete blood counts are recommended weekly, or more frequently if counts are low.

Neutropenia typically occurs during the first or second week of treatment. Severe neutropenia (<500 cells /µL) requires a dose interruption. For less severe neutropenia a reduction in the total daily dose may be adequate. Cell counts usually normalize within 3 to 7 days after discontinuing the drug or decreasing the dose. As evidence of marrow recovery becomes apparent gradual increases in dose, with careful monitoring of white blood cell counts, may be appropriate.

2.3 Contraindications
Cymevene is contraindicated in patients with hypersensitivity to ganciclovir, valganciclovir or to any component of the product.

Cymevene is contraindicated in women who are breast feeding.

2.4 Warnings and Precautions
2.4.1 General
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
In animal studies ganciclovir, was found to be mutagenic, teratogenic,carcinogenic, and to impair fertility. Cymevene should therefore be considered a potential teratogen and carcinogen in humans with the potential

to cause birth defects and cancers.

Prior to initiation of ganciclovir treatment, patients should be advised of the potential risks to the fetus and to use contraceptive measures.

Based on clinical and nonclinical studies, Cymevene may cause temporary or permanent inhibition of spermatogenesis (see sections *2.5.1. Females and Males of Reproductive Potential*, *2.5.2 Pregnancy, 2.5.3 Lactation, 2.6 Undesirable effects, 3.3 Nonclinical Safety, and 4.2 Special Instructions for Use, Handling and Disposal*).

Myelosuppression
Cymevene should be used with caution in patients with pre-existing hematological or a history of drug related hematological cytopenia and in patients receiving radiotherapy.

Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anemia have been observed in patients treated with Cymevene.

In a study of 314 AIDS patients there was no relationship between baseline neutrophil count and the occurrence of neutropenia, therefore the risk of neutropenia may not be predicted from pretreatment cell counts. Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µL or the platelet count is less than 25,000 cells/µL or the hemoglobin is less than 8 g/dL (see sections *2.2.1 Special Dosage Instructions* and *2.6 Undesirable Effects*).

Patients being treated with immunosuppressive drugs were more likely to develop lowered platelet counts than patients with AIDS. Patients with platelet count less than 100.000/µL were also at an increased risk of thrombocytopenia.

It is recommended that complete blood counts and platelet counts be monitored in all patients during therapy, particularly in patients with renal impairment (see sections *2.2.1 Special Dosage Instructions and 2.5.4 Pediatric Use*).

In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia, treatment with hematopoietic growth factors and/or the interruption of therapy is recommended (see sections *2.2.1 Special Dosage Instructions* and *2.6 Undesirable Effects*).

Use with other medicines
Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir. Cymevene should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section *2.8 Interactions with other Medicinal Products and other Forms of Interactions*).

Zidovudine and Cymevene each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage (see section *2.8 Interactions with other Medicinal Products and other Forms of Interactions*).

Didanosine plasma concentrations may increase during concomitant use with Cymevene. Therefore, patients should be closely monitored for didanosine toxicity (see section *2.8 Interactions with other Medicinal Products and other Forms of Interactions*).

Concomitant use of other drugs that are known to be myelosuppressive or associated with renal impairment with Cymevene may result in added toxicity (see section 2.*8 Interactions with other Medicinal Products*

and other Forms of Interactions).

Administration of Cymevene by intravenous infusion should be accompanied by adequate hydration, since Cymevene is excreted by the kidneys and normal clearance depends upon adequate renal function if renal function is impaired, dosage adjustment are required. Such adjustment should be based on serum creatinine (see section *2.2 Dosage and Administration*).

2.4.2 Drug Abuse and Dependence
No information is available for drug abuse and dependence with Cymevene.

2.4.3 Ability to Drive and Use Machines
No studies on the effect on the ability to drive and use machines have been performed.

Based on the adverse reaction profile, ganciclovir may have a major influence on the ability to drive and use machines.

Adverse reactions, for example seizure, dizziness, and confusion may occur in patients receiving Cymevene (see section 2.6 Undesirable Effects).

If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

2.5 Use in Special Populations
2.5.1 Females and Males of Reproductive Potential
Fertility
In animal studies ganciclovir was found to impair fertility (see section 3.3.3 Impairment of Fertility). In a clinical study renal transplant patients receiving Valcyte (which is a pro-drug of Cymevene) for CMV prophylaxis for up to 200 days were compared to an untreated control group. Spermatogenesis was inhibited during treatment with Valcyte. At follow-up, approximately six months after treatment discontinuation, the mean sperm density in treated patients was comparable to that observed in the untreated control group. In Valcyte treated patients, all patients with normal sperm density (n=7) and 8/13 patients with low sperm density at baseline, recovered to normal counts after treatment cessation. In the control group, all patients with normal sperm density (n=6) and 2/4 patients with low sperm density at baseline, had normal density at the end of follow-up.

Contraception
Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment with Cymevene. Sexually active men are recommended to use condoms during and for at least 90 days after cessation of treatment with Cymevene, unless it is certain that the female partner is not at risk of becoming pregnant (see sections *2.4.1 Warnings and Precautions, General* and *3.3.4 Nonclinical Safety, Reproductive Toxicity*).

2.5.2 Pregnancy

In animal studies, ganciclovir was associated with reproductive toxicity and teratogenicity (see sections *3.3.3 Impairment of Fertility and 3.3.4 Nonclinical Safety, Reproductive Toxicity*).

The safety of Cymevene in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. The use of Cymevene should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the fetus.

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

2.5.3 Lactation

Adverse effects were observed in the offspring of lactating animals. Peri- and postnatal development has not been studied with ganciclovir but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats. Therefore, CYMEVENE should not be given to lactating mothers. Nursing should not be resumed until 72 hours after the last dose of Cymevene.

2.5.4 Pediatric Use

The use of Cymevene in pediatric patients warrants caution due to the potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should outweigh the risks.

See sections *2.2.1 Special Dosage Instructions*, *3.2.5 Pharmacokinetics in Special Populations* and 3.3 Nonclinical Safety.

2.5.5 Geriatric Use

See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*.

2.5.6 Renal Impairment

In patients with renal impairment, dosage adjustments based on creatinine clearance are required (see sections *2.2.1 Special Dosage Instructions* and 3.2.5 *Pharmacokinetics in Special Populations*)

2.5.7 Hepatic Impairment

The safety and efficacy of Cymevene have not been studied in patients with hepatic impairment (see sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*).

2.6 Undesirable Effects

2.6.1 Clinical Trials

Valganciclovir is a pro-drug of ganciclovir, and adverse reactions associated with valganciclovir can be expected to occur with ganciclovir. Therefore, adverse drug reactions reported with IV or oral ganciclovir (no longer available) or with valganciclovir are included in the table of adverse reactions (see Table 1).

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

The frequencies presented in the table of adverse reactions are derived from a pooled population of HIVinfected patients (n=1704) receiving maintenance therapy with ganciclovir (GAN1697, GAN1653, GAN2304, GAN1774, GAN2226, AVI034, GAN041) or valganciclovir (WV15376, WV15705). Exception is made for agranulocytosis, granulocytopenia and anaphylactic reaction; the frequencies of which are derived from post-marketing experience. Frequencies are presented as percentages and as CIOMS frequency categories defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

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

candida infections, depression, severe neutropenia (ANC < 500 µL) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction is reported more frequently in organ transplant recipients.

Table 1. Frequency of Ganciclovir/Valganciclovir ADRs Reported in HIV Patients Receiving Maintenance Therapy (n=1704).

ADR (MedDRA) System Organ Class	**Percentage**	**Frequency Category**
Infections and infestations:		
Candida infections including oral candidiasis	22.42%	Very common
Upper respiratory tract infection	16.26%	
Sepsis	6.92%	Common
Influenza	3.23%	
Urinary tract infection	2.35%	
Cellulitis	1.47%	
Blood and lymphatic disorders:		
Neutropenia	26.12%	Very Common
Anemia	19.89%	
Thrombocytopenia	7.34%	Common
Leukopenia	3.93%	
Pancytopenia	1.06%	
Bone marrow failure	0.29%	Uncommon
Aplastic anemia	0.06%	Rare
Agranulocytosis*	0.02%	
Granulocytopenia*	0.02%	
Immune system disorders:		
Hypersensitivity	1.12%	Common
Anaphylactic reaction*	0.02%	Rare
Metabolic and nutrition disorders:		
Decreased appetite	12.09%	Very Common
Weight decreased	6.46%	Common
Psychiatric disorders:		
Depression	6.69%	Common
Confusional state	2.99%	
Anxiety	2.64%	
Agitation	0.59%	Uncommon
Psychotic disorder	0.23%	
Thinking abnormal	0.18%	
Hallucinations	0.18%	
Nervous system disorders:		
Headache	17.37%	Very common
Insomnia	7.22%	Common
Neuropathy peripheral	6.16%	
Dizziness	5.52%	
Paraesthesia	3.58%	

Hypoaesthesia	2.58%	
Seizures	2.29%	
Dysgeusia (taste disturbance)	1.35%	
Tremor	0.88%	Uncommon
Eye disorders:		
Visual impairment	7.10%	Common
Retinal detachment**	5.93%	
Vitreous floaters	3.99%	
Eye pain	2.99%	
Conjunctivitis	1.58%	
Macular edema	1.06%	
Ear and labyrinth disorders:		
Ear pain	1.17%	Common
Deafness	0.65%	Uncommon
Cardiac disorders:		
Arrhythmia	0.47%	Uncommon
Vascular disorders:		
Hypotension	2.05%	Common
Respiratory, thoracic and mediastinal disorders:		
Cough	18.31%	Very common
Dyspnoea	11.80%	
Gastrointestinal disorders:		
Diarrhea	34.27%	Very common
Nausea	26.35%	
Vomiting	14.85%	
Abdominal pain	10.97%	
Dyspepsia	4.81%	Common
Flatulence	4.58%	
Abdominal pain upper	4.58%	
Constipation	3.70%	
Mouth ulceration	3.17%	
Dysphagia	2.93%	
Abdominal distention	2.41%	
Pancreatitis	1.64%	
Hepato-biliary disorders:		
Blood alkaline phosphatase increased	3.58%	Common
Hepatic function abnormal	3.23%	
Aspartate aminotransferase increased	1.88%	
Alanine aminotransferase increased	1.23%	
Skin and subcutaneous tissues disorders:		
Dermatitis	11.80%	Very common
Night sweats	7.92%	Common
Pruritus	4.58%	
Rash	2.52%	
Alopecia	1.29%	
Dry skin	0.94%	Uncommon
Urticaria	0.70%	
Musculo-skeletal and connective tissue disorders:		
Back pain	4.46%	Common

Myalgia	3.52%	
Arthralgia	3.35%	
Muscle spasms	2.99%	
Renal and urinary disorders:		
Renal impairment	2.52%	Common
Creatinine clearance renal decreased	2.35%	
Blood creatinine increased	1.88%	
Renal failure	0.76%	Uncommon
Hematuria	0.70%	
Reproductive system and breast disorders:		
Infertility male	0.23%	Uncommon
General disorders and administration site conditions:		
Pyrexia	33.51%	Very common
Fatigue	18.96%	
Injection site reaction	6.98%	Common
Pain	5.81%	
Chills	5.40%	
Malaise	2.11%	
Asthenia	2.00%	
Chest pain	0.88%	Uncommon

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

Description of selected adverse reactions
Neutropenia
The risk of neutropenia is not predictable on the basis of the number of neutrophils before treatment. Neutropenia usually occurs during the first or second week of induction therapy. The cell count usually normalizes within 2 to 5 days after discontinuation of the drug or dose reduction (see section *2.4 Warnings and Precautions*).

Thrombocytopenia
Patients with low baseline platelet counts (< 100,000/µL) have an increased risk of developing thrombocytopenia. Patients with iatrogenic immunosuppression due to treatment with immunosuppressive drugs are at greater risk of thrombocytopenia than patients with HIV (see section *2.4 Warnings and Precautions*). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Laboratory Abnormalities
Laboratory abnormalities in HIV infected patients
Laboratory abnormalities reported from three clinical trials in HIV infected patients receiving intravenous ganciclovir as maintenance treatment for CMV retinitis are listed below in Table 2. One hundred seventynine patients were eligible for the laboratory abnormality analysis.

Table 2. Laboratory abnormalities

Laboratory abnormalities	**N=179**
Neutropenia (ANC /mm3)	

< 500	25.1%
500 – < 750	14.3%
750 – < 1000	26.3%
Anemia (hemoglobin g/dL)	
< 6.5	4.6%
6.5 – < 8.0	16.0%
8.0 – < 9.5	25.7%
Thrombocytopenia (platelets/mm3)	
< 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%

2.6.1 Post Marketing
Safety reports from post-marketing setting are consistent with safety data from clinical trials with ganciclovir and valganciclovir (see section 2.6.1 Undesireable Effects, Table 1).

2.7 Overdose
Overdose experience with intravenous ganciclovir
Reports of overdoses with intravenous 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:
– Hematological toxicity: myelosuppression including pancytopenia, bone marrow failure, medullary aplasia, leukopenia, neutropenia, granulocytopenia
– Hepatotoxicity: hepatitis, liver function disorder
– Renal toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine.
– Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting
– Neurotoxicity: generalized tremor, seizure

Hemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of ganciclovir (see section *3.2.5 Pharmacokinetics in Special Populations*).

Toxic manifestations seen in animals given very high single intravenous doses of ganciclovir (500 mg/kg) included emesis, hypersalivation, anorexia, bloody diarrhoea, inactivity, cytopenia, abnormal liver function tests and blood urea nitrogen (BUN), testicular atrophy and death.

Overdose experience with valganciclovir
One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patients degree of renal impairment (decreased creatinine clearance).

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction
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 nucleoside analogues (e.g. zidovudine, didanosine, stavudine), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vincristine, vinblastine, hydroxyurea), and antiinfectives

(e.g. trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these drugs should only be considered for concomitant use with ganciclovir if the potential benefits outweigh the potential risks (see section *2.4.1 Warnings and Precautions, General*).

It is also possible that drugs which inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogenia, and germinal layers of skin and gastro-intestinal mucosa might have combined additive toxic effects when used concomitantly with, before, or after Cymevene.

Imipenem-cilastatin
Convulsions have been reported in patients who received ganciclovir and imipenem-cilastatin concomitantly and a pharmacodynamic interaction between these two drugs cannot be discounted. These drugs should not be used concomitantly unless the potential benefits outweigh the risks (see section *2.4.1 Warnings and Precautions, General*).

Zidovudine
Both zidovudine and Cymevene have the potential to cause neutropenia and anemia. A pharmacodynamic interaction may occur during concomitant administration of these drugs and some patients may not tolerate concomitant therapy at full dosage (see section 2.4.1 Warnings and Precautions, General). In addition, data from a small number of patients studied to date indicate that maintenance ganciclovir treatment plus zidovudine at the recommended dose resulted in severe neutropenia in most individuals.

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, confirming a pharmacokinetic interaction during the concomitant administration of these drugs. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis) (see section *2.4.1 Warnings and Precautions, General*).

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

It is possible that other drugs which also inhibit renal tubular secretion or resorption may reduce renal clearance of ganciclovir and could increase the plasma half-life of ganciclovir.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Ganciclovir (9-(1,3-dihydroxy-2-propoxymethyl guanine) is a synthetic analogue of 2'-deoxyguanosine which inhibits replication of herpes viruses in vitro and in vivo. Sensitive human viruses include human cytomegalovirus (HCMV), herpes-simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6, -7 and -8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus. However, clinical studies have been limited to assessment 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 metabolized intracellularly. This has been shown to occur in HSV- and HCMV-infected cells with half-lives of 18 and between 6 and 24 hours respectively after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation

of ganciclovir occurs preferentially in virus-infected cells.

In CMV- infected cells there is approximately a 10-fold increased concentration of both cellular kinases and ganciclovir triphosphate. Thus, there is a preferential phosphorylation of ganciclovir in virus-infected cells. In such cells ganciclovir triphosphate is metabolized slowly, with 60 to 70% remaining 18 hours after removal of ganciclovir from the extracellular fluid.

The virustatic activity of ganciclovir is due to 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. Typical anti-viral IC_{50} against CMV *in vitro* is in the range 0.14 µM (0.04 µg/mL) to 14 µM (3.5 µg/mL).

3.1.2 Clinical/Efficacy Studies
No text on clinical studies

Viral resistance
Emergence of viral resistance has been reported based on in vitro sensitivity testing of CMV isolates from patiens receiving Cymevene treatment.

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 crossresistance to other antivirals targeting the viral polymerase, and vice versa. Amino acid substitutions in UL54 conferring cross-resistance to ganciclovir and cidofovir are generally located within the exonuclease domains and region V, however amino acid substitutions conferring cross-resistance to foscarnet are diverse, but concentrate at and between regions II (codon 696-742) and III (codon 805-845).

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

3.1.3 Immunogenicity
Not applicable.

3.2 Pharmacokinetic Properties

The pharmacokinetics of IV ganciclovir is linear over the range of 1.6-5.0 mg/kg.

The systemic exposure (AUC0-∞) 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 µg.h/mL (CV% 40). In this patient population, peak plasma concentration (Cmax) was on average 12.2 µg/mL (CV% 24).

3.2.1 Absorption
Not applicable

3.2.2 Distribution
For IV ganciclovir, the volume of distribution is correlated with body weight with values for the steady

state volume of distribution ranging from0.54 to 0.87 L/kg. Ganciclovir penetrates the cerebrospinal fluid, and diffuses across the placenta... Binding to plasma proteins was 1% - 2% over ganciclovir concentrations of 0.5 and 51 µg/mL.

3.2.3 Metabolism
Ganciclovir is not metabolized to a significant extent.

3.2.4 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, 89.6 ±5.0% (N=4) of IV administered ganciclovir was recovered unmetabolized in the urine within 24 hours. In patients with normal renal function, systemic clearance ranged from 2.64 ±0.38 (N=15) to 4.52 ±2.79 (N=6) mL/min/kg and renal clearance ranged from 2.57 ±0.69 (N=15) to 3.48 ±0.68 (N=20) mL/min/kg, corresponding to 90% - 101% of administered ganciclovir. Half-lives in patients without renal impairment ranged from 2.73 ±1.29 (N=6) to 3.98 ±1.78 (N=8) hours.

3.2.5 Pharmacokinetics in Special Populations
Pediatric population
Ganciclovir pharmacokinetics were studied in 27 neonates aged 2 to 49 days at intravenous doses of 4 mg/kg (N=14) and 6 mg/kg (N=13). Mean C_{max} was 5.5 ±6 µg/mL and 7.0 ±1.6 µg/mL the lower and higher dose levels respectively. Mean values for Vss (0.7 L/kg) and systemic clearance (3.15 ±0.47 mL/min/kg at 4 mg/kg and 3.55 ±0.35 mL/min/kg at 6 mg/kg) were comparable to those observed in adults with normal renal function.

Ganciclovir pharmacokinetics were also studied in 10 children with normal renal function, aged 9 months to 12 years. The pharmacokinetic characteristics of ganciclovir were the same after single and multiple (q12h) IV doses (5 mg/kg). Exposure as measured by mean AUC_{∞} on days 1 and 14 were 19.4 ±7.1 and 24.1 ±14.6 µg.h/mL respectively and the corresponding Cmax values were 7.59 ±3.21 (day 1) and 8.31±4.9 µg/mL (day 14). These range of exposures are comparable to those observed in adults. The steady state volume of distribution after a single dose on day 1 and at the end of the repeat dose period (day 14) was 0.68 ± 020 L/kg. Systemic clearance for the same study days was 4.66 ±1.72 (day 1) and 4.86 ±2.96 mL/min/kg (day 14). The respective mean values for renal clearance (0 – 12 h) were 3.49 ±2.40 on day 1 and 3.49 ±1.19 mL/min/kg on day 14. The corresponding mean values for the half-life were 2.49 ±0.57 (day 1) and 2.22 ±0.76 h (day 14). The pharmacokinetics of ganciclovir from this study were consistent with those in neonates and adults.

Geriatric Population
No ganciclovir pharmacokinetic studies have been conducted in adults older than 65 years of age. However, because ganciclovir is mainly excreted by renal and since renal clearance decreases with age, a decrease in ganciclovir total body clearance and prolongation of ganciclovir elimination half-life can be anticipated in the elderly (see section *2.2.1 Special Dosage Instructions*).

Renal impairment
The total body clearance of ganciclovir is linearly correlated with creatinine clearance. In patients with mild, moderate, and severe renal impairment, mean systemic clearances of 2.1, 1.0 and 0.3 mL/min/kg were observed. Patients with renal impairment show an increased elimination half-life. In patients with severe renal impairment elimination half-life was increased by 10-fold (see section *2.2.1 Special Dosage Instructions, Renal impairment).*

The major route of excretion of ganciclovir is via glomerular filtration of the unchanged drug. In patients with normal renal function the plasma half-life of ganciclovir following a 1-hour IV infusion of 5 mg/kg averaged 2.9 hours with a mean systemic clearance of 3.64 mL/min/kg.

Twice- daily administration of 5 mg/kg for 14 days did not cause accumulation in plasma. Renal impairment leads to altered kinetics of ganciclovir as indicated below.

	Ganciclovir	
Serum creatinine (micromol/L)	Systemic plasma clearance (mL/min/kg)	Plasma half-life (hours)
<124 (n=22)	3.64	2.9
125 – 225 (n=9)	2.01	5.3
226 – 398 (n=3)	1.11	9.7
>398	0.33	28.5

Patients undergoing hemodialysis
Plasma concentrations of ganciclovir are reduced by about 50% during a 4-hour hemodialysis session (see section *2.7 Overdose*).

During intermittent hemodialysis, 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 hemodialysis, 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 (see section 3.2.5 Pharmacokinetics Properties, Elimination).

3.3 Nonclinical Safety
3.3.1 Carcinogenicity
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.

3.3.2 Genotoxicity
Ganciclovir was mutagenic in mouse lymphoma cells and clastogenic in mammalian cells.

3.3.3 Impairment of Fertility
Ganciclovir causes impaired fertility and teratogenicity in animals (see section *2.4 Warnings and Precautions*).
Based upon animals studies where aspermia was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir could cause inhibition of human spermatogenesis (see section 2.5.1 *Females and Males of Reproductive Potential*).

3.3.4 Reproductive Toxicity
Ganciclovir causes teratogenicity in animals.

3.3.5 Other

No additional information is available.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Store below 30°C.
This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 Special Instructions for Use, Handling and Disposal

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 (see section *2.4 Warnings and Precautions*). 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. For eye exposure, rinse eyes thoroughly with plain water.

Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the vials and the table after reconstitution.

Incompatibilities
Cymevene should not be mixed with other IV products.

Preparation of Cymevene reconstituted solution

1. Lyophilized Cymevene should be reconstituted by injecting 10 mL of sterile water for injection into the vial. Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), since these are incompatible with Cymevene sterile powder and may cause precipitation.
2. The vial should be gently swirled in order to ensure complete wetting of the product. Continue swirling until a clear reconstituted solution is obtained. Reconstituted solution should be inspected for particulate matter prior to proceeding with admixture preparation.
3. 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.

Preparation of Cymevene infusion solution
Based on patient weight, the appropriate calculated dose volume should be removed from the Cymevene vial (concentration 50 mg/mL) and added to an acceptable infusion fluid.
Normal saline, dextrose 5% in water, Ringer's or lactated Ringer's solution are determined chemically or physically compatible with Cymevene. Infusion concentrations greater than 10 mg/mL are not recommended.

From a microbiological perspective, because Cymevene is reconstituted with nonbacteriostatic sterile water, the infusion solution should be used as soon as possible. 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.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.

- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Dispose of the full container and of the administration system according to local requirements.

Medicine: Keep out of reach of children
Obat: Jauhkan dari jangkauan anak-anak
On Medical Prescription Only
Harus dengan resep dokter

PACK
Box1 vial Reg No:

Manufactured by
BSP Pharmaceuticals S.p.A., Via Appia Km. 65, 561,
04013 Latina Scalo LT, Italy

for CHEPLAPHARM Arzeinmittel GmbH, Ziegelhof 24,
17489 Greifswald, Germany

Registered by:
PT. Pyridam Farma Tbk.
Kabupaten Cianjur, Indonesia

PI version date	
BPOM approval date	
Description of change	
CDS version reference	: 5.0 (September 2020)