SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

CYMEVENE® Freeze dried powder

COMPOSITION

Each vial of CYMEVENE sterile powder contains 546 mg of sterile freeze dried ganciclovir sodium equivalent to 500 mg ganciclovir

PHARMACOLOGICAL CLASSIFICATION

A 20.2.8 - Antiviral agents

PHARMACOLOGICAL 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 herpes virus 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 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 of ganciclovir 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 hours and between 6 and 24 hours respectively after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

The virustatic activity of ganciclovir is due to the inhibition of viral DNA synthesis by ganciclovir triphosphate competitively inhibiting the incorporation of deoxyguanosine triphosphate into DNA, by DNA polymerase and 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)

The current working definition of CMV resistance to ganciclovir, based on *in vitro* assays, is a median inhibitory concentration (IC_{50}) > 1,5 µg/mℓ (6,0 µM). CMV resistance to ganciclovir is uncommon (~ 1 %). It has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. During the first 6 months of treatment for CMV retinitis with CYMEVENE *IV*, viral resistance is detected in 3 % to 8 % of patients. Most patients with worsening CMV retinitis while on treatment do not shed resistant CMV. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with CYMEVENE *IV.* In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.

The possibility of viral resistance should be considered in patients who repeatedly show poor clinical response or experience persistent viral excretion during therapy. The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate moiety; resistant viruses have been described that contain mutations in the UL97 gene of CMV that controls phosphorylation of ganciclovir. Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir, and virus with this mutation may be resistant to other CMV drugs.

Pharmacokinetics

Absorption: The systemic exposure (AUC_{0-24}) reported following dosing with a single 1-hour ***IV*** **infusion** of 5 mg/kg ganciclovir in HIV^+/CMV^+ patients or in adult AIDS patients ranged from 21,4 ± 3,1 (N = 16) to 26,0 ± 6,06 (N = 16) µg.h/mℓ. In this patient population peak plasma concentration (C_{max}) ranged from 7,59 ± 3,21 (N = 10), 8,27 ± 1,02 (N = 16) to 9,03 ± 1,42 (N = 16) µg/mℓ.

Distribution: For *IV* ganciclovir, volume of distribution is correlated with body weight with values for the steady state volume of distribution ranging from 0,536 ± 0,078 (N = 15) to 0,870 ± 0,116 (N = 16) ℓ/kg**.** Cerebrospinal fluid concentrations obtained 0,25 - 5,67 hours postdose in 2 patients who received 2,5 mg/kg ganciclovir *IV* eight or twelve hourly, ranged from 0,31 - 0,68 µg/mℓ, representing 24 - 70 % of the respective plasma concentrations.

Elimination: When administered *IV*, ganciclovir exhibits linear pharmacokinetics over the range of 1,6 - 5,0 mg/kg and when administered orally, ganciclovir exhibits linear kinetics up to a total daily dose of 4 g/day, provided each unit dose does not exceed 1 g. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination. In patients with normal renal function, 91,3 ± 5,0 % of *IV* administered

ganciclovir was recovered unmetabolised in the urine. In subjects with normal renal function, 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).

Pharmacokinetics in special populations:

Patients with renal impairment: Both plasma half-life as well as peak plasma levels of ganciclovir are increased in patients with a decreased creatinine clearance. Dosage adjustments based on creatinine clearance are necessary in patients with impairment of renal function.

Patients undergoing haemodialysis: Haemodialysis reduces plasma concentrations of ganciclovir by about 50 % after *IV* administration.

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 – 63 %.

Elderly: No studies have been conducted in adults older than 65 years of age.

Children: The pharmacokinetics of *IV* ganciclovir in neonates and children are similar to those observed in adults.

INDICATIONS

CYMEVENE vials are indicated for the prevention and treatment of life-threatening or sight-threatening cytomegalovirus disease (CMV) in immuno-compromised individuals and for the prevention of CMV disease in transplant recipients.

CONTRA-INDICATIONS

- Pregnancy and lactation.
- Patients with known hypersensitivity to ganciclovir, valganciclovir or to any component of the product. Due to the similarity of the chemical structure of CYMEVENE and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these drugs is possible.

- Absolute neutrophil count less than 500 cells/µℓ, platelet count less than 25 000 cells/µℓ, haemoglobin less than 8 g/dℓ. (see WARNINGS, Special dosage instructions and Precautions.)
- CYMEVENE is not indicated for the treatment of congenital or neonatal CMV infections.
- Treatment with myelosuppressive medicines.

WARNINGS

- Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with CYMEVENE. Therapy should not be initiated or continued if the absolute neutrophil count is less than 500 cells/µℓ or the platelet count is less than 25 000 cells/µℓ, or the haemoglobin is less than 8 g/dℓ (see CONTRA-INDICATIONS, Special dosage instructions and Precautions).
- *Effects on ability to drive and use machines:* Convulsions, sedation, dizziness, ataxia, 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.
- *Impairment of fertility:* In animal studies ganciclovir was found to be mutagenic, teratogenic and carcinogenic. CYMEVENE should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. Temporary and permanent inhibition of spermatogenesis in male animals and permanent suppression of fertility in female animals have occurred. Because of the teratogenicity observed in animals, women of childbearing potential should use effective contraception during treatment. Men should be advised to practice barrier contraception during treatment and for 90 days following treatment.

INTERACTIONS

Binding of CYMEVENE to plasma proteins is only about 1 to 2 % and drug interactions involving binding site displacement are not anticipated.

Probenecid: Probenecid, given with oral ganciclovir, resulted in 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.

Zidovudine: When zidovudine was given in the presence of oral ganciclovir, there was a small (17 %) but statistically significant increase in the AUC of zidovudine. There was also a trend towards lower ganciclovir concentrations when administered with zidovudine, although this was not statistically significant. However, since both zidovudine

and CYMEVENE have the potential to cause neutropenia and anaemia, some patients may not tolerate concomitant therapy at full dosage (see Precautions).

Didanosine: Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both intravenous and oral). At ganciclovir oral doses of 3 and 6 g/day, an increase in the AUC of didanosine ranging from 38 to 67 % has been observed. This increase cannot be explained by competition for renal tubular secretion, as there was an increase in the percentage of didanosine dose excreted. This increase could arise from either increased bioavailability or decreased metabolism. There was no clinically significant effect on ganciclovir concentrations. However, given the increase in didanosine plasma concentrations in the presence of ganciclovir, patients should be closely monitored for didanosine toxicity (e.g. pancreatitis) (see Precautions).

Imipenem-cilastatin: Convulsions have been reported in patients taking CYMEVENE and imipenem-cilastatin concomitantly. These drugs should not be used concomitantly.

Zalcitabine: Zalcitabine increased the AUC_{0-8} of oral ganciclovir by 13 %. There were no statistically significant changes in any of the other pharmacokinetic parameters assessed. Additionally, there were no clinically relevant changes in zalcitabine pharmacokinetics in the presence of oral ganciclovir, although a small increase in the elimination rate constant was observed.

Trimethoprim: Trimethoprim statistically significantly decreased the renal clearance of oral ganciclovir by 13,3 % and this was associated with a statistically significant decrease in the terminal elimination rate and corresponding increase in half-life by 15 %. However, these changes are unlikely to be clinically significant, as AUC_{0-8} and C_{max} were unaffected. The only statistically significant change in trimethoprim pharmacokinetic parameters when co-administered with ganciclovir, was an increase in C_{max}. However, this is unlikely to be of clinical significance and no dose adjustment is recommended

Cyclosporin: There was no evidence that introduction of ganciclovir affects the pharmacokinetics of cyclosporin based on the comparison of cyclosporin trough concentrations. However, there was some evidence of increases in the maximum serum creatinine value observed following initiation of ganciclovir therapy.

Mycophenolate mofetil: Based on the results of a single dose administration study of recommended doses of *IV* ganciclovir and oral mycophenolate and the known effects of renal impairment on the pharmacokinetics of ganciclovir and mycophenolate, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in ganciclovir concentration and MPAG (inactive metabolite of mycophenolate). No substantial alteration of MPA (active metabolite of mycophenolate)

pharmacokinetics is anticipated and mycophenolate adjustment is not required. In patients with renal impairment in which ganciclovir and mycophenolate are co-administered, the dose recommendations for ganciclovir should be observed and patients carefully monitored.

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 (such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, nucleoside analogues and hydroxyurea). Therefore, these drugs should be considered for concomitant use with ganciclovir only if the potential benefits outweigh the potential risks (see Precautions**)**.

PREGNANCY AND LACTATION

CYMEVENE is contra-indicated in pregnancy and lactation. Please refer to CONTRA-INDICATIONS and WARNINGS.

DOSAGE AND DIRECTIONS FOR USE

Because of individual patient variations in the clinical response to CMV infections and the sensitivity to the myelosuppressive effects of CYMEVENE, the treatment of each patient should be considered individually. Changes in dose should be based on regular clinical and haematological assessment. Due to the myelosuppressive nature of CYMEVENE, it is recommended that white blood cell counts be performed every two days for the first fourteen days of CYMEVENE administration.

Standard IV dosage for treatment of CMV retinitis

Induction treatment: 5 mg/kg infused intravenously at a constant rate, over one hour, every 12 hours (10 mg/kg/day) for 14 to 21 days for patients with normal renal function.

Maintenance treatment: 5 mg/kg given as an *IV* infusion over one hour, once daily for 7 days per week or 6 mg/kg once daily for 5 days per week.

Treatment of disease progression: Indefinite treatment may be required in patients with AIDS, but even with continued maintenance treatment, patients may have progression of retinitis. If this occurs, patients should be given the induction treatment again.

Standard IV dosage for prevention in transplant recipients

Induction treatment: 5 mg/kg given as an *IV* infusion over one hour, every 12 hours for 7 - 14 days in patients with normal renal function.

Maintenance treatment: 5 mg/kg given as an *IV* infusion over one hour, once daily for 7 days per week or 6 mg/kg once daily for 5 days per week.

Reconstitution of the vial

1. The contents of the vial should be reconstituted by the addition of 10 mℓ sterile water for injection immediately before being used for preparation of the infusion solution. Do not use bacteriostatic water for injection containing parahydroxybenzoates, since these are incompatible with ganciclovir sterile powder and may cause precipitation.
2. The vial should be shaken to dissolve the drug.
3. Reconstituted solution should be inspected for particulate matter prior to proceeding with admixture preparation.
4. Reconstituted solution in the vial is stable at room temperature for 12 hours (i.e. the appropriate dose-volume must be removed from the vial and added to the infusion bag within 12 hours). It should not be refrigerated.

Preparation and administration of infusion solution

Based on patient weight and therapeutic indication, the appropriate calculated dose-volume should be removed from the vial (ganciclovir concentration 50 mg/mℓ) and added (normally 100 mℓ) to a suitable infusion fluid 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 ganciclovir:

1. Sodium chloride intravenous infusion (0,9 % w/v).
2. Dextrose 5 % in water.
3. Ringer's or lactated Ringer's solution.

CYMEVENE should not be mixed with other *IV* products. The infusion solution containing the reconstituted CYMEVENE should be used within 24 hours of adding the dose-volume from the reconstituted vial to infusion bag. This infusion solution should be refrigerated. Freezing is not recommended.

Caution - Do not administer by rapid bolus or *IV* injection. The toxicity of CYMEVENE may be increased as a result of excessive plasma levels.

Caution - *IM* or *SC* injection may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions.

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

Special IV dosage instructions

a) Patients with renal impairment: If renal function is impaired, dosage adjustments are required, as shown in the table below. Creatinine clearance can be related to serum creatinine by the following formulae:

For males = $\frac{(140 - \text{age in years}) \times \text{body weight in kg}}{72 \times (0{,}011 \times \text{serum creatinine [µmol/ℓ]})}$

For females = 0,85 x male value

Creatinine clearance (mℓ/min)	**Induction dose**	**Maintenance dose**
≥ 70 mℓ/min	5,0 mg/kg, 12 hourly	5,0 mg/kg/day
50 - 69 mℓ/min	2,5 mg/kg, 12 hourly	2,5 mg/kg/day
25 - 49 mℓ/min	2,5 mg/kg, daily	1,25 mg/kg/day
10 - 24 mℓ/min	1,25 mg/kg/day	0,625 mg/kg/day
< 10 mℓ/min	1,25 mg/kg 3 x a week after haemodialysis	0,625 mg/kg 3 x a week after haemodialysis

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

b) Patients with leukopenia, severe neutropenia, anaemia and thrombocytopenia: Severe leucopenia neutropenia, anaemia, thrombocytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with ganciclovir.

c) Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µℓ, or the haemoglobin is less than 8 g/dℓ (see CONTRA-INDICATIONS, WARNINGS and Precautions)

d) Elderly: Since elderly individuals often have reduced renal function, CYMEVENE should be administered to elderly patients with special consideration of their renal status.

e) *Children:* Safety and efficacy of ganciclovir in paediatrics have not been established, including the use for the treatment of congenital or neonatal CMV infections. The use of CYMEVENE in children warrants extreme caution due to potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should outweigh the risks.

Handling instructions

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

HIV infected patients

Experience with intravenous/oral ganciclovir: The safety of intravenous and oral ganciclovir in AIDS patients was studied in several clinical trials. The pooled safety information of the use of intravenous ganciclovir and oral ganciclovir (3 g daily per *os*) in the treatment of CMV disease in HIV infected patients 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 that occurred in equal to or more than 2 % of patients taking intravenous or oral ganciclovir, regardless of causal relationship or seriousness, but which occurred in higher frequency in the intravenous ganciclovir arm compared to the control arm are summarised in the Table 1.

Table 1. Percentage of patients with adverse events occurring at a frequency of equal to or more than 2 % of patients receiving oral/intravenous ganciclovir

Body systems Adverse events	**Oral ganciclovir** N = 536	***IV* ganciclovir** N = 412	**Control** N = 119
Blood and lymphatic system			
Neutropenia	22,6 %	25,7 %	11,8 %
Anaemia	17,2 %	19,7 %	16,8 %
Thrombocytopenia	6,9 %	6,6 %	5,0 %
Leucopenia	3,4 %	3,2 %	0,8 %
Lymphadenopathy	-	2,9 %	1,7 %

Gastrointestinal system			
Diarrhoea	31,2 %	26,5 %	24,4 %
Nausea	24,6 %	-	21,8 %
Vomiting	12,9 %	-	12,6 %
Abdominal pain	9,5 %	9,0 %	7,6 %
Flatulence	3,5 %	-	1,7 %
Oesophageal candidiasis	2,6 %	-	1,7 %
Dysphagia	2,2 %	2,7 %	1,7 %
Loose stools	2,4 %	-	1,7 %
Oesophageal candidiasis	-	2,2 %	1,7 %
Body as a whole			
Pyrexia	-	35,9 %	35,3 %
Candida	6,2 %	10,4 %	4,2 %
Injection site infection	-	8,0 %	0,8 %
Sepsis	-	6,1 %	3,4 %
Sepsis, secondary	-	5,8 %	-
Anorexia	5,8 %	4,9 %	-
Mycobacterium avium complex	5,0 %	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 %	-
Malaise	2,6 %	-	0,8 %
Asthenia	2,4 %	-	0,8 %
Toxoplasmosis	3,5 %	-	-
Central and peripheral nervous system			
Confusion	4,7 %	-	2,5 %
Hypoesthesia	2,1 %	3,2 %	1,7 %
Anxiety	-	2,4 %	1,7 %
Skin and appendages			
Pruritis	4,7 %	3,2 %	2,5 %
Respiratory system			
Cough	-	16,0 %	15,1 %
Pneumocystis carinii pneumonia	6,3 %	7,3 %	2,5 %
Productive cough	3,5 %	3,6 %	2,5 %
Upper respiratory tract infection	2,4 %	-	0,8 %
Sinus congestion	3,7 %	3,4 %	2,5 %
Lower respiratory tract infections	2,2 %	-	1,7 %
Special senses			
Taste disturbance	2,1 %	-	-
Metabolic and nutritional disorders			
Blood alkaline phosphatase increased	4,5 %	4,4 %	4,2 %
Blood creatinine increased	2,1 %	3,2 %	1,7 %

Urogenital system			
Creatinine renal clearance decreased	2,4 %		-
Musculoskeletal system			
Arthralgia	-	2,4 %	1,7 %

Laboratory abnormalities in HIV-infected patients

Laboratory abnormalities reported from 3 clinical trials in HIV-infected patients receiving oral/intravenous ganciclovir (326 and 179 patients, respectively) as maintenance treatment for CMV retinitis are listed below.

Table 2. Laboratory abnormalities

	Oral ganciclovir N = 326	***IV* ganciclovir** N = 179
Neutropenia: ANC/mm³		
< 500	18,4 %	25,1 %
500 - < 750	16,6 %	14,3 %
750 - < 1 000	19,1 %	26,3 %
Anaemia: Haemoglobin g/dℓ		
< 6,5	1,6 %	4,6 %
6,5 - < 8,0	10,0 %	16,0 %
8,0 - < 9,5	24,7 %	25,7 %
Serum creatinine mg/dℓ		
> 2,5	0,9 %	1,7 %
> 1,5 - 2,5	12,2 %	13,9 %
Thrombocytopenia: Platelets/mm³		
< 25 000	1,3 %	2,9 %
25 000 - < 50 000	8,1 %	5,1 %
50 000 - < 100 000	20,0 %	22,9 %

Transplant patients

Several studies have investigated oral/intravenous ganciclovir for the treatment or prevention of CMV disease in transplant patients. The safety data of a randomised, placebo-controlled study of oral/intravenous ganciclovir (3 g per day) for the prevention of CMV disease in liver/bone marrow transplant recipients is given below. Clinical side effects which occurred in 5 % of patients in these studies, regardless of causal relationship or seriousness, but which occurred in a higher frequency in the oral/intravenous ganciclovir arm compared to placebo, are summarised in Table 3.

Table 3. Percentage of patients with adverse events that occurred in more than 5 % of patients

Body system Adverse event	**Liver transplant patients**		**Bone marrow transplant patients**	
	Oral ganciclovir N = 150	**Oral placebo** N = 154	***IV* ganciclovir** N = 122	**Placebo/ observational control** N = 120
Blood and lymphatic system				
Pancytopenia	-	-	31 %	25 %
Anaemia	20,7 %	18,2 %	-	-
Leucopenia	16,0 %	12,3 %	20 %	7 %
Leukocytosis	15,3 %	9,1 %	-	-
Body as a whole				
Pain	32,0 %	30,5 %	-	-
Headache	34,7 %	26,6 %	15 %	13 %
Back pain	30,0 %	25,3 %	-	-
Ascites	23,3 %	15,6 %	-	-
Mucous membrane disorder	-	-	14 %	13 %
Asthenia	12,0 %	9,1 %	-	-
Pyrexia	-	-	11 %	8 %
Rigors	-	-	7 %	4 %
Sepsis	-	-	7 %	2 %
Anorexia	-	-	7 %	5 %
Face oedema	-	-	5 %	2 %
Haemorrhage	7,3 %	1,9 %	-	-
Peritonitis	5,3 %	1,9 %	-	-
Digestive system				
Diarrhoea	30,0 %	28,6 %	24 %	23 %
Nausea	22,0 %	17,5 %	20 %	19 %
Constipation	22,0 %	16,2 %		
Vomiting	14,0 %	12,3 %		
Dyspepsia	10,0 %	7,8 %	8 %	6 %
Abdominal distension	6,0 %	3,2 %	8 %	6 %
Cholangitis	6,7 %	4,5 %		
Metabolic and nutritional disorders				
Oedema, peripheral	22,7 %	20,8 %	-	-
Hepatic function, abnormal	28,0 %	26,0 %	11 %	10 %
Blood creatinine increased	-	-	16 %	13 %
Hyponatremia	9,3 %	6,5 %	-	-
Hypocalcemia	-	-	9 %	8 %
Hypokalemia	-	-	9 %	8 %
Blood magnesium, decreased	8,7 %	6,5 %	11 %	10 %
Diabetes mellitus	8,0 %	3,2 %	-	-
Hypoproteinemia	5,3 %	2,6 %	-	-

Central and peripheral nervous system				
Tremor	22,7 %	14,3 %	8 %	7 %
Paraesthesia	11,3 %	9,7 %	-	-
Depression	10,0 %	6,5 %	-	-
Anxiety	8,0 %	7,8 %	-	-
Confusion	9,3 %	3,9 %	5 %	3 %
	6,0 %	3,9 %	-	-
Skin and appendages				
Dermatitis, exfoliative	-	-	10 %	9 %
Respiratory system				
Pleural effusion	18,0 %	16,2 %	-	-
Dyspnea	12,7 %	10,4 %	6 %	4 %
Rhinitis	-	-	9 %	5 %
Upper respiratory tract infection	10,0 %	4,5 %	-	-
Cardiovascular system				
Vasodilation	6,0 %	3,2 %	-	-
Tachycardia	5,3 %	2,6 %	16 %	15 %
Hypotension	-	-	11 %	7 %
Urogenital system				
Renal impairment	17,3 %	12,3 %	-	-
Haematuria present	-	-	16 %	13 %
Renal failure, acute	10,0 %	5,2 %	-	-
Renal failure	8,0 %	3,2 %	-	-
Special senses				
Eye haemorrhage	-	-	5 %	3 %
Amblyopia	6,7 %	2,6 %	-	-
Musculoskeletal system				
Myalgia	-	-	5 %	3 %
Hepatic system				
Cholestatic jaundice	12,0 %	10,4 %	-	-

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 %)

Other adverse events

Relevant adverse events with oral/*IV* ganciclovir, which are not listed above, as they did not fulfill the criteria for inclusion into any of the tables in previous sections are given below.

Blood and lymphatic system: aplastic anaemia, bone marrow depression, splenomegaly, eosinophilia

Gastrointestinal system: mouth ulceration, eructation, oesophagitis, faecal incontinence, gastritis, gastrointestinal disorder, gastrointestinal haemorrhage, pancreatitis, tongue disorder

Infections: events related to bone marrow depression and immune system compromise such as local and systemic infections and sepsis

Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia

Body as a whole: cachexia, dehydration, fatigue, injection site thrombosis, injection site abscess, injection site oedema, injection site pain, injection site haemorrhage, malaise, photosensitivity reaction

Central and peripheral nervous system: agitation, convulsions, hallucinations, psychotic disorder, abnormal dreams, thinking abnormal, amnesia, ataxia, coma, dry mouth, emotional disturbance, hyperkinetic syndrome, hypertonia, libido decreased, myoclonic jerks, somnolence, euphoric mood, nervousness

Hepatic system: hepatitis, jaundice

Skin and appendages: dermatitis, acne, alopecia, dry skin, herpes simplex, urticaria

Special senses: retinal detachment, vision abnormal, blindness, deafness, eye pain, glaucoma, earache, tinnitus, vitreous disorder.

Cardiovascular system: arrhythmia (including ventricular arrhythmia), thrombophlebitis (deep), migraine, phlebitis.

Metabolic and nutritional system: blood creatine phosphokinase increased, blood lactic dehydrogenase increased, blood glucose decreased

Urogenital system: impotence, urinary frequency

Musculoskeletal system: myasthenic syndrome.

Post-marketing experience*: Adverse events from post-marketing spontaneous reports with intravenous and oral ganciclovir that were reported in HIV-infected or other immunocompromised patients such as transplant recipients, which are not mentioned in any section above, and for which a causal relationship cannot be excluded, are listed below.*

Anaphylaxis, decreased fertility in males.

Adverse events that have been reported during post-marketing period are consistent with those seen in clinical trials with ganciclovir. Convulsions 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 INTERACTIONS).

Precautions

It is recommended that complete blood counts and platelet counts be monitored during therapy. In patients with severe leucopenia, neutropenia, anemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered (see **CONTRA-INDICATIONS**, **WARNINGS** and **Special dosage instructions**).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see Special dosage instructions and Pharmacokinetics in special populations).

Convulsions 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 INTERACTIONS).

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

Didanosine plasma concentrations may increase during concomitant use with CYMEVENE, thus patients should be closely monitored for didanosine toxicity (see 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 INTERACTIONS**)**.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdose experience with IV ganciclovir: Reports of overdoses with intravenous ganciclovir 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: pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia

Hepatotoxicity: hepatitis, liver function disorder

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

Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting

Neurotoxicity: generalised tremor, convulsion

In addition, one adult received an excessive volume of *IV* ganciclovir solution by intravitreal injection, and experienced temporary loss of vision and central retinal artery acclusion secondary to increased intraocular pressure related to the injected fluid volume.

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 patient's degree of renal impairment (decreased creatinine clearance).

IDENTIFICATION

White to off-white plug.

PRESENTATION

Packs of 5 x 10 mℓ clear glass vials.

STORAGE INSTRUCTIONS

Vials: Store in a dry place below 30 ˚C. Keep out of reach of children

Reconstituted vial: The contents of the vial should be reconstituted immediately before being used for preparation of the infusion solution. The reconstituted vial is stable at room temperature for 12 hours and should not be refrigerated.

Prepared infusion solution: This solution may be stored for up to 24 hours, provided it is refrigerated. The infusion

solution should not be frozen. This medicine should not be used after the expiry date shown on the pack.

REFERENCE NUMBER

Y/20.2.8/291

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd.

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DATE OF PUBLICATION OF THE PACKAGE INSERT

Registration: 18 June 1992

Revision: 26 January 2005