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.

Excipients: Sodium hydroxide, hydrochloric acid and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A 20.2.8 - Antiviral agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 0,08 µM (0,02 µg/mL to 14 µM (3,5 µg/mL).

Viral resistance

Viruses resistant to ganciclovir can arise after chronic dosing with ganciclovir or valganciclovir by selection of mutations in either the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation or the viral polymerase gene (UL54). UL97 mutations arise earlier and more frequently than mutations in UL54. Virus containing mutations in the UL97 gene is resistant to ganciclovir alone, with M460V/I, H520Q, C592G, A594V, L595S, C603W being the most frequently reported ganciclovir resistance-associated substitutions. Mutations in the UL54 gene may show cross-resistance to other antivirals targeting the viral polymerase, and vice versa [106, 107, 108]. 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.

Pharmacokinetic properties

The pharmacokinetics of IV ganciclovir is linear over the range of 1,6 – 5,0 mg/kg. The systemic exposure ($AUC_{0-\infty}$) 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 (C_{max}) was on average 12,2 µg/mL (CV% 24).

Absorption: Not applicable.

Distribution: For IV ganciclovir, volume of distribution is correlated with body weight with values for the steady state volume of distribution ranging from 0,54 to 0,87 ℓ/kg**.** Ganciclovir penetrates the cerebrospinal fluid, and diffuses across the placenta. Binding to plasma proteins was 1 % - 2 % over ganciclovir concentrations of 0,5 and 51 µg/mL.

Metabolism: Ganciclovir is not metabolised to a significant extent.

Elimination: Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination. In patients with normal renal function, greater than 90 % of IV administered ganciclovir was recovered unmetabolised in the urine within 24 hours. In patients 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 patients without renal impairment ranged from 2,73 ± 1,29 (N = 6) to 3,98 ± 1,78 hours (N = 8).

Pharmacokinetics in special populations:

Renal impairment: The total body clearance of ganciclovir is linearly correlated with creatinine clearance. In patients with mild, moderate, and severe renal impairment, mean systemic clearances of 2,1; 1,0 and 0,3 mL/min/kg were observed. Patients with renal impairment show an increased elimination half-life. In patients with severe renal impairment elimination half-life was increased by 10-fold (see Special Dosage Instructions, Renal impairment).

Patients undergoing haemodialysis: Plasma concentrations of ganciclovir are reduced by about 50 % during a 4 hour haemodialysis session (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

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 Population: No ganciclovir pharmacokinetic studies have been conducted in adults older than 65 years of age. However, because ganciclovir is mainly excreted by the kidneys 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 Special Dosage Instructions, Elderly population).

Paediatric population: The pharmacokinetics of IV ganciclovir were investigated across two studies in paediatric liver (N=18) and renal (N=25) transplant patients aged 3 months to 16 years and evaluated using a population pharmacokinetic model. The mean total clearance was 5,4 ℓ/hr (90 mL/min) for a child with a creatinine clearance of 70,4 mL/min. The steady state volume of distribution and peripheral volume of distribution were on average 20 and 15 ℓ, respectively. CrCl was identified as statistically significant covariate for ganciclovir clearance and height of the patient as statistically significant covariate for ganciclovir clearance, steady state volume and peripheral volume of distribution. Neither age, gender, nor types of organ transplant were significant covariates in these populations. *Table 1* gives the estimated pharmacokinetic parameters by age group.

Table 1 Pharmacokinetic parameters in renal and liver solid organ transplant patients expressed as medians (minimum-maximum)

	< 6 years	**6 to <12 years**	**≥12 to <16 years**
	n=17	n=9	n=17
CL(ℓ/h)	4,23 (2,11-7,92)	4,03 (1,88-7,8)	7,53 (2,89-16,8)
V_{cent} (ℓ)	1,83 (0,45-5,05)	6,48 (3,34-9,95)	12,1 (3,6-18,4)
V_{periph} (ℓ)	5,81 (2,9-11,5)	16,4 (11,3-20,1)	27 (10,6-39,3)
V_{ss} (ℓ)	8,06 (3,35-16,6)	22,1 (14,6-30,1)	37,9 (16,5-57,2)

Pharmacokinetics of IV ganciclovir given according to the dosing regimen approved for adults (5 mg/kg IV infusion administered over 1 hour) were studied in a small group of infants and children with normal renal function, aged 9 months to 12 years (n = 10, average 3,1 years). Exposure as measured

by mean AUC_{∞} on Day 1 (n = 10) and AUC_{0-12} on Day 14 (n = 7) 14 were 19,4 ± 7,1 and 24,1 ± 14,6 μg.h/mL with corresponding C_{max} values of 7,59 ± 3,21 and 8,31 ± 4,9 μg/mL (Days 1 and 14) respectively.

A trend towards lower exposures in younger paediatric patients was observed with body weight based dosing used in this study. In paediatric patients up to 5 years the average values for $AUC_{0-\infty}$ on Day 1 (n=7) and AUC_{0-12h} on Day 14 (n=4) were 17,7 ± 5,5 and 17,1 ± 7,5 μg.h/mL.

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

Table 2 Simulated* ganciclovir AUC_{0-24h} (μg • h/mL) for paediatric patients treated with ganciclovir dose (mg) of 3x BSA x CrCl given as 1 hour infusion.

	< 4 months	≥ 4 months to ≤ 2 years	> 2 to < 6 years	≥ 6 to < 12 years	≥ 12 to ≤ 16 years	All Patients
No. patients simulated	781	384	86	96	126	1473
Median	55,6	56,9	54,4	51,3	51,4	55,4
Mean	57,1	58,0	55,1	52,6	51,8	56,4
Min	24,9	24,3	16,5	23,9	22,6	16,5
Max	124,1	133,0	105,7	115,2	94,1	133,0

Patients	89	38	13	23	28	191
AUC < 40 μg • h/mL	(11 %)	(10 %)	(15 %)	(24 %)	(22 %)	(13 %)
Patients	398	195	44	41	63	741
AUC	(51 %)	(51 %)	(51 %)	(43 %)	(50 %)	(50 %)
40–60 μg • h/mL						
Patients	294	151	29	32	35	541
AUC > 60 μg • h/mL	(38 %)	(39 %)	(34 %)	(33 %)	(28 %)	(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=1473 data records).

INDICATIONS

CYMEVENE is indicated for the treatment of cytomegalovirus disease (CMV) in immuno-compromised patients ≥ 12 years of age.

CYMEVENE is indicated for the prevention of CMV disease using pre-emptive therapy in patients with medicine-induced immunosuppression following organ transplantation or cancer chemotherapy in patients ≥ 12 years of age.

CYMEVENE is also indicated for the prevention of CMV disease using universal prophylaxis in patients with medicine-induced immunosuppression following organ transplantation or cancer chemotherapy in patients ≥ 12 years of age.

CONTRAINDICATIONS

- Pregnancy and lactation.
- Patients with known hypersensitivity to ganciclovir, valganciclovir or to any of the excipients.

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

WARNINGS AND SPECIAL PRECAUTIONS

- *Cross hypersensitivity*: Due to the similarity of the chemical structure of ganciclovir and that of aciclovir and penciclovir, a cross-hypersensitivity reaction between these medicines 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).
- *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, bone marrow failure 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, and/or the platelet count is less than 25 000 cells/µℓ, and/or the haemoglobin is less than 8 g/dℓ (see CONTRAINDICATIONS and SIDE-EFFECTS).
- *Mutagenicity, carcinogenicity teratogenicity, fertility and contraception:* In animal studies ganciclovir was found to be mutagenic, teratogenic, carcinogenic and to impair fertility. CYMEVENE should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. 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. Based on clinical and non-clinical studies, CYMEVENE may cause temporary or permanent inhibition of spermatogenesis (see PREGNANCY AND LACTATION and SIDE-EFFECTS).

It is recommended that complete blood counts and platelet counts be frequently monitored in all patients during therapy, particularly in patients with renal impairment. In patients with severe leukopenia, neutropenia, anaemia and/or thrombocytopenia, treatment with haematopoietic growth factors and/or dose interruption of therapy is recommended (see CONTRAINDICATIONS and SIDE-EFFECTS). In patients with impaired renal function, dosage adjustments based on creatinine clearance is required (see Special dosage instructions and Pharmacokinetics in special populations).

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 there is no other appropriate treatment option (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 monitored for didanosine toxicity (see INTERACTIONS).
- Concomitant use of other medicines that are known to be myelosuppressive or associated with renal impairment with CYMEVENE may result in added toxicity (see INTERACTIONS).

Effects on ability to drive and use machines: No studies on the effect on the ability to drive and use machines have been performed. Based on the adverse reaction profile, ganciclovir may influence the ability to drive and use machines.

Adverse reactions for example seizures, dizziness, visual impairment, fatigue and confusion may occur in patients receiving CYMEVENE. If they occur, such effects may affect tasks requiring alertness, including the patient's ability to drive and operate machinery.

INTERACTIONS

Imipenem-cilastatin: Seizures have been reported in patients taking CYMEVENE and imipenem-cilastatin concomitantly and a pharmacodynamic interaction between these two medicines cannot be excluded. These medicines should not be used concomitantly unless there is no other appropriate treatment option (see WARNINGS AND SPECIAL PRECAUTIONS).

Potential drug interactions: Toxicity may be enhanced when ganciclovir is co-administered with other medicines known to be myelosuppressive or associated with renal impairment. This includes nucleoside analogues (e.g. zidovudine, didanosine, stavudine), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vincristine, vinblastine, hydroxyurea), and anti-infectives (e.g. trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these medicines should only be considered for concomitant use with ganciclovir if no other appropriate treatment option is available (see WARNINGS AND SPECIAL PRECAUTIONS).

Zidovudine: Both zidovudine and CYMEVENE have the potential to cause neutropenia and anaemia, a pharmacodynamic interaction may occur during concomitant administration of these medicines, some patients may not tolerate concomitant therapy at full dosage (see WARNINGS AND SPECIAL PRECAUTIONS).

Didanosine: Didanosine plasma concentrations were found to be consistently raised when given IV 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 medicines. Patients should be monitored for didanosine toxicity (e.g. pancreatitis) (see WARNINGS AND SPECIAL PRECAUTIONS).

Probenecid: Probenecid, given with oral ganciclovir, resulted in a decreased renal clearance of ganciclovir (20 %) and an increase ganciclovir exposure of 40 %. These changes were consistent with a mechanism of interaction involving competition for renal tubular excretion. Therefore, patients taking probenecid and CYMEVENE should be monitored for ganciclovir toxicity.

PREGNANCY AND LACTATION

Females and Males of Reproductive Potential

Fertility

Temporary and permanent inhibition of spermatogenesis in male animals and permanent suppression of fertility in female animals have occurred. Based on the occurrence of aspermatogenesis at ganciclovir exposures below therapeutic levels in animal studies, it is considered likely that ganciclovir may cause temporary or permanent inhibition of human spermatogenesis.

In a clinical study of renal transplant patients receiving valganciclovir (which is a pro-drug of ganciclovir) for CMV prophylaxis for up to 200 days were compared to an untreated control group. Spermatogenesis was inhibited during treatment with valganciclovir. At follow-up, approximately 6 months after treatment discontinuation, the mean sperm density in treated patients was comparable to that observed in the untreated control group. In valganciclovir 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 advised 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.

Pregnancy

CYMEVENE is contraindicated in pregnancy and lactation. Please refer to CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS.

In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity.

The safety of CYMEVENE in pregnant women has not been established. Ganciclovir readily diffuses across the human placenta. The safe use of CYMEVENE during labour and delivery has not been established.

Lactation

Women on treatment with CYMEVENE must be advised not to breastfeed their infants

Peri- and postnatal development has not been studied with ganciclovir but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breastfeeding infant cannot be excluded. Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats.

Paediatric Use

There is a high risk of haematological cytopenias in neonates and infants and CYMEVENE should not be used in neonates, infants and patients less than 12 years of age. The potential for long-term carcinogenicity and reproductive toxicity in paediatric patients is also a serious concern (See INDICATIONS, Special Dosage Instructions, SIDE-EFFECTS and Pharmacokinetics in Special Populations).

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 frequent 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.

Dose and duration of therapy

Table 3 Dose and duration of therapy

Indication	**Dose and duration of therapy**
Treatment of CMV disease	*Induction treatment:* 5 mg/kg every 12 hours for 14 - 21 days.
*Patients ≥ 12 years with normal renal function**	*Maintenance treatment:* For immunocompromised patients at risk of relapse maintenance therapy may be given. 5 mg/kg

	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.
	Treatment of disease progression: Any patient, in whom CMV disease progresses, either while on maintenance treatment or because treatment with CYMEVENE has been withdrawn, may be re-treated using the induction treatment regimen.
Prevention of CMV disease using pre-emptive therapy *Patients ≥ 12 years with normal renal function**	*Induction treatment:* 5 mg/kg every 12 hours for 7 – 14 days.
	Maintenance treatment: 5 mg/kg once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration of maintenance treatment is based on the risk of CMV disease and should be determined on an individual basis.
Prevention of CMV disease using universal prophylaxis *Patients >16 years of age with normal renal function**	5 mg/kg once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration of universal prophylaxis is based on the risk of CMV disease and should be determined on an individual basis.
Prevention of CMV disease using universal prophylaxis *Patients > 12 years of age*	See Special Dosage Instructions
* For dosing in patients with renal impairment refer to Special Dosage Instructions	

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 dosage instructions

Paediatric patients

The once daily dose in mg for prevention of CMV disease using universal prophylaxis in patients from birth to 16 years of age is calculated using the formulae: 3 x BSA x CrCl*. Although a dose for universal prophylaxis can be calculated for patients from birth to 16 years of age, there is insufficient clinical information on efficacy, safety and benefit/harm balance from adequate and well controlled clinical studies with the calculated CYMEVENE dose to support universal prophylaxis in patients from birth to less than 12 years of age. CYMEVENE should not be used for universal prophylaxis in the age category from birth to less than 12 years of age.

The dose is based on body surface area (BSA) using the Mosteller BSA formula and creatinine clearance derived from Schwartz formula (CrCl), 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.

*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:

$$Mosteller\ BSA\ (m^2) = \sqrt{\frac{Height\ (cm) x\ Weight\ (kg)}{3600}}$$

$$Schwartz\ Creatinine\ Clearance\ (ml/\min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dl)}$$

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.

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 during prophylaxis.

CYMEVENE is not indicated for treatment of CMV disease or pre-emptive therapy in children under 12 years of age due to insufficient clinical data on safety, efficacy and benefit/harm balance from adequate well-controlled clinical studies. The use of CYMVENE for treatment of congenital or neonatal CMV is contraindicated.

Elderly patients

No studies have been conducted in adults older than 65 years of age. Since renal clearance decreases with age, CYMEVENE should be administered to elderly patients with special consideration of their renal status (see *Table 3* and Pharmacokinetics in Special Populations, Elderly population).

Patients with renal impairment

Paediatric patients ≥ 12 years of age with renal impairment receiving a dose of CYMEVENE for universal prophylaxis, calculated using the 3 x BSA x CrCl dosing algorithm, do not require further dose modification because this dose is already adjusted for creatinine clearance.

For patients ≥12 years with renal impairment, treated on a mg/kg body weight base for pre-emptive therapy and treatment of CMV disease the mg/kg dose of CYMEVENE should be modified as shown in the table below.

Table 4 CYMEVENE dosing for patients with renal impairment receiving mg/kg dosing

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

Estimated 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

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

Hepatic impairment

The safety and efficacy of CYMEVENE have not been studied in patients with hepatic impairment (see Pharmacokinetics in Special Populations, Hepatic impairment).

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 AND SPECIAL PRECAUTIONS). 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

HIV infected patients

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 5*).

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

The frequencies presented in the table of adverse reactions are derived from a pooled population of HIV-infected patients (n=1704) receiving maintenance therapy with ganciclovir (GAN1697, GAN1653, GAN2304, GAN1774, GAN2226, AVI034, GAN041) or valganciclovir (WV15376, WV15705).

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 diarrhoea compared to oral valganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC <500µℓ) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction is reported more frequently in organ transplant recipients.

Table 5 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
Anaemia	19,89 %	
Thrombocytopenia	7,34 %	Common
leukopenia	3,93 %	
Pancytopenia	1,06 %	

Bone marrow failure	0,29 %	Uncommon
Aplastic anaemia	0,06 %	Rare
Agranulocytosis*		
Granulocytopenia*		
Immune system disorders*:*		
Hypersensitivity	1,12 %	Common
Anaphylactic reaction*		
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 %	
Hypoesthesia	2,58 %	
Convulsion	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 oedema	1,06 %	
Ear and labyrinth disorders*:*		
Ear pain	1,17 %	Common
Deafness	0,65 %	Uncommon
Cardiac disorders*:*		
Cardiac dysrhythmias	0,47 %	Uncommon
Vascular disorders*:*		
Hypotension	2,05 %	Common
Respiratory, thoracic and mediastinal disorders*:*		
Cough	18,31 %	Very common
Dyspnoea	11,80 %	
Gastrointestinal disorders*:*		
Diarrhoea	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

Haematuria	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
** These adverse reactions are derived from post-marketing experience and cannot be linked to frequencies or percentages.* *** Retinal detachment has only been reported in studies in HIV patients treated with CYMEVENE for CMV retinitis.*		

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 6*.

Table 6 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 %	-	-
Leukopenia	16,0 %	12,3 %	20 %	7 %
Leucocytosis	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 %	-	-
Hypocalcaemia	-	-	9 %	8 %
Hypokalaemia	-	-	9 %	8 %
Blood magnesium, decreased	8,7 %	6,5 %	11 %	10 %
Diabetes mellitus	8,0 %	3,2 %	-	-
Hypoproteinaemia	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 %	-	-
Dyspnoea	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 %)

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 normalises within 2 to 5 days after discontinuation of the ~~drug~~ medicine or dose reduction (see WARNINGS AND SPECIAL 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 medicines are at greater risk of thrombocytopenia than patients with HIV (see WARNINGS AND SPECIAL PRECAUTIONS). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Laboratory abnormalities in HIV-infected patients

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

Table 7 Laboratory abnormalities

	IV ganciclovir **N = 179**
Neutropenia: ANC/mm^3	
< 500	25,1 %
500 - < 750	14,3 %
750 - < 1 000	26,3 %

Anaemia: Haemoglobin g/dℓ	
< 6,5	4,6 %
6,5 - < 8,0	16,0 %
8,0 - < 9,5	25,7 %
Serum creatinine µmol/ℓ	
> 221.1	1,7 %
> 162.6 – 221.1	13,9 %
Thrombocytopenia: Platelets/mm^3	
< 25 000	2,9 %
25 000 - < 50 000	5,1 %
50 000 - < 100 000	22,9 %

***Post-marketing*:** (See SIDE-EFFECTS – *Table 6*).

Adverse events that have been reported during post-marketing period are consistent with those seen in clinical trials with ganciclovir/valganciclovir. Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir. CYMEVENE should not be used concomitantly with imipenem-cilastatin unless no other appropriate treatment option is available (see INTERACTIONS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdose experience with IV ganciclovir: Reports of overdoses with intravenous ganciclovir, some with fatal outcomes, have been received from clinical trials and during post-marketing experience. The majority of patients experienced one or more of the following adverse events:

Haematological toxicity: myelosuppression including pancytopenia, medullary aplasia, leukopenia, neutropenia, granulocytopenia thrombocytopenia.

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.

An excessive volume of IV ganciclovir solution given by intravitreal injection caused a temporary loss of vision and central retinal artery occlusion due to increased intraocular pressure related to the injected fluid volume.

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

IDENTIFICATION

White to off-white plug.

PRESENTATION

Packs of 5 x 10 mL clear glass vials.

STORAGE INSTRUCTIONS

Vials: Store in a dry place at or 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.

Disposal of unused/expired medicines: The release of pharmaceuticals in the environment should be minimised. 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.

REGISTRATION NUMBER

Y/20.2.8/291

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DATE OF PUBLICATION OF THIS PACKAGE INSERT

Registration: 18 June 1992

Last Revision: 09 March 2023