CYMEVENE® 500 MG

FULL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

CYMEVENE® 500 MG

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 543 mg ganciclovir sodium equivalent to 500 mg ganciclovir.

For a full list of excipients, see section 9.

PHARMACEUTICAL FORM

Powder for solution for infusion
white to off-white powder.

CLINICAL PARTICULARS

1 INDICATIONS AND USAGE

CYMEVENE 500 MG is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). CYMEVENE 500 MG is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease.

THE SAFETY AND EFFICACY OF **CYMEVENE 500 MG** HAVE NOT BEEN ESTABLISHED FOR CONGENITAL OR NEONATAL CMV DISEASE; NOR FOR THE TREATMENT OF ESTABLISHED CMV DISEASE OTHER THAN RETINITIS; NOR FOR USE IN NON-IMMUNOCOMPROMISED INDIVIDUALS.

2 DOSAGE AND ADMINISTRATION

CAUTION - DO NOT ADMINISTER CYMEVENE 500 MG SOLUTION BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF CYMEVENE 500 MG MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS.

CAUTION - INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF RECONSTITUTED CYMEVENE 500 MG SOLUTION MAY RESULT IN SEVERE TISSUE IRRITATION DUE TO HIGH pH (11).

Dosage

THE RECOMMENDED DOSE FOR CYMEVENE 500 MG SOLUTION SHOULD NOT BE EXCEEDED. THE RECOMMENDED INFUSION RATE FOR CYMEVENE 500 MG SOLUTION SHOULD NOT BE EXCEEDED.

For Treatment of CMV Retinitis in Patients with Normal Renal Function

Induction Treatment
The recommended initial dosage for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days.

Maintenance Treatment
Following induction treatment, the recommended maintenance dosage of CYMEVENE 500 MG solution is 5 mg/kg given as a constant-rate intravenous infusion over 1 hour once daily, 7 days per week, or 6 mg/kg once daily, 5 days per week.

For patients who experience progression of CMV retinitis while receiving maintenance treatment with CYMEVENE 500 MG, reinduction treatment is recommended.

For the Prevention of CMV Disease in Transplant Recipients with Normal Renal Function
The recommended initial dosage of CYMEVENE 500 MG solution for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7 to 14 days, followed by 5 mg/kg once daily, 7 days per week or 6 mg/kg once daily, 5 days per week.

The duration of treatment with CYMEVENE 500 MG solution in transplant recipients is dependent upon the duration and degree of immunosuppression. In controlled clinical trials in bone marrow allograft recipients, treatment with CYMEVENE 500 MG was continued until day 100 to 120 post transplantation. CMV disease occurred in several patients who discontinued treatment with CYMEVENE 500 MG solution prematurely. In heart allograft recipients, the onset of newly diagnosed CMV disease occurred after treatment with CYMEVENE 500 MG was stopped at day 28 posttransplant, suggesting that continued dosing may be necessary to prevent late occurrence of CMV disease in this patient population (see **INDICATIONS AND USAGE** section for a more detailed discussion).

Renal Impairment
For patients with impairment of renal function, refer to **Table 8** for recommended doses of CYMEVENE 500 MG solution and adjust the dosing interval as indicated:

Table 1 Dosing for Patients with Renal Impairment

Creatinine Clearance* (mL/min)	CYMEVENE 500 MG Induction Dose (mg/kg)	Dosing Interval (hours)	CYMEVENE 500 MG Maintenance Dose (mg/kg)	Dosing Interval (hours)
≥70	5.0	12	5.0	24
50–69	2.5	12	2.5	24
25–49	2.5	24	1.25	24
10–24	1.25	24	0.625	24
<10	1.25	3 times per week, following hemodialysis	0.625	3 times per week, following hemodialysis

* Creatinine clearance can be related to serum creatinine by the formulas given below.

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age[yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

Hemodialysis

Dosing for patients undergoing hemodialysis should not exceed 1.25 mg/kg 3 times per week, following each hemodialysis session. CYMEVENE 500 MG should be given shortly after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50%.

Patient Monitoring

Due to the frequency of granulocytopenia, anemia and thrombocytopenia in patients receiving ganciclovir (see **ADVERSE EVENTS**), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in cytopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment. Patients should have serum creatinine or creatinine clearance values followed carefully to allow for dosage adjustments in renally impaired patients (see **DOSAGE AND ADMINISTRATION**).

Reduction of Dose

Dosage reductions in renally impaired patients are required for CYMEVENE 500 MG (see **Renal Impairment**). Dosage reductions should also be considered for those with neutropenia, anemia and/or thrombocytopenia (see **ADVERSE EVENTS**). Ganciclovir should not be administered in patients with severe neutropenia (ANC less than 500/μL) or severe thrombocytopenia (platelets less than 25,000/μL).

Method of Preparation of CYMEVENE 500 MG Solution

Each 10 mL clear glass vial contains ganciclovir sodium equivalent to 500 mg of ganciclovir and 46 mg of sodium. The contents of the vial should be prepared for administration in the following manner:

1. Reconstituted Solution:

    a. Reconstitute lyophilized CYMEVENE 500 MG by injecting 10 mL of Sterile Water for Injection, USP, into the vial.
    DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING PARABENS. IT IS INCOMPATIBLE WITH CYMEVENE 500 MG AND MAY CAUSE PRECIPITATION.
    b. Shake the vial to dissolve the drug.
    c. Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion solution. Discard the vial if particulate matter or discoloration is observed.
    d. Reconstituted solution in the vial is stable at room temperature for 12 hours. It should not be refrigerated.

2. Infusion Solution:

    Based on patient weight, the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) should be removed from the vial and added to an acceptable infusion fluid (typically 100 mL) for delivery over the course of 1 hour. Infusion concentrations greater than 10 mg/mL are not recommended. The following infusion fluids have been determined to be chemically and physically compatible with CYMEVENE 500 MG solution: 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection and Lactated Ringer's Injection, USP.

    CYMEVENE 500 MG, when reconstituted with sterile water for injection, further diluted with 0.9% sodium chloride injection, and stored refrigerated at 2-8°C in polyvinyl chloride (PVC) bags, remains physically and chemically stable for 24 hours.

Because CYMEVENE 500 MG is reconstituted with nonbacteriostatic sterile water, it is recommended that the infusion solution be used within 24 hours of dilution to reduce the risk of bacterial contamination. The infusion should be refrigerated. Do not Freeze.

Handling and Disposal

Caution should be exercised in the handling and preparation of solutions of CYMEVENE 500 MG. Solutions of CYMEVENE 500 MG are alkaline (pH 11). Avoid direct contact of the skin or mucous membranes with CYMEVENE 500 MG solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Wearing disposable gloves is recommended.

Because ganciclovir shares some of the properties of antitumor agents (i.e., carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs.

3 CONTRAINDICATIONS

CYMEVENE 500 MG is contraindicated in patients who have experienced hypersensitivity to the active ingredient (ganciclovir), valganciclovir, or any excipients listed in section 9. Due to the similarity of the chemical structure of CYMEVENE and that of acyclovir and its pro- drug valacyclovir, a cross-hypersensitivity reaction between these drugs is possible.

4 WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The clinical toxicity of CYTOVENE (ganciclovir for injection) includes severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure, and aplastic anemia.
- In animal and *in vitro* studies, ganciclovir was mutagenic, teratogenic, carcinogenic and caused aspermia; therefore it should be considered a potential teratogen and carcinogen in humans.
- CYTOVENE is indicated for use only in immunocompromised patients, where the potential benefit outweighs the risks stated herein.
- The safety and efficacy of CYTOVENE have not been evaluated for congenital or neonatal CMV disease, nor for treatment of CMV infection in non- immunocompromised individuals (see INDICATIONS AND CLINICAL USE).

General

In clinical studies with CYMEVENE, the maximum single dose studied has been 6 mg/kg infused intravenously over one hour. Larger doses have resulted in increased toxicity. It is likely that more rapid infusions would also result in increased toxicity.

Administration of CYMEVENE should be accompanied by adequate hydration. Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED. Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION: Renal Impairment).

For patients on hemodialysis (CrCl < 10 mL/min) it is recommended that intravenous ganciclovir be used (see DOSAGE AND ADMINISTRATION: Renal Impairment).

Hemodialysis reduces plasma concentrations of ganciclovir by approximately 50% during a 4 hour hemodialysis session (See DOSAGE AND ADMINISTRATION: Hemodialysis).

Carcinogenesis and Mutagenesis

Ganciclovir caused point mutations and chromosomal damage in mammalian cells *in vitro* and *in vivo,* but did not cause point mutations in bacterial or yeast cells, dominant lethality in mice, or morphologically transformed cells *in vitro.*

In a study conducted over 18 months, ganciclovir was carcinogenic in the mouse after oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 1.4x, respectively, based on area under the plasma concentration curve [AUC] comparisons). The principally affected tissues at the dose of 1000 mg/kg/day were the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues and liver in females. At dose of 20 mg/kg/day, slightly increased tumor incidences occurred in the preputial and harderian glands in males, forestomach in males and females, and liver in females. All ganciclovir-induced tumours were of epithelial or vascular origin except for histiocytic sarcoma of the liver. No carcinogenic effect occurred at 1 mg/kg/day (estimated as 0.01x the human dose based on AUC comparison). The preputial and clitoral glands, forestomach and harderian glands of mice have no human counterpart.
CYMEVENE should be considered a potential carcinogen in humans.

Hematologic

CYMEVENE should not be administered 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 80 g/L. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anemia have been observed in patients treated with CYMEVENE. The frequency and severity of these events vary widely in different patient populations (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests; DOSAGE AND ADMINISTRATION, Patients with severe leukopenia, neutropenia, anemia, thrombocytopenia and/or pancytopenia; ADVERSE REACTIONS). CYMEVENE should therefore, be used with caution in patients with pre-existing cytopenias, or with a history of cytopenic reactions to other drugs, chemicals, or irradiation.

It is recommended that complete blood counts including platelet counts be monitored in all patients during therapy, particularly in patients with renal impairment (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia, treatment with hematopoietic growth factors and/or the interruption of therapy is recommended (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION: Patient Monitoring, Reduction of Dose).

Neutropenia: Neutropenia typically occurs during the first or second week of induction therapy and prior to

administration of a total cumulative dose of 200 mg/kg of CYMEVENE but may occur at any time during treatment with either formulation. Evidence of recovery of cell counts usually occurs within 3 to 7 days after discontinuing the drug. Colony stimulating factors have been shown to increase neutrophil and white blood cell counts in patients receiving CYMEVENE for treatment of CMV retinitis.

Thrombocytopenia: Thrombocytopenia (platelet count of less than 50,000 cells/µL) was observed in patients treated with CYMEVENE. Immunodeficient patients without AIDS were more likely to develop lowered platelet counts than those with AIDS. Patients with initial platelet counts less than 100,000 cells/µL were also at increased risk of this toxicity of CYMEVENE.

Renal

Monitoring renal function during therapy with CYMEVENE is essential, especially for elderly patients and those patients receiving concomitant agents that may cause nephrotoxicity.

It is possible that probenecid, as well as other drugs which inhibit renal tubular secretion or resorption, may reduce renal clearance of ganciclovir and could increase its plasma half-life.

Use In Patients With Renal Impairment: CYMEVENE should be used with caution in patients with impaired renal function. Both the plasma half-life of ganciclovir as well as peak plasma levels are increased in patients with elevated serum creatinine levels.

Patients undergoing Hemodialysis: Plasma concentrations of ganciclovir are reduced by about 50% during a 4 hour hemodialysis session (See DOSAGE AND ADMINISTRATION: Hemodialysis).

Acute Kidney Injury

Acute kidney injury may occur in:

- Elderly patients with or without reduced renal function. Caution should be exercised when administering CYMEVENE to geriatric patients, and dosage reduction is recommended for those with impaired renal function (see DOSAGE AND ADMINISTRATION, Use in Specific Populations).
- Patients receiving potential nephrotoxic drugs. Caution should be exercised when administering CYMEVENE to patients receiving potential nephrotoxic drugs.
- Patients without adequate hydration. Adequate hydration should be maintained for all patients.

Sexual Function/Reproduction

Mutagenesis and Carcinogenesis

Prior to initiation of treatment with CYMEVENE, women should be advised of the potential mutagenic and teratogenic risk of ganciclovir to the fetus. Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment with CYMEVENE. Similarly men are recommended to use condoms with female partners during and for at least 90 days following treatment with CYMEVENE (see WARNINGS AND PRECAUTIONS: Carcinogenesis and Mutagenesis). If pregnancy does occur during treatment or within 30 days from stopping treatment the patient must be advised of the potential significant teratogenic risk of ganciclovir to the fetus.

CYMEVENE is considered to be a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see DOSAGE AND ADMINISTRATION: handling and disposal).

Impairment of Fertility

CYMEVENE inhibit spermatogenesis in humans based on a clinical study, suppression of fertility in females may occur based on animal data. Advise patients that fertility may be impaired with the use of CYMEVENE. Animal data indicate that administration of ganciclovir caused inhibition of spermatogenesis and subsequent infertility, which were reversible at lower doses and irreversible at higher doses (see WARNINGS AND PRECAUTIONS, Sexual Function / Reproduction).

Female mice exhibited decreased fertility, decreased mating behaviour, and increased embryolethality after daily intravenous doses of 90 mg/kg (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons).

In male mice, fertility was decreased after daily intravenous doses of ≥ 2 mg/kg and daily oral doses of ≥ 10 mg/kg. These effects were reversible after daily intravenous doses of 2 mg/kg and daily oral doses of 10 mg/kg, but were irreversible or incompletely reversible after daily intravenous doses of 10 mg/kg and daily oral doses of 100 or 1000 mg/kg. Ganciclovir has also caused hypospermatogenesis in rats after daily oral doses of ≥ 100 mg/kg and in dogs after daily intravenous and oral doses of ≥ 0.4 mg/kg and 0.2 mg/kg, respectively.

Fetal Toxicity

Ganciclovir may cause fetal toxicity when administered to pregnant women based on findings in animal studies. When given to pregnant rabbits at dosages resulting in 2-times the human exposure (based on AUC), ganciclovir caused malformations in multiple organs of the fetuses. Maternal and fetal toxicity were also observed in pregnant mice and rabbits. Therefore, CYMEVENE has the potential to cause birth defects. Pregnancy should be avoided in female patients taking CYMEVENE and in females with male partners taking CYMEVENE.

Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

Daily intravenous doses of 90 mg/kg ganciclovir administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach. The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Skin

Initially reconstituted solutions of CYMEVENE have a high pH (pH 11). Despite further dilution in intravenous fluids, phlebitis and/or pain may occur at the site of intravenous infusion. Care must be taken to infuse solutions containing CYMEVENE only into veins with adequate blood flow to permit rapid dilution and distribution (see DOSAGE AND ADMINISTRATION).

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 minor influence on the ability to drive and use machines. Adverse reactions, for example seizures, dizziness 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.

Special Populations

CYMEVENE inhibit spermatogenesis in humans based on a clinical study, suppression of fertility in females may occur based on animal data. Advise patients that fertility may be impaired with the use of CYMEVENE. Animal data indicate that administration of ganciclovir caused inhibition of spermatogenesis and subsequent infertility, which were reversible at lower doses and irreversible at higher doses (see WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction).

Because of the mutagenic and teratogenic potential of ganciclovir, women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment with CYMEVENE. Similarly men should be advised to use condoms during and for at least 90 days following treatment with CYMEVENE, unless it is certain that the female partner is not at risk of becoming pregnant (see WARNINGS AND PRECAUTIONS: Sexual Function/Reproduction).

CYMEVENE is considered to be a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see DOSAGE AND ADMINISTRATION: handling and disposal).

Pregnant Women: 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.

Data obtained using an *ex vivo* human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion.

Nursing Women: Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats. Since many drugs are, and, because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely. CYMEVENE should not be given to breastfeeding mothers. Mothers should be instructed to discontinue the drug or discontinue nursing if they are receiving CYMEVENE.

Pediatric Use: The safety and efficacy of CYMEVENE in children has not been established. The use of CYMEVENE warrants extreme caution due to the probability of long-term carcinogenicity and reproductive toxicity. Administration to children should be undertaken only after careful evaluation and only if the potential benefits of treatment outweigh these considerable risks.

There has been very limited clinical experience using CYMEVENE for the treatment of CMV retinitis in patients under the age of 12 years.

The safety and efficacy of CYMEVENE have not been evaluated for congenital or neonatal CMV disease, nor for treatment of CMV infection in non-immunocompromised individuals (see INDICATIONS AND CLINICAL USE).

Geriatric Use: No studies on the efficacy or safety of CYMEVENE specifically in elderly patients have been conducted. Since elderly individuals may have reduced renal function, CYMEVENE is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug is greater in patients with impaired renal function. CYMEVENE should be administered to the elderly patients with care and will special consideration of their renal status. **Renal function should be monitored and dosage adjustments should be made accordingly** (see DOSAGE AND ADMINISTRATION: Renal Impairment).

Use In Patients with Renal Impairment: CYMEVENE should be used with caution in patients with impaired renal function. Both the plasma half-life of ganciclovir as well as peak plasma levels are increased in patients with elevated serum creatinine levels.

Use In Patients with Hepatic Impairment: The safety and efficacy of CYMEVENE have not been studied in patients with hepatic impairment.

Patients undergoing Hemodialysis: Hemodialysis reduces plasma concentrations of ganciclovir by approximately 50% after i.v. administration during a 4 hour hemodialysis session (See DOSAGE AND ADMINISTRATION: Hemodialysis).

Patients with HIV and CMV retinitis: CYMEVENE is not a cure for CMV retinitis, and immunocompromised patients may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4 to 6 weeks while being treated with CYMEVENE. Some patients will require more frequent follow-up.

Patients with HIV may be receiving zidovudine (ZDV); patients should be counselled that as zidovudine and CYMEVENE each have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy (see DRUG INTERACTIONS).

Transplant Recipients: Transplant recipients should be counselled regarding the high frequency of impaired renal function in transplant recipients who received CYMEVENE in controlled clinical trials, particularly in patients receiving concomitant administration of nephrotoxic agents such as cyclosporine and amphotericin B. Although the specific mechanism of this toxicity, which in most cases was reversible, has not been determined, the higher rate of renal impairment in patients receiving CYMEVENE compared with those who received placebo in the same trials may indicate that CYMEVENE played a significant role.

Monitoring and Laboratory Tests

Due to the frequency of neutropenia, anemia or thrombocytopenia observed in patients receiving CYMEVENE (see ADVERSE REACTIONS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom CYMEVENE or other nucleoside analogs have previously resulted in leukopenia, or in whom pretreatment neutrophil counts are less than 1000 cells/μL at the beginning of treatment.

Because dosing modifications based on estimated creatinine clearance are required in patients with renal impairment and because of the incidence of increased serum creatinine levels observed in transplant recipients treated with CYMEVENE, patients should have serum creatinine or estimated creatinine clearance monitored carefully (see DOSAGE AND ADMINISTRATION: Renal Impairment and DOSAGE AND ADMINISTRATION: Patient monitoring).

5 ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 (not 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.

HIV-1 INFECTED SUBJECTS

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). Exception is made for agranulocytosis, granulocytopenia and anaphylactic reaction; the frequencies of which are derived from post-marketing experience.

The overall safety profile of ganciclovir/valganciclovir is consistent in HIV and transplant populations except that retinal detachment has only been reported in HIV infected 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 <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 2 Frequency of Ganciclovir/Valganciclovir ADRs Reported in HIV Patients Receiving Maintenance Therapy (n=1704).

ADR (MedDRA) System Organ Class	**Percentage**
Infections and infestations:	
Candida infections including oral candidiasis	22.42%
Upper respiratory tract infection	16.26%
Sepsis	6.92%
Influenza	3.23%
Urinary tract infection	2.35%
Cellulitis	1.47%

Blood and lymphatic disorders:	
Neutropenia	26.12%
Anemia	19.89%
Thrombocytopenia	7.34%
Leukopenia	3.93%
Pancytopenia	1.06%
Bone marrow failure	0.29%
Aplastic anemia	0.06%
Agranulocytosis*	0.02%
Granulocytopenia*	0.02%
Immune system disorders:	
Hypersensitivity	1.12%
Anaphylactic reaction*	0.02%
Metabolic and nutrition disorders:	
Decreased appetite	12.09%
Weight decreased	6.46%
Psychiatric disorders:	
Depression	6.69%
Confusional state	2.99%
Anxiety	2.64%
Agitation	0.59%
Psychotic disorder	0.23%
Thinking abnormal	0.18%
Hallucinations	0.18%
Nervous system disorders:	
Headache	17.37%
Insomnia	7.22%
Neuropathy peripheral	6.16%
Dizziness	5.52%
Paraesthesia	3.58%
Hypoaesthesia	2.58%
Seizure	2.29%
Dysgeusia (taste disturbance)	1.35%
Tremor	0.88%
Eye disorders:	
Visual impairment	7.10%
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%
Deafness	0.65%
Cardiac disorders:	
Arrhythmias	0.47%
Vascular disorders:	
Hypotension	2.05%
Respiratory, thoracic and mediastinal disorders:	
Cough	18.31%
Dyspnoea	11.80%
Gastrointestinal disorders:	
Diarrhea	34.27%
Nausea	26.35%
Vomiting	14.85%
Abdominal pain	10.97%
Dyspepsia	4.81%
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%
Hepatic function abnormal	3.23%
Aspartate aminotransferase increased	1.88%
Alanine aminotransferase increased	1.23%
Skin and subcutaneous tissue disorders:	
Dermatitis	11.80%
Night sweats	7.92%
Pruritus	4.58%
Rash	2.52%
Alopecia	1.29%
Dry skin	0.94%
Urticaria	0.70%
Muscolo-skeletal and connective tissue disorders:	
Back pain	4.46%
Myalgia	3.52%
Arthralgia	3.35%

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

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

Adverse events that occurred during clinical trials of CYMEVENE (ganciclovir for injection) are summarized below, according to the participating study subject population.

Adverse events seen in studies using CYMEVENE might also occur in studies using ganciclovir capsules, and vice versa.The safety of CYMEVENE in HIV-1 infected patients was studied in several clinical trials. The pooled safety information of the use of CYMEVENE for the treatment of CMV disease in HIV infected patients in six clinical trials is displayed below. The data is shown in comparison to the control arm (oral placebo plus intravitreal ganciclovir implant) of

one of these studies. Clinical adverse events, which occurred in ≥2% of patients taking intravenous ganciclovir, regardless of causal relationship or seriousness, however at a greater frequency than in the control arm, are summarized in Table 2.

Table 3: Percentage of Patients with Adverse Events Occurring in ≥ 2% of All Patients Receiving Intravenous Ganciclovir

Body systems Adverse events	**Intravenous Ganciclovir (N=412)**	**Control (N=119)**
Hemic and lymphatic system		
Neutropenia	25.7%	11.8%
Anemia	19.7%	16.8%
Thrombocytopenia	6.6%	5.0%
Leukopenia	3.2%	0.8%
Lymphadenopathy	2.9%	1.7%
Gastrointestinal system		
Diarrhea	26.5%	24.4%
Nausea	-	21.8%
Vomiting	-	12.6%
Abdominal pain	9.0%	7.6%
Flatulence	-	1.7%
Loose stools	-	1.7%
Dysphagia	2.7%	1.7%
Esophageal candidiasis	2.2%	1.7%
Body as a whole		
Pyrexia	35.9%	35.3%
Headache	18.7%	16.0%
Candida	10.4%	4.2%
Injection site infection	8.0%	0.8%
Sepsis	6.1%	3.4%
Sepsis secondary	5.8%	-
Anorexia	4.9%	-
Mycobacterium avium complex	4.9%	4.2%
Pain	4.6%	2.5%
Chest pain	4.4%	3.4%
Malaise	-	0.8%
Asthenia	-	0.8%
Blood culture positive	3.2%	1.7%
Injection site inflammation	2.2%	-
Central and peripheral nervous system		
Confusion	-	2.5%
Hypoesthesia	3.2%	1.7%
Anxiety	2.4%	1.7%
Skin and appendages		
Pruritus	3.2%	2.5%
Respiratory system		
Cough	16.0%	15.1%
Pneumocystis carinii pneumonia	7.3%	2.5%
Productive cough	3.6%	2.5%
Upper respiratory tract infection	-	0.8%
Lower respiratory tract infection	-	1.7%

Body systems Adverse events	**Intravenous Ganciclovir (N=412)**	**Control (N=119)**
Sinus congestion	3.4%	2.5%
Metabolic and nutritional disorders		
Blood alkaline phosphatase increased	4.4%	4.2%
Blood creatinine increased	3.2%	1.7%
Musculoskeletal system		
Arthralgia	2.4%	1.7%

Retinal Detachment

Retinal detachment has been observed in subjects with CMV retinitis both before and after initiation of therapy with CYMEVENE. The relationship of retinal detachment to therapy with CYMEVENE is unknown. Retinal detachment occurred in 11% of patients treated with CYMEVENE and in 8% of patients treated with ganciclovir capsules. Patients with CMV retinitis should have frequent ophthalmologic evaluations to monitor the status of their retinitis and to detect any other retinal pathology.

Laboratory abnormalities reported from three clinical trials in HIV infected patients taking oral or intravenous ganciclovir as maintenance treatment for CMV retinitis are listed below. Three hundred twenty-six patients receiving ganciclovir capsules and 179 patients receiving CYMEVENE (ganciclovir for injection) were eligible for the laboratory abnormality analysis.

Table 4: Laboratory Data

Minimum ANC, Hemoglobin, and Platelets and Maximum Serum Creatinine Values during Treatment with CYMEVENE (ganciclovir for injection) and ganciclovir capsules in Three Controlled Clinical Trials*

	% of subjects Oral Ganciclovir Capsules† (3000 mg/day) (n= 326)	**% of subjects Intravenous Solution‡ 5mg/kg/day (n= 179)**
Neutropenia [n(%)] **ANC/µL**		
<500	18.4	25.1
500 to <750	16.6	14.3
750 to <1000	19.1	26.3
Anemia [n(%)] **Hemoglobin g/dL**		
< 6.5	1.6	4.6
6.5 to <8.0	10.0	16.0
8.0 to <9.5	24.7	25.7
Thrombocytopenia **Platelets/µL**		
<25,000	1.3	2.9
25,000 to <50,000	8.1	5.1
50000 to <100000	20.0	22.9

	% of subjects Oral Ganciclovir Capsules† (3000 mg/day) (n= 326)	% of subjects Intravenous Solution‡ 5mg/kg/day (n= 179)
Serum Creatinine (SeCr)		
SeCr mg/dL		
≥2.5	0.9	1.7
≥1.5 to <2.5	12.2	13.9

* Data from Study ICM 1653, Study ICM 1774, and Study AVI034 pooled.

† Mean time on therapy = 103 days, including allowed reinduction treatment periods

‡ Mean time on therapy = 91 days, including allowed reinduction treatment periods

Overall, patients treated with CYMEVENE (ganciclovir for injection) experienced lower minimum ANCs and hemoglobin levels, consistent with more neutropenia and anemia, compared with those who received ganciclovir capsules; P=0.024 for neutropenia; P=0.027 for anemia.

For the majority of subjects, maximum serum creatinine levels were less than 1.5 mg/dL and no difference was noted between CYMEVENE and ganciclovir capsule for the occurrence of renal impairment. Serum creatinine elevations ≥2.5 mg/dL occurred in <2% of all subjects and no significant differences were noted in the time from the start of maintenance to the occurrence of elevations in serum creatinine values.

TRANSPLANT RECIPIENTS

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

Summarized below are clinical adverse events, which occurred in ≥ 5% of patients taking i.v. ganciclovir in three pooled bone marrow studies, regardless of causal relationship or seriousness. Adverse events which occurred in a higher frequency in the placebo / observational control arm compared to the i.v. ganciclovir arm, have not been included in the Table 4 below.

Table 5: Adverse Events Occurring in ≥ 5% of Patients Taking IV Ganciclovir

Body system Adverse event	**Bone marrow transplant Patients (ICM 1308, 1570 and 1689)**	
	IV ganciclovir (N=122)	**Placebo/ observational control (N=120)**
Hemic and lymphatic system		
Pancytopenia	31%	25%
Leukopenia	20%	7%
Body as a whole		
Headache	15%	13%
Mucous membrane disorder	14%	13%
Pyrexia	11%	8%
Rigors	7%	4%
Sepsis	7%	2%
Anorexia	7%	5%

Body system Adverse event	**Bone marrow transplant Patients (ICM 1308, 1570 and 1689)**	
	IV ganciclovir (N=122)	**Placebo/ observational control (N=120)**
Face edema	5%	2%
Gastrointestinal system		
Diarrhea	24%	23%
Nausea	20%	19%
Dyspepsia	8%	6%
Abdominal distension	8%	6%
Metabolic and nutritional disorders		
Blood creatinine increased	16%	13%
Hepatic function abnormal	11%	10%
Blood magnesium decreased	11%	10%
Hypocalcemia	9%	8%
Hypokalemia	9%	8%
Central and peripheral nervous system		
Tremor	8%	7%
Confusion	5%	3%
Skin and appendages		
Dermatitis exfoliative	10%	9%
Respiratory system		
Rhinitis	9%	5%
Dyspnea	6%	4%
Cardiovascular system		
Tachycardia	16%	15%
Hypotension	11%	7%
Urogenital system		
Hematuria present	16%	13%
Special senses		
Eye hemorrhage	5%	3%
Musculoskeletal system		
Myalgia	5%	3%

Clinical adverse events, which occurred in 5% of patients taking i.v. ganciclovir in a placebo controlled heart transplant study (ICM 1496), regardless of causal relationship or seriousness, but which occurred in a higher frequency in the i.v. 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: edema (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%), kidney injury (12%)

Less Common Clinical Trial Adverse Events (<1%)

Relevant adverse events, which are not listed above, as they did not fulfil the criteria for inclusion into any of the tables of previous sections are given below.

Body as a Whole: cachexia, dehydration, fatigue, injection site abscess, injection site edema, injection site hemorrhage, injection site pain, injection site thrombosis, malaise, photosensitivity reaction.

Gastrointestinal system: pancreatitis, gastrointestinal disorder, gastrointestinal hemorrhage, eructation, esophagitis, fecal incontinence, gastritis, mouth ulceration, tongue disorder.

Hemic and Lymphatic System: aplastic anemia, bone marrow failure, eosinophilia, splenomegaly.

Central and Peripheral Nervous System: hallucinations, psychotic disorder, euphoric mood, emotional disturbance, hyperkinetic syndrome, myoclonic jerks, abnormal dreams, agitation, amnesia, ataxia, coma, seizure, dry mouth, hypertonia, libido decreased, nervousness, somnolence, thinking abnormal.

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

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

Metabolic and Nutritional Disorders: blood creatine phosphokinase increased, blood glucose decreased, blood lactic dehydrogenase increased.

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

Urogenital System: impotence, urinary frequency.

Musculoskeletal System: myasthenic syndrome

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

Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia.

Hepatic System: hepatitis, jaundice

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory data from three controlled clinical trials of CYMEVENE (ganciclovir for injection) for the prevention of CMV disease in transplant recipients are summarized below.

Table 6: Laboratory Data

Neutropenia and Thrombocytopenia in Trials for the Prevention of CMV Disease in Transplant Recipients

	CYMEVENE intravenous*			
	Heart Allograft§		Bone Marrow Allograft†	
	CYMEVENE	Placebo	CYMEVENE	Placebo
Subjects (number)	**n=76**	**n=73**	**n=57**	**n=55**
Neutropenia (ANC/µL)				
<500	4%	3%	12%	6%
500 - 1000	3%	8%	29%	17%
Thrombocytopenia (platelets/µL)				
<25,000	3%	1%	32%	28%
25,000 - 50,000	5%	3%	25%	37%

§ Study ICM 1496: Mean duration of treatment = 28 days

† Studies ICM 1570 and ICM 1689: Mean duration of treatment = 45 days

* ganciclovir for injection

The following table shows the frequency of elevated serum creatinine values in these controlled clinical trials.

Table 7: Laboratory Data

Elevated Serum Creatinine Values in Trials for the Prevention of CMV Disease in Transplant Recipients

	CYMEVENE intravenous*					
	Heart Allograft ICM 1496		Bone Marrow Allograft			
			ICM 1570		ICM 1689	
Maximum Serum Creatinine Levels	**CYMEVENE (N=76)**	**Placebo (n=73)**	**CYMEVENE (n=20)**	**Control (n=20)**	**CYMEVENE (n=37)**	**Placebo (n=35)**
Serum Creatinine (□ 2.5 mg/dL)	18%	4%	20%	0%	0%	0%
Serum Creatinine (□1.5-<2.5 mg/dL)	58%	69%	50%	35%	43%	44%

*ganciclovir for injection

Patients receiving CYMEVENE had elevated serum creatinine levels when compared to those receiving placebo. Most patients in these studies also received cyclosporine. The mechanism of impairment of renal function is not known. However, careful monitoring of renal function during therapy with CYMEVENE is essential, especially for those patients receiving concomitant agents that may cause nephrotoxicity.

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 WARNINGS AND PRECAUTIONS: Hematologic).

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 HIV infected patients (see WARNINGS AND PRECAUTIONS: Hematologic). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Post-Market Adverse Events

The following adverse events have been reported since the marketing introduction of CYMEVENE and are not listed under adverse reactions above. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either the seriousness frequency of reporting, the apparent causal connection, or a combination of these factors:

Blood and lymphatic system disorders: hemolytic anemia, hemolytic-uremic syndrome

Cardiac Disorders: cardiac arrest, cardiac conduction abnormality, ischemia, Torsades de Pointes, ventricular tachycardia

Central and peripheral nervous system disorders: extrapyramidal reaction, hallucinations, loss of sense of smell, peripheral oculomotor nerve paralysis

Congenital, familial and genetic disorders: congenital anomaly

Eye disorders: cataracts, dry eyes,

Gastrointestinal disorders: cholelithiasis, cholestasis, intestinal ulceration

Hepatic system disorders: hepatic failure, hepatitis

Immune system disorders: allergic reaction, anaphylactic reaction

Metabolism and nutritional disorders: acidosis, elevated triglyceride levels, hyponatremia inappropriate serum ADH, hypercalcemia

Musculoskeletal and connective tissue disorder: arthritis, rhabdomyolysis,

Nervous system disorders: dysesthesia, facial palsy, intracranial hypertension, loss of memory, myelopathy, dysphasia

Reproductive system and breast disorders: infertility, testicular hypotrophy

Respiratory, thoracic and mediastinal disorders: bronchospasm, pulmonary fibrosis

Skin and subcutaneous tissue disorders: exfoliative dermatitis, Stevens-Johnson syndrome,

Social circumstances: irritability

Urogenital system disorders: renal tubular disorder

Vascular disorders: stroke, vasculitis

Adverse events from post-marketing spontaneous reports with 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 can not be excluded, are: anaphylaxis, decreased fertility in males.

Females and Males of Reproductive Potential

In animal studies ganciclovir was found to impair fertility. In a clinical study renal transplant patients receiving valganciclovir (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 valganciclovir. 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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

In addition, you may report suspected adverse reactions by sending an e-mail message to safety@tzamal-medical.co.il

6 DRUG INTERACTIONS

Ganciclovir

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

Zidovudine

At a dose of 1000 mg of ganciclovir capsules every 8 hours, there was a trend for decreased ganciclovir AUC in the presence of zidovudine, 100 mg every 4 hours (18%), but the decrease was not statistically significant. There was a statistically significant increase in AUC for zidovudine (15%) in the presence of ganciclovir.

Since both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, many patients will not tolerate combination therapy with these two drugs at full dosage strength. A pharmacodynamic interaction may occur during concomitant administration of these drugs.

Didanosine

At an oral dose of 1000 mg of ganciclovir capsules every 8 hours, the steady state AUC_{0-12} for didanosine, 200 mg every 12 hours, increased approximately 80% when didanosine was administered 2 hours prior to or concurrently with administration of ganciclovir capsules.
Decreased steady state AUC (23%) was observed for ganciclovir in the presence of didanosine when the drug was administered 2 hours prior to administration of ganciclovir capsules, but AUC was not affected by the presence of didanosine when the two drugs were administered simultaneously. There were no significant changes in renal clearance for either drug.

When the standard CYMEVENE induction dose (5 mg/kg infused over 1 hour every 12 hours) was co-administered with didanosine at a dose of 200 mg orally every 12 hours, the steady state didanosine AUC_{0-12} increased 70±40% (range, 3 to 121%, n=11) and C_{max} increased 49±48% (range, -28 to 125%). In a separate study, when the standard CYMEVENE maintenance dose (5 mg/kg infused over 1 hour every 24 hours) was co-administered with didanosine at a dose of 200 mg orally every 12 hours, didanosine AUC_{0-12} increased 50±26% (range, 22 to 110%, n=11) and C_{max} increased 36±36% (range, -27 to 94%) over the first didanosine dosing interval. Didanosine plasma concentrations (AUC_{12-24}) were unchanged during the dosing intervals when CYMEVENE was not co-administered. Ganciclovir pharmacokinetics were not affected by didanosine. In neither study were there significant changes in the renal clearance of either drug.

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.This increase in didanosine plasma concentration 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. However, given the increase in didanosine plasma concentrations in the presence of ganciclovir, patients should be closely monitored for didanosine toxicity (ie. pancreatitis).

Didanosine has been associated with pancreatitis. In three controlled trials, pancreatitis was reported in 2% of patients taking didanosine and CYMEVENE. The rates of pancreatitis were similar in the intravenous solution and capsule groups.

Other than laboratory abnormalities, concomitant treatment with zidovudine, didanosine, or zalcitabine did not appear to affect the type or frequency of reported adverse events, with the exception of moderately increased rates of diarrhea. Among patients taking CYMEVENE, the diarrhea rates were 51% and 49% respectively with didanosine versus 39% and 35% respectively, without didanosine.

Stavudine

No statistically significant pharmacokinetic interaction was observed when stavudine and oral ganciclovir were given in combination.

Trimethoprim

Trimethoprim statistically significantly decreased the renal clearance of oral ganciclovir by 16.3% 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_{min}. 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.

Imipenem-cilastatin

Seizures have been reported in patients who received CYMEVENE (ganciclovir for injection) 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.

Mycophenolate Mofetil

Following single-dose administration to twelve stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and CYMEVENE (5 mg/kg). Mean (±SD) ganciclovir AUC and C_{max} were 54.3 (±19.0) µg•h/mL and 11.5 (±1.8) µg/mL, respectively after coadministration of the two drugs, compared to 51.0 (±17.0) µg•h/mL and 10.6 (±2.0) µg/mL, respectively after administration of CYMEVENE alone. The mean (±SD) AUC and C_{max} of MPA (active metabolite of mycophenolate) after coadministration were 80.9 (±21.6) µg•h/mL and 27.8 (±13.9) µg/mL, respectively compared to values of 80.3 (±16.4) µg•h/mL and 30.9 (±11.2) µg/mL, respectively after administration of mycophenolate mofetil alone. However, based on the known effects of renal impairment on the pharmacokinetics of ganciclovir and mycophenlate, it is anticipated that coadministration of these agents (which have the potential to compete for mechanisms of renal tubular secretion) will result in increases in ganciclovir concentration and MPAG (inactive metabolite of mycophenolate). In patients with renal impairment in which ganciclovir and mycophenolate are co-administered, the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Probenecid

At a dose of 1000 mg of ganciclovir capsules every 8 hours, ganciclovir serum concentrations increased 45% in the presence of probenecid, 500 mg every 6 hours. Renal clearance of ganciclovir decreased 22%, which is consistent with an interaction involving competition for renal tubular secretion. Patients taking probenecid and ganciclovir capsules should be closely monitored for ganciclovir toxicity.

It is possible that drugs that inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia, and germinal layers of skin and gastrointestinal mucosa, may have additive toxicity when administered concomitantly with CYMEVENE. In addition, toxicity may be enhanced when ganciclovir is co-administered with other drugs known to be myelosuppressive or associated with renal impairment. Therefore, drugs known to be myelosuppressive or associated with renal impairment including 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) should only be considered for concomitant use with CYMEVENE if the potential benefits are judged to outweigh the risks.

Since ganciclovir is excreted through the kidney via glomerular filtration and active tubular secretion (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Excretion), coadministration of ganciclovir with drugs that share the tubular secretion pathway may change the plasma concentrations of ganciclovir and/or the coadministered drug.

Allograft recipients treated with CYMEVENE in three controlled clinical studies also received a variety of concomitant medications, including amphotericin B, azathioprine, cyclosporine, muromonab-CD3 (OKT3), and/or prednisone. Increases in serum creatinine were observed in patients treated with CYMEVENE plus either cyclosporine or amphotericin B, drugs with known potential for nephrotoxicity (see ADVERSE REACTIONS). In a retrospective analysis of 93 liver allograft recipients receiving ganciclovir (5 mg/kg infused over 1 hour every 12 hours) and oral cyclosporine (at therapeutic doses), there was no evidence of an effect on cyclosporine whole blood concentrations.

7 OVERDOSAGE

Treatment: Hemodialysis may be useful in reducing serum concentrations, given that it reduces plasma concentrations of ganciclovir by approximately 50% during a 4 hour hemodialysis session (see DOSAGE AND ADMINISTRATION: Hemodialysis). Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered.

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: mylosuppression including pancytopenia, bone marrow failure, 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

In addition, one adult received 0.4 mL (instead of 0.1 mL) CYMEVENE by intravitreal injection, and experienced temporary loss of vision and central retinal artery occlusion secondary to increased intraocular pressure related to the injected fluid volume.

Overdose Experience with Valganciclovir

One adult developed fatal bone marrow failure (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).

8 ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

CYMEVENE (ganciclovir for injection) is a synthetic nucleoside analogue of guanine which inhibits the replication of herpes viruses both in vitro and in vivo.
Intracellular ganciclovir is phosphorylated to ganciclovir monophosphate by a cellular deoxyguanosine kinase. Further phosphorylation occurs by several cellular kinases to produce ganciclovir triphosphate. It has been shown in vitro that the levels of ganciclovir triphosphate are as much as 100-fold greater in CMV-infected cells than non-infected cells. Thus, there is a preferential phosphorylation of ganciclovir in virus-infected cells. In virus-infected cells, ganciclovir triphosphate is metabolized slowly, with 60 to 70% remaining intracellularly 18 hours after removal of ganciclovir from the extracellular fluid. The antiviral activity of ganciclovir is the result of inhibition of viral DNA synthesis by two modes: (1)

ganciclovir triphosphate competitively inhibits dGTP incorporation into DNA by DNA polymerase and (2) incorporation of ganciclovir triphosphate into viral DNA causes subsequent termination or very limited viral DNA elongation.

Ganciclovir inhibits mammalian cell proliferation in vitro at concentrations from 10 to 60 µg/mL, with bone marrow colony forming cells being most sensitive (IC50 of 10 µg/mL).

Pharmacokinetics

The pharmacokinetics of CYMEVENE have been evaluated in immunocompromised patients with serious CMV disease. In patients with normal renal function, the plasma half-life was 2.9 ± 1.3 hours. Dose independent kinetics were demonstrated over the range of 1.6 to 5.0 mg/kg. Renal excretion through both glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir (see WARNINGS AND PRECAUTIONS: for use in patients with renal impairment). At the end of a one-hour intravenous infusion of 5 mg/kg CYMEVENE (ganciclovir for injection), total ganciclovir area under the serum concentration vs. time curve

(AUC) ranged between 22.1±3.2 (n=16) and 26.8±6.1 µg•hr/mL(n=16) and maximum serum concentration (Cmax) ranged between 8.27±1.02 (n=16) and 9.0±1.4 µg/mL (n=16).

9 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

CYMEVENE 500 MG (ganciclovir sodium) for injection is supplied in 10 mL sterile vials, each containing ganciclovir sodium equivalent to 500 mg of ganciclovir as a white to off-white powder. The concentration of ganciclovir in the reconstituted solution is 50 mg/mL. CYMEVENE 500 MG is supplied in cartons of 5 single dose vials.

Shelf-life

The expiry date of the product is indicated on the packaging materials.

Storage

Do not store above 30°C.
Store reconstituted solution in the vial at 25°C for no longer than 12 hours. Do not refrigerate or freeze. Discard any unused portion of the reconstituted solution.
Store diluted infusion solution under refrigeration at 2° to 8°C for no longer than 24 hours. Do not freeze.

Composition

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

The non-active ingredients are: hydrochloric acid and sodium hydroxide.

MANUFACTURER
Cheplapharm Arzeimittel GmbH, Greifswald, Germany

LICENSE HOLDER
Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Kiryat Matalon, Petah-Tikva

LICENSE NUMBER
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