

GANCICLOVIR MEDI-MARKET 500 MG

FULL PRESCRIBING INFORMATION

WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS

- **Hematologic Toxicity:** Granulocytopenia, anemia, thrombocytopenia, and pancytopenia have been reported in patients treated with intravenous GANCICLOVIR 500 MG [see *Warnings and Precautions (5.1)*].
- **Impairment of Fertility:** Based on animal data and limited human data, GANCICLOVIR MEDI-MARKET 500 MG may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females [see *Warnings and Precautions (5.3)*].
- **Fetal Toxicity:** Based on animal data, GANCICLOVIR MEDI-MARKET 500 MG has the potential to cause birth defects in humans [see *Warnings and Precautions (5.4)*].
- **Mutagenesis and Carcinogenesis:** Based on animal data, GANCICLOVIR MEDI-MARKET 500 MG has the potential to cause cancers in humans [see *Warnings and Precautions (5.5)*].

NAME OF THE MEDICINAL PRODUCT

GANCICLOVIR MEDI-MARKET 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 11.

PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
white lyophilized powder for concentrate for solution for infusion.

CLINICAL PARTICULARS

1 INDICATIONS AND USAGE

GANCICLOVIR MEDI-MARKET 500 MG is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). GANCICLOVIR MEDI-MARKET 500 MG is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease (see *Clinical Studies 14.1, 14.2*).

SAFETY AND EFFICACY OF GANCICLOVIR MEDI-MARKET 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 GANCICLOVIR MEDI-MARKET 500 MG SOLUTION BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF GANCICLOVIR MEDI-MARKET 500 MG MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS.

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

Dosage

THE RECOMMENDED DOSE FOR GANCICLOVIR MEDI-MARKET 500 MG SOLUTION SHOULD NOT BE EXCEEDED. THE RECOMMENDED INFUSION RATE FOR GANCICLOVIR MEDI-MARKET 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 GANCICLOVIR MEDI-MARKET 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 GANCICLOVIR MEDI-MARKET 500 MG, reinduction treatment is recommended.

For the Prevention of CMV Disease in Transplant Recipients with Normal Renal Function

The recommended initial dosage of GANCICLOVIR MEDI-MARKET 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 GANCICLOVIR MEDI-MARKET 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 intravenous GANCICLOVIR 500 MG was continued until day 100 to 120 post transplantation. CMV disease occurred in several patients who discontinued treatment with intravenous GANCICLOVIR 500 MG solution prematurely. In heart allograft recipients, the onset of newly diagnosed CMV disease occurred after treatment with intravenous GANCICLOVIR 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 GANCICLOVIR MEDI-MARKET 500 MG solution and adjust the dosing interval as indicated:

Table 8 Dosing for Patients with Renal Impairment

Creatinine Clearance* (mL/min)	GANCICLOVIR MEDI-MARKET 500 MG Induction Dose (mg/kg)	Dosing Interval (hours)	GANCICLOVIR MEDI-MARKET 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
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* Creatinine clearance can be related to serum creatinine by the formulas given below.

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

Creatinine clearance for females = 0.85 x male value

Dosing for patients undergoing hemodialysis should not exceed 1.25 mg/kg 3 times per week, following each hemodialysis session. GANCICLOVIR MEDI-MARKET 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 GANCICLOVIR MEDI-MARKET 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 GANCICLOVIR MEDI-MARKET 500 MG Solution

Each 10 mL clear glass vial contains ganciclovir sodium equivalent to 500 mg of ganciclovir and approximately 43 mg of sodium. The contents of the vial should be prepared for administration in the following manner:

1. Reconstituted Solution:

- a. Reconstitute lyophilized GANCICLOVIR MEDI-MARKET 500 MG by injecting 10 mL of Sterile Water for Injection into the vial. **DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING PARABENS. IT IS INCOMPATIBLE WITH GANCICLOVIR MEDI-MARKET 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. Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated at 20-25°C for 12 hours. Do not refrigerate or freeze. For further information see section 15.

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 GANCICLOVIR MEDI-MARKET 500 MG solution: 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection and Lactated Ringer's Injection..

GANCICLOVIR MEDI-MARKET 500 MG, when reconstituted with sterile water for injection (non-bacteriostatic), further diluted with 0.9% sodium chloride injection or other acceptable infusion fluid as specified above, and stored refrigerated at 2-8°C, remains physically and chemically stable for 24 hours.

Because GANCICLOVIR MEDI-MARKET 500 MG is reconstituted with non-bacteriostatic 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.

For further information see section 15.

Handling and Disposal

Caution should be exercised in the handling and preparation of solutions of GANCICLOVIR MEDI-MARKET 500 MG. Solutions of GANCICLOVIR MEDI-MARKET 500 MG are alkaline (pH 11). Avoid direct contact of the skin or mucous membranes with GANCICLOVIR MEDI-MARKET 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 [*see How Supplied/Storage and Handling (15)*].

3 DOSAGE FORMS AND STRENGTHS

See section 15.

4 CONTRAINDICATIONS

GANCICLOVIR MEDI-MARKET 500 MG is contraindicated in patients who have experienced hypersensitivity to the active ingredient (ganciclovir), valganciclovir, or any excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity

Granulocytopenia (neutropenia), anemia, thrombocytopenia and pancytopenia have been observed in patients treated with intravenous GANCICLOVIR 500 MG. The frequency and severity of these events vary widely in different patient populations [*see Adverse Reactions (6.1)*]. GANCICLOVIR MEDI-MARKET 500 MG is not recommended if the absolute neutrophil count is less than 500 cells/ μ L, hemoglobin is less than 8 g/dL, or the platelet count is less than 25,000 cells/ μ L. GANCICLOVIR MEDI-MARKET 500 MG should also be used with caution in patients with pre-existing cytopenias and in patients receiving myelosuppressive drugs or irradiation. Granulocytopenia (neutropenia) usually occurs during the first or second week of treatment but may occur at any time during treatment. Cell counts usually begin to recover within 3 to 7 days after discontinuing drug. Colony-stimulating factors have been shown to increase neutrophil and white blood cell counts in patients receiving intravenous GANCICLOVIR 500 MG solution for treatment of CMV retinitis.

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving intravenous GANCICLOVIR 500 MG [*see Adverse Reactions (6.1)*], complete blood counts with differential and platelet counts should be performed frequently in all patients, especially in patients with renal impairment and in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/ μ L at the beginning of treatment [*see Dosage and Administration (2.2)*].

5.2 Renal Impairment

GANCICLOVIR MEDI-MARKET 500 MG should be used with caution in patients with impaired renal function because the half-life and plasma/serum concentrations of ganciclovir will be increased due to reduced renal clearance. If renal function is impaired, dosage adjustments are recommended [*see Dosage and Administration (2.5), Use in Specific Populations (8.5, 8.6)*].

Increased serum creatinine levels have been reported in elderly patients and in transplant recipients receiving concomitant nephrotoxic medications (i.e., ciclosporin and amphotericin B). Monitoring renal function during therapy with GANCICLOVIR MEDI-MARKET 500 MG is essential, especially for elderly patients and those patients receiving concomitant agents that may cause nephrotoxicity [*see Dosage and Administration (2.5), Drug Interactions (7), Use in Specific Populations (8.5)*].

5.3 Impairment of Fertility

Based on animal data and limited human data, GANCICLOVIR MEDI-MARKET 500 MG at the recommended human dose (RHD) may cause temporary or permanent inhibition of spermatogenesis in males, and may cause suppression of fertility in females. Advise patients that fertility may be impaired with the use of GANCICLOVIR MEDI-MARKET 500 MG [see *Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)*].

5.4 Fetal Toxicity

GANCICLOVIR MEDI-MARKET 500 MG may cause fetal toxicity when administered to pregnant women based on findings in animal studies. Systemic exposure of ganciclovir in animals at approximately 2 times the RHD caused fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes in animals included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with GANCICLOVIR MEDI-MARKET 500 MG. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with GANCICLOVIR MEDI-MARKET 500 MG [see *Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)*].

5.5 Mutagenesis and Carcinogenesis

Animal data indicate that ganciclovir is mutagenic and carcinogenic. GANCICLOVIR MEDI-MARKET 500 MG should therefore be considered a potential carcinogen in humans [see *Dosage and Administration (2.7), Nonclinical Toxicology (13.1)*].

5.6 Excipients

This medicinal product contains approximately 43mg (2 mmol) sodium per 500 mg dose. To be taken into consideration by patients on a controlled sodium diet.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Hematologic Toxicity [see *Warnings and Precautions (5.1)*]
- Renal Impairment [see *Warnings and Precautions (5.2)*]
- Impairment of Fertility [see *Warnings and Precautions (5.3)*]
- Fetal Toxicity [see *Warnings and Precautions (5.4)*]
- Mutagenesis and Carcinogenesis [see *Warnings and Precautions (5.5)*]

6.1 Clinical Trial Experience in Adult Patients

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice. The most common adverse reactions and laboratory abnormalities reported in at least 20% of patients were pyrexia, diarrhea, leukopenia, nausea, anemia, asthenia, headache, cough, decreased appetite, dyspnea, abdominal pain, sepsis, hyperhidrosis, and blood creatinine increased.

Selected adverse reactions that occurred during clinical trials of intravenous GANCICLOVIR 500 MG are summarized below, according to the participating study patient population.

Adverse Reactions in Patients with CMV Retinitis: Three controlled, randomized, phase 3 trials comparing intravenous GANCICLOVIR 500 MG and ganciclovir capsules for maintenance treatment of CMV retinitis have been completed. During these trials, intravenous GANCICLOVIR 500 MG or ganciclovir capsules were prematurely discontinued in 9% of subjects because of adverse reactions. Selected adverse reactions and laboratory abnormalities reported during the conduct of these controlled trials are summarized in Table 2 and Table 3, respectively [see *Clinical Studies (14.1)*].

Table 2. Pooled Selected Adverse Reactions Reported in $\geq 5\%$ of Subjects Comparing Intravenous GANCICLOVIR 500 MG to Ganciclovir Capsules for Maintenance Treatment of CMV Retinitis

Adverse Reaction	Maintenance Treatment Studies	
	Intravenous GANCICLOVIR 500 MG (n=179)	Ganciclovir Capsules (n=326)
Pyrexia	48%	38%
Diarrhea	44%	41%
Leukopenia	41%	29%
Anemia	25%	19%
Total catheter events	22%	6%
Catheter infection	9%	4%
Catheter sepsis	8%	1%
Other catheter related events	5%	1%
Sepsis	15%	4%
Decreased appetite	14%	15%
Vomiting	13%	13%
Infection	13%	9%
Hyperhidrosis	12%	11%
Chills	10%	7%
Neuropathy peripheral	9%	8%
Thrombocytopenia	6%	6%
Pruritus	5%	6%

Retinal Detachment: Retinal detachment has been observed in subjects with CMV retinitis both before and after initiation of therapy with ganciclovir. Its relationship to therapy with ganciclovir is unknown. Retinal detachment occurred in 11% of patients treated with intravenous GANCICLOVIR 500 MG and in 8% of patients treated with ganciclovir capsules.

Table 3. Selected Laboratory Abnormalities in Trials for Treatment of CMV Retinitis

Laboratory Abnormalities	CMV Retinitis Treatment*	
	Intravenous GANCICLOVIR 500 MG † 5 mg/kg/day (N=175) %	Ganciclovir Capsules‡ 3000 mg/day (N=320) %
Neutropenia with Absolute Neutrophil Count (ANC) per μL :		
<500	25%	18%
500 – <749	14%	17%
750 – <1000	26%	19%
Anemia with Hemoglobin (g/dL):		
<6.5 g/dL	5%	2%
6.5 – <8.0	16%	10%
8.0 – <9.5	26%	25%
Serum Creatinine (mg/dL):		
≥ 2.5	2%	1%
≥ 1.5 – <2.5	14%	12%

* Pooled data from Treatment Studies: ICM 1653, ICM 1774 and AVI 034

† Mean time on therapy = 103 days, including allowed re-induction treatment periods

‡ Mean time on therapy = 91 days, including allowed re-induction treatment periods

Adverse Reactions in Transplant Recipients: There have been three controlled clinical trials of Intravenous GANCICLOVIR 500 MG for the prevention of CMV disease in transplant recipients. Selected laboratory abnormalities are summarized in Table 4 and Table 5 below. Table 4 shows the frequency of neutropenia and thrombocytopenia and Table 5 shows the frequency of elevated serum creatinine values observed in these trials [see *Clinical Studies (14.2)*].

Table 4. Laboratory Abnormalities in Controlled Trials—Transplant Recipients who Received Intravenous GANCICLOVIR 500 MG, Placebo or Control

	Intravenous GANCICLOVIR 500 MG			
	Heart Allograft*		Bone Marrow Allograft†	
	Intravenous GANCICLOVIR 500 MG (n=76)	Placebo (n=73)	Intravenous GANCICLOVIR 500 MG (n=57)	Control (n=55)
Neutropenia				
Absolute Neutrophil Count (ANC) per μL				
<500	4%	3%	12%	6%
500-1000	3%	8%	29%	17%
Total ANC $\leq 1000/\mu\text{L}$	7%	11%	41%	23%
Thrombocytopenia				
Platelet count per μL				
<25,000	3%	1%	32%	28%
25,000-50,000	5%	3%	25%	37%
Total Platelet Count $\leq 50,000/\mu\text{L}$	8%	4%	57%	65%

* Study ICM 1496. Mean duration of treatment = 28 days

† Study ICM 1570 and ICM 1689. Mean duration of treatment = 45 days

Table 5. Serum Creatinine Levels in Controlled Trials—Transplant Recipients who Received Intravenous GANCICLOVIR 500 MG or Placebo

Serum Creatinine Levels (mg/dL)	Heart Allograft ICM 1496		Bone Marrow Allograft ICM 1570		Bone Marrow Allograft ICM 1689	
	Intravenous GANCICLOVIR 500 MG (n=76)	Placebo (n=73)	Intravenous GANCICLOVIR 500 MG (n=20)	Control (n=20)	Intravenous GANCICLOVIR 500 MG (n=37)	Placebo (n=35)
≥ 2.5 mg/dL	18%	4%	20%	0%	0%	0%
$\geq 1.5 - < 2.5$	58%	69%	50%	35%	43%	44%

Other Adverse Reactions in Clinical Trials in Patients with CMV Retinitis and in Transplant Recipients

Adverse drug reactions with Intravenous GANCICLOVIR 500 MG or ganciclovir capsules in controlled clinical studies in either subjects with AIDS or transplant recipients are listed below [see *Clinical Studies (14)*]. All these events occurred in at least 3 subjects.

Blood and lymphatic disorders: pancytopenia, bone marrow failure

Cardiac disorders: arrhythmia

Ear and labyrinth disorders: tinnitus, ear pain, deafness

Eye disorders: visual impairment, vitreous disorders, eye pain, conjunctivitis, macular edema

Gastrointestinal disorders: nausea, abdominal pain, dyspepsia, flatulence, constipation, mouth ulceration, dysphagia, abdominal distention, pancreatitis, gastrointestinal perforation, eructation, dry mouth

General disorders and administration site conditions: fatigue, injection site inflammation, edema, pain, malaise, asthenia, chest pain, multiple organ failure

Immune system disorders: hypersensitivity

Infections and infestations: candida infections including oral candidiasis, upper respiratory infection, influenza, urinary tract infection, cellulitis

Investigations: blood alkaline phosphatase increased, hepatic function abnormal, aspartate aminotransferase increased, alanine aminotransferase increased, creatinine clearance decreased

Metabolism and nutrition disorders: weight decreased

Musculoskeletal and connective tissue disorders: back pain, myalgia, arthralgia, muscle spasms, leg cramps, myasthenia

Nervous system disorders: headache, insomnia, dizziness, paresthesia, hypoesthesia, seizure, somnolence, dysgeusia (taste disturbance), tremor

Psychiatric disorders: depression, confusional state, anxiety, agitation, psychotic disorder, thinking abnormal, abnormal dreams

Renal and urinary disorders: kidney failure, renal function abnormal, urinary frequency, hematuria

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Skin and subcutaneous tissues disorders: dermatitis, alopecia, dry skin, urticaria, rash

Vascular disorders: hypotension, hypertension, phlebitis, vasodilation

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of intravenous GANCICLOVIR 500 MG or ganciclovir capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic disorders: hemolytic anemia, agranulocytosis, granulocytopenia

Cardiac disorders: cardiac arrest, conduction disorder, torsade de pointes, ventricular tachycardia

Congenital, familial and genetic disorders: congenital anomaly

Endocrine disorders: inappropriate antidiuretic hormone secretion

Eye disorders: cataracts, dry eyes

Gastrointestinal disorders: intestinal ulcer

Hepatobiliary disorders: cholelithiasis, cholestasis, hepatic failure, hepatitis

Immune system disorders: anaphylactic reaction, allergic reaction, vasculitis

Investigations: blood triglycerides increased

Metabolism and nutrition disorders: acidosis, hypercalcemia, hyponatremia

Musculoskeletal and connective tissue disorders: arthritis, rhabdomyolysis

Nervous system disorders: dysesthesia, dysphasia, extrapyramidal disorder, facial paralysis, amnesia, anosmia, myelopathy, cerebrovascular accident, third cranial nerve paralysis, aphasia, encephalopathy, intracranial hypertension

Psychiatric disorders: irritability, hallucinations

Renal and urinary disorders: renal tubular disorder, hemolytic uremic syndrome

Reproductive system and breast disorders: infertility, testicular hypotrophy

Respiratory, thoracic and mediastinal disorders: bronchospasm, pulmonary fibrosis

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

Vascular disorders: peripheral ischemia

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>

7 DRUG INTERACTIONS

Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of GANCICLOVIR MEDI-MARKET 500 MG and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

Established and other potentially significant drug interactions conducted with ganciclovir are listed in Table 6 [see *Clinical Pharmacology (12.3)*].

Table 6. Established and Other Potentially Significant Drug Interactions with Ganciclovir

Name of the Concomitant Drug	Change in the Concentration of Ganciclovir or Concomitant Drug	Clinical Comment
Imipenem-cilastatin	Unknown	Coadministration with imipenem-cilastatin is not recommended because generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin.
Ciclosporin or amphotericin B	Unknown	Monitor renal function when GANCICLOVIR MEDI-MARKET 500 MG is coadministered with ciclosporin or amphotericin B because of potential increase in serum creatinine [see <i>Warnings and Precautions (5.2)</i>].

Mycophenolate mofetil (MMF)	↔ Ganciclovir (in patients with normal renal function) ↔ MMF (in patients with normal renal function)	Based on increased risk, patients should be monitored for hematological and renal toxicity.
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Name of the Concomitant Drug	Change in the Concentration of Ganciclovir or Concomitant Drug	Clinical Comment
Other drugs associated with myelosuppression or nephrotoxicity (e.g., dapsone, doxorubicin, flucytosine, hydroxyurea, pentamidine, tacrolimus, trimethoprim/ sulfamethoxazole, vinblastine, vincristine and zidovudine)	Unknown	Because of potential for higher toxicity, coadministration with GANCICLOVIR MEDI-MARKET 500 MG should be considered only if the potential benefits are judged to outweigh the risks.
Didanosine	↔ Ganciclovir ↑ Didanosine	Patients should be closely monitored for didanosine toxicity (e.g., pancreatitis).
Probenecid	↑ Ganciclovir	GANCICLOVIR MEDI-MARKET 500 MG dose may need to be reduced. Monitor for evidence of ganciclovir toxicity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In animal studies, ganciclovir caused maternal and fetal toxicity and embryo-fetal mortality in pregnant mice and rabbits as well as teratogenicity in rabbits at exposures two times the exposure at the recommended human dose (RHD). Although placental transfer of ganciclovir has been shown to occur based on ex vivo experiments with human placenta and in at least one case report in a pregnant woman, no adequate human data are available to establish whether GANCICLOVIR MEDI-MARKET 500 MG poses a risk to pregnancy outcomes. The background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

Most maternal CMV infections are asymptomatic or they may be associated with a self-limited mononucleosis-like syndrome. However, in immunocompromised patients (i.e., transplant patients or patients with AIDS), CMV infections may be symptomatic and may result in significant maternal morbidity and mortality. The transmission of CMV to the fetus is a result of maternal viremia and transplacental infection. Perinatal infection can also occur from exposure of the neonate to CMV shedding in the genital tract. Approximately 10% of children with congenital CMV infection are symptomatic at birth. Mortality in symptomatic infants is about 10% and approximately 50–90% of symptomatic surviving newborns experience significant morbidity, including mental retardation, sensorineural hearing loss, microcephaly, seizures, and other medical problems. The risk of congenital CMV infection resulting from primary maternal CMV infection may be higher and of greater severity than that resulting from maternal reactivation of CMV infection.

Data

Animal Data

Daily intravenous doses of ganciclovir were administered to pregnant mice (108 mg/kg/day) and rabbits (60 mg/kg/day), and also to female mice (90 mg/kg) prior to mating, during gestation, and during lactation. Fetal resorptions were present in at least 85% of rabbits and mice. Additional effects observed in rabbits included fetal growth retardation, embryoletality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly, and brachygnathia. In pre/postnatal development studies in mice, there were maternal/fetal toxicity and embryoletality which included fetal effects of hypoplasia of the testes and seminal vesicles in the male offspring, as well as pathologic changes in the nonglandular region of the stomach. The systemic exposure (AUC) of ganciclovir during these studies was approximately 2 times (pregnant mice and rabbits) and 1.7 times (pre/postnatal mice) the exposure in humans at the RHD [see *Nonclinical Toxicology (13.1)*].

8.2 Lactation

Risk Summary

No data are available regarding the presence of ganciclovir in human milk, the effects on the breastfed infant, or the effects on milk production. When ganciclovir was administered to lactating rats, ganciclovir was present in milk. Advise nursing mothers that breastfeeding is not recommended during treatment with GANCICLOVIR MEDI-MARKET 500 MG because of the potential for serious adverse reactions in nursing infants [see *Warnings and Precautions (5.1, 5.3, 5.4, 5.5), Nonclinical Toxicology (13.1)*]. Furthermore, the Centers for Disease Control and Prevention recommends that HIV-infected mothers not breastfeed their infants to avoid potential postnatal transmission of HIV.

Data

Animal Data

Ganciclovir administered intravenously (at 0.13 mg/h) to lactating rats (on lactation day 15) resulted in passive transfer into milk. The milk-to-serum ratio for ganciclovir at steady state was 1.6 ± 0.33 .

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Females of reproductive potential should undergo pregnancy testing before initiation of treatment with GANCICLOVIR MEDI-MARKET 500 MG [see *Dosage and Administration (2.2), Use in Specific Populations (8.1)*].

Contraception

Females

Because of the mutagenic and teratogenic potential of GANCICLOVIR MEDI-MARKET 500 MG, females of reproductive potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with GANCICLOVIR MEDI-MARKET 500 MG [see *Dosage and Administration (2.2), Warnings and Precautions (5.4), Nonclinical Toxicology (13.1)*].

Males

Because of its mutagenic potential, males should be advised to practice barrier contraception during and for at least 90 days following treatment with GANCICLOVIR MEDI-MARKET 500 MG [see *Warnings and Precautions (5.4), Nonclinical Toxicology (13.1)*].

Infertility

GANCICLOVIR MEDI-MARKET 500 MG at the recommended doses may cause temporary or permanent female and male infertility [see *Warnings and Precautions (5.3), Nonclinical Toxicology (13.1)*].

Data

Human Data

In a small, open-label, non-randomized clinical study, adult male renal transplant patients receiving valganciclovir (the prodrug of ganciclovir) for CMV prophylaxis for up to 200 days post-transplantation were compared to an untreated control group. Patients were followed-up for six months after valganciclovir discontinuation. Among 24 evaluable patients in the valganciclovir group, the mean sperm density at the end of treatment visit decreased by 11 million/mL from baseline; whereas, among 14 evaluable patients in the control group the mean sperm density increased by 33 million/mL. However, at the follow-up visit among 20 evaluable patients in the valganciclovir group, the mean sperm density was comparable to that observed among 10 evaluable patients in the untreated control group (the mean sperm density at the end of follow-up visit increased by 41 million/mL from baseline in the valganciclovir group and by 43 million/mL in the untreated group).

8.4 Pediatric Use

Safety and efficacy of GANCICLOVIR MEDI-MARKET 500 MG have not been established in pediatric patients.

A total of 120 pediatric patients with serious CMV infections participated in clinical trials. Granulocytopenia and thrombocytopenia were the most common adverse reactions. The pharmacokinetic characteristics of ganciclovir after administration of intravenous GANCICLOVIR 500 MG were studied in 27 neonates (aged 2 to 49 days) and 10 pediatric patients, aged 9 months to 12 years. In neonates, the pharmacokinetic parameters after ganciclovir intravenous doses of 4 mg/kg (n=14) and 6 mg/kg (n=13) were C_{\max} 5.5 ± 1.6 and 7.0 ± 1.6 mcg/mL, systemic clearance 3.14 ± 1.75 and 3.56 ± 1.27 mL/min/kg, and $t_{1/2}$ of 2.4 hours (harmonic mean) for both doses, respectively.

In pediatric patients 9 months to 12 years of age, the pharmacokinetic characteristics of ganciclovir were the same after single and multiple (every 12 hours) intravenous doses (5 mg/kg). The steady-state volume of distribution was 0.64 ± 0.22 L/kg, C_{\max} was 7.9 ± 3.9 mcg/mL, systemic clearance was 4.7 ± 2.2 mL/min/kg, and $t_{1/2}$ was 2.4 ± 0.7 hours.

Although the pharmacokinetics of intravenous GANCICLOVIR 500 MG in pediatric patients were similar to those observed in adults, the safety and efficacy of ganciclovir at these exposures in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of intravenous GANCICLOVIR 500 MG did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. GANCICLOVIR MEDI-MARKET 500 MG is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because renal clearance decreases with age, GANCICLOVIR MEDI-MARKET 500 MG should be administered to elderly patients with special consideration of their renal status. Renal function should be monitored and dosage adjustments should be made accordingly [see *Dosage and Administration* (2.5), *Warnings and Precautions* (5.2), *Use in Specific Populations* (8.6)].

8.6 Renal Impairment

Dose reduction is recommended when administering GANCICLOVIR MEDI-MARKET 500 MG to patients with renal impairment [see *Dosage and Administration* (2.5), *Warnings and Precautions* (5.2)].

8.7 Hepatic Impairment

The safety and efficacy of GANCICLOVIR MEDI-MARKET 500 MG have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

Reports of adverse reactions after overdoses with intravenous GANCICLOVIR 500 MG, some with fatal outcomes, have been received from clinical trials and during postmarketing experience. One or more of the following adverse reactions has been reported with overdoses:

Hematological toxicity: myelosuppression including pancytopenia, leukopenia, neutropenia, granulocytopenia, thrombocytopenia, bone marrow failure

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

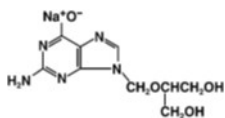
Neurotoxicity: seizure

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of GANCICLOVIR MEDI-MARKET 500 MG [see *Clinical Pharmacology (12.3)*]. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered in patients with cytopenias [see *Warnings and Precautions (5.1)*].

11 DESCRIPTION

GANCICLOVIR MEDI-MARKET 500 MG contains ganciclovir, in the form of the sodium salt for intravenous injection. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).

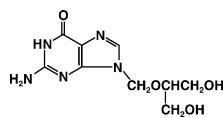
Chemically, ganciclovir is 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine and ganciclovir sodium is 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine, monosodium salt. The chemical structures of ganciclovir sodium and ganciclovir are:



ganciclovir sodium

$C_9H_{12}N_5NaO_4$,

M.W. =277.22



ganciclovir

$C_9H_{13}N_5O_4$

M.W. =255.23

Ganciclovir is a white lyophilized powder. Ganciclovir is a polar hydrophilic compound with a solubility of 2.6 mg/mL in water at 25°C and an n-octanol/water partition coefficient of 0.022. The pK_as for ganciclovir are 2.2 and 9.4.

GANCICLOVIR MEDI-MARKET 500 MG (ganciclovir), is a sterile white lyophilized powder.

Each vial contains ganciclovir sodium equivalent to 500 mg ganciclovir.

All doses in this package insert are specified in terms of ganciclovir.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ganciclovir is an antiviral drug with activity against CMV [see *Microbiology (12.4)*].

12.3 Pharmacokinetics

Absorption

At the end of a 1-hour intravenous infusion of 5 mg/kg ganciclovir, total AUC ranged between 22.1 ± 3.2 (n=16) and 26.8 ± 6.1 mcg·hr/mL (n=16) and C_{max} ranged between 8.27 ± 1.02 (n=16) and 9.0 ± 1.4 mcg/mL (n=16).

Distribution

The steady-state volume of distribution of ganciclovir after intravenous administration was 0.74 ± 0.15 L/kg (n=98). Ganciclovir diffuses across the placenta. Cerebrospinal fluid concentrations obtained 0.25 to 5.67 hours post-dose in 3 patients who received 2.5 mg/kg ganciclovir intravenously every 8 hours or every 12 hours ranged from 0.31 to 0.68 mcg/mL, representing 24% to 70% of the respective plasma concentrations. Binding to plasma proteins was 1% to 2% over ganciclovir concentrations of 0.5 and 51 mcg/mL.

Elimination

When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6 to 5.0 mg/kg. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. In patients with normal renal function, $91.3 \pm 5.0\%$ (n=4) of intravenously administered ganciclovir was recovered unmetabolized in the urine. Systemic clearance of intravenously administered ganciclovir was 3.52 ± 0.80 mL/min/kg (n=98) while renal clearance was 3.20 ± 0.80 mL/min/kg (n=47), accounting for $91 \pm 11\%$ of the systemic clearance (n=47). Half-life was 3.5 ± 0.9 hours (n=98) following intravenous administration.

Specific Populations

Pharmacokinetics in Patients with Renal Impairment

The pharmacokinetics following intravenous administration of GANCICLOVIR 500 MG solution were evaluated in 10 immunocompromised patients with renal impairment who received doses ranging from 1.25 to 5.0 mg/kg. Decreased renal function results in decreased clearance of ganciclovir (Table 7).

Table 7. Ganciclovir Pharmacokinetics in Patients with Renal Impairment

Estimated Creatinine Clearance (mL/min)	n	Dose	Clearance (mL/min) Mean \pm SD	Half-life (hours) Mean \pm SD
50–79	4	3.2–5 mg/kg	128 ± 63	4.6 ± 1.4
25–49	3	3–5 mg/kg	57 ± 8	4.4 ± 0.4
<25	3	1.25–5 mg/kg	30 ± 13	10.7 ± 5.7

Plasma concentrations of ganciclovir are reduced by about 50% during a 4 hour hemodialysis session.

Pharmacokinetics in Geriatric Patients

The pharmacokinetic profiles of GANCICLOVIR MEDI-MARKET 500 MG in patients 65 years of age and older have not been established. As ganciclovir is mainly renally excreted and since renal clearance decreases with age, a decrease in ganciclovir total body clearance and a prolongation of ganciclovir half-life can be anticipated in patients 65 years of age and older [see *Dosage and Administration (2.5)*, *Use in Specific Populations (8.5)*].

Drug Interaction Studies

Table 8 and Table 9 provide a listing of established drug interaction studies with ganciclovir. Table 8 provides the effects of coadministered drug on ganciclovir plasma pharmacokinetic parameters, whereas Table 9 provides the effects of ganciclovir on plasma pharmacokinetic parameters of coadministered drug.

Table 8. Results of Drug Interaction Studies with Ganciclovir: Effects of Coadministered Drug on Ganciclovir Pharmacokinetic Parameters

Coadministered Drug	Ganciclovir Dosage	N	Ganciclovir Pharmacokinetic (PK) Parameter
Mycophenolate mofetil (MMF) 1.5 g single dose	5 mg/kg IV single dose	12	No effect on ganciclovir PK parameters observed (patients with normal renal function)
Trimethoprim 200 mg once daily	1000 mg orally every 8 hours	12	No effect on ganciclovir PK parameters observed.
Didanosine 200 mg every 12 hours simultaneously administered with ganciclovir	5 mg/kg IV twice daily	11	No effect on ganciclovir PK parameters observed
	5 mg/kg IV once daily	11	No effect on ganciclovir PK parameters observed

Coadministered Drug	Ganciclovir Dosage	N	Ganciclovir Pharmacokinetic (PK) Parameter
Probenecid 500 mg every 6 hours	1000 mg orally every 8 hours	10	AUC \uparrow $53 \pm 91\%$ (range: -14% to 299%) Ganciclovir renal clearance \downarrow $22 \pm 20\%$ (range: -54% to -4%)

Table 9. Results of Drug Interaction Studies with Ganciclovir: Effects of Ganciclovir on Pharmacokinetic Parameters of Coadministered Drug

Coadministered Drug	Ganciclovir Dosage	N	Coadministered Drug Pharmacokinetic (PK) Parameter
Oral ciclosporin at therapeutic doses	5 mg/kg infused over 1 hour every 12 hours	93	In a retrospective analysis of liver allograft recipients, there was no evidence of an effect on ciclosporin whole blood concentrations.
Mycophenolate mofetil (MMF) 1.5 g single dose	5 mg/kg IV single dose	12	No PK interaction observed (patients with normal renal function)
Trimethoprim 200 mg once daily	1000 mg orally every 8 hours	12	No effect on trimethoprim PK parameters observed.
Didanosine 200 mg every 12 hours	5 mg/kg IV twice daily	11	AUC ₀₋₁₂ \uparrow $70 \pm 40\%$ (range: 3% to 121%) C _{max} \uparrow $49 \pm 48\%$ (range: -28% to 125%)
Didanosine 200 mg every 12 hours	5 mg/kg IV once daily	11	AUC ₀₋₁₂ \uparrow $50 \pm 26\%$ (range: 22% to 110%) C _{max} \uparrow $36 \pm 36\%$ (range: -27% to 94%)

12.4 Microbiology

Mechanism of Action

Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of human CMV in cell culture and *in vivo*. In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly. 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 inhibition of the viral DNA polymerase, pUL54, by ganciclovir triphosphate.

Antiviral Activity

The quantitative relationship between the cell culture susceptibility of human herpes viruses to antivirals and clinical response to antiviral therapy has not been established, and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit the growth of virus in cell culture by 50% (EC₅₀), vary greatly depending upon a number of factors including the assay used. Thus the median concentration of ganciclovir that inhibits CMV replication (EC₅₀ value) in cell culture (laboratory strains or clinical isolates) has ranged from 0.08 to 13.6 μM (0.02 to 3.48 mcg/mL). Ganciclovir inhibits mammalian cell proliferation (CC₅₀ value) in cell culture at higher concentrations ranging from 118 to 2840 μM (30 to 725 mcg/mL). Bone marrow-derived colony-forming cells are more sensitive [CC₅₀ value = 0.1 to 2.7 μM (0.028 to 0.7 mcg/mL)]. The relationship between the antiviral activity in cell culture and clinical response has not been established.

Viral Resistance

Cell Culture: CMV isolates with reduced susceptibility to ganciclovir have been selected in cell culture. Growth of CMV strains in the presence of ganciclovir resulted in the selection of amino acid substitutions in the viral protein kinase pUL97 and the viral DNA polymerase pUL54.

In vivo: Viruses resistant to ganciclovir can arise after prolonged treatment or prophylaxis with ganciclovir by selection of substitutions in pUL97 and/or pUL54. Limited clinical data are available on the development of clinical resistance to ganciclovir and many pathways to resistance likely exist. In clinical isolates, seven canonical pUL97 substitutions, (M460V/I, H520Q, C592G, A594V, L595S, C603W) are the most frequently reported ganciclovir resistance-associated substitutions. These and other substitutions less frequently reported in the literature, or observed in clinical trials, are listed in Table 10.

Table 10. Summary of Resistance-associated Amino Acid Substitutions Observed in the CMV of Patients Failing Ganciclovir Treatment or Prophylaxis

pUL97	L405P, A440V, M460I/V/T/L, V466G/M, C518Y, H520Q, P521L, del 590-593, A591D/V, C592G, A594E/G/T/V/P, L595F/S/T/W, del 595, del 595-603, E596D/G/Y, K599E/M, del 600-601, del 597-600, del 601-603, C603W/R/S/Y, C607F/S/Y, I610T, A613V
pUL54	E315D, N408D/K/S, F412C/L/S, D413A/E/N, L501F/I, T503I, K513E/N/R, D515E, L516W, I521T, P522A/L/S, V526L, C539G, L545S/W, Q578H/L, D588E/N, G629S, S695T, I726T/V, E756K, L773V, V781I, V787L, L802M, A809V, T813S, T821I, A834P, G841A/S, D879G, A972V, del 981-982, A987G

Note: Many additional pathways to ganciclovir resistance likely exist

CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with intravenous GANCICLOVIR 500 MG. In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.

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

Cross-Resistance

Cross-resistance has been reported for amino acid substitutions selected in cell culture by ganciclovir, cidofovir or foscarnet. In general, amino acid substitutions in pUL54 conferring cross-resistance to ganciclovir and cidofovir are located within the

exonuclease domains and region V of the viral DNA polymerase. Whereas, amino acid substitutions conferring cross-resistance to foscarnet are diverse, but concentrate at and between regions II (codons 696-742) and III (codons 805-845). The amino acid substitutions that resulted in reduced susceptibility to ganciclovir and either cidofovir and/or foscarnet are summarized in Table 11.

Table 11. Summary of pUL54 Amino Acid Substitutions with Cross-resistance between Ganciclovir, Cidofovir, and/or Foscarnet

Cross-resistant to cidofovir	D301N, N408D/K, N410K, F412C/L/S/V, D413E/N, P488R, L501I, T503I, K513E/N, L516R/W, I521T, P522S/A, V526L, C539G/R, L545S/W, Q578H, D588N, I726T/V, E756K, L773V, V812L, T813S, A834P, G841A, del 981-982, A987G
Cross-resistant to foscarnet	F412C, Q578H/L, D588N, V715A/M, E756K, L773V, V781I, V787L, L802M, A809V, V812L, T813S, T821I, A834P, G841A/S, del 981-982

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, Mutagenesis

Ganciclovir was carcinogenic in mice at the same mean drug exposure in humans as at the RHD (5 mg/kg). At the dose of 1000 mg/kg/day (1.4 times the exposure at the RHD), there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the dose of 20 mg/kg/day (0.1 times the exposure at the RHD), a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (exposure estimated as 0.01 times the RHD). Except for histiocytic sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestomach and harderian glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans.

Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations between 50 to 500 and 250 to 2000 µg/mL, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (2.8 to 10 times the exposure at the RHD) but not at doses of 50 mg/kg (exposure approximately comparable to the RHD). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 µg/mL.

Impairment of Fertility

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryoletality in female mice following doses of 90 mg/kg/day (exposures approximately 1.7 times the RHD). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1 times the exposure at the RHD.

14 CLINICAL STUDIES

14.1 Treatment of CMV Retinitis

In a retrospective, non-randomized, single-center analysis of 41 patients with AIDS and CMV retinitis diagnosed by ophthalmologic examination between August 1983 and April 1988, treatment with intravenous GANCICLOVIR 500 MG solution resulted in a delay in mean (median) time to first retinitis progression compared to untreated controls [105 (71) days from diagnosis vs 35 (29) days from diagnosis]. Patients in this series received induction treatment of intravenous GANCICLOVIR 500 MG 5 mg/kg twice daily for 14 to 21 days followed by maintenance treatment with either 5 mg/kg once daily, 7 days per week or 6 mg/kg once daily, 5 days per week.

In a controlled, randomized study conducted between February 1989 and December 1990, immediate treatment with intravenous GANCICLOVIR 500 MG was compared to delayed treatment in 42 patients with AIDS and peripheral CMV retinitis; 35 of 42 patients (13 in the immediate-treatment group and 22 in the delayed-treatment group) were included in the analysis of time to retinitis progression. Based on masked assessment of fundus photographs, the mean [95% CI] and median [95% CI] times to progression of retinitis were 66 days [39, 94] and 50 days [40, 84], respectively, in the immediate-treatment group compared to 19 days [11, 27] and 13.5 days [8, 18], respectively, in the delayed-treatment group.

Data from trials ICM 1653, ICM 1774, and AVI 034, which were performed comparing intravenous GANCICLOVIR 500 MG to oral ganciclovir for treatment of CMV retinitis in patients with AIDS, are shown in Table 12 and Figures 1, 2, and 3, and are discussed below.

Table 12. Population Characteristics in Studies ICM 1653, ICM 1774 and AVI 034

Demographics		ICM 1653 (n=121)	ICM 1774 (n=225)	AVI 034 (n=159)
Median age (years)		38	37	39
Range		24-62	22-56	23-62
Sex	Males	116 (96%)	222 (99%)	148 (93%)
	Females	5 (4%)	3 (1%)	10 (6%)
Ethnicity	Asian	3 (3%)	5 (2%)	7 (4%)
	Black	11 (9%)	9 (4%)	3 (2%)
	Caucasian	98 (81%)	186 (83%)	140 (88%)
	Other	9 (7%)	25 (11%)	8 (5%)

Demographics		ICM 1653 (n=121)	ICM 1774 (n=225)	AVI 034 (n=159)
Median CD ₄ Count		9.5	7.0	10.0
Range		0-141	0-80	0-320
Mean (SD)				
Observation Time (days)		107.9 (43.0)	97.6 (42.5)	80.9 (47.0)

Trial ICM 1653: In this randomized, open-label, parallel group trial, conducted between March 1991 and November 1992, patients with AIDS and newly diagnosed CMV retinitis received a 3-week induction course of Intravenous GANCICLOVIR 500 MG solution, 5 mg/kg twice daily for 14 days followed by 5 mg/kg once daily for 1 additional week. Following the 21-day intravenous induction course, patients with stable CMV retinitis were randomized to receive 20 weeks of maintenance treatment with either intravenous GANCICLOVIR 500 MG solution, 5 mg/kg once daily, or ganciclovir capsules, 500 mg 6 times daily (3000 mg/day). The study showed that the mean [95% CI] and median [95% CI] times to progression of CMV retinitis, as assessed by masked reading of fundus photographs, were 57 days [44, 70] and 29 days [28, 43], respectively, for patients on oral therapy compared to 62 days [50, 73] and 49 days [29, 61], respectively, for patients on intravenous therapy. The difference [95% CI] in the mean time to progression between the oral and intravenous therapies (oral - IV) was -5 days [-22, 12]. See Figure 1 for comparison of the proportion of patients remaining free of progression over time.

Trial ICM 1774: In this three-arm, randomized, open-label, parallel group trial, conducted between June 1991 and August 1993, patients with AIDS and stable CMV retinitis following from 4 weeks to 4 months of treatment with intravenous GANCICLOVIR 500 MG solution were randomized to receive maintenance treatment with intravenous GANCICLOVIR 500 MG solution, 5 mg/kg once daily, ganciclovir capsules, 500 mg 6 times daily, or ganciclovir capsules, 1000 mg three times daily for 20 weeks. The study showed that the mean [95% CI] and median [95% CI] times to progression of CMV retinitis, as assessed by masked reading of fundus photographs, were 54 days [48, 60] and 42 days [31, 54], respectively, for patients on oral therapy compared to 66 days [56, 76] and 54 days [41, 69], respectively, for patients on intravenous therapy. The difference [95% CI] in the mean time to progression between the oral and intravenous therapies (oral - IV) was -12 days [-24, 0]. See Figure 2 for comparison of the proportion of patients remaining free of progression over time.

Trial AVI 034: In this randomized, open-label, parallel group trial, conducted between June 1991 and February 1993, patients with AIDS and newly diagnosed (81%) or previously treated (19%) CMV retinitis who had tolerated 10 to 21 days of induction treatment with intravenous GANCICLOVIR 500 MG, 5 mg/kg twice daily, were randomized to receive 20 weeks of maintenance treatment with either ganciclovir capsules, 500 mg 6 times daily, or intravenous GANCICLOVIR 500 MG solution, 5 mg/kg/day. The mean [95% CI] and median [95% CI] times to progression of CMV retinitis, as assessed by masked reading of fundus photographs, were 51 days [44, 57] and 41 days [31, 45], respectively, for patients on oral therapy compared to 62 days [52, 72] and 60 days [42, 83], respectively, for patients on intravenous therapy. The difference [95% CI] in the mean time to progression between the oral and intravenous therapies (oral - IV) was -11 days [-24, 1]. See Figure 3 for comparison of the proportion of patients remaining free of progression over time.

Comparison of other CMV retinitis outcomes between oral and IV formulations (development of bilateral retinitis, progression into Zone 1, and deterioration of visual acuity), while not definitive, showed no marked differences between treatment groups in these studies. Because of low event rates among these endpoints, these studies are underpowered to rule out significant differences in these endpoints.

Figure 1 Trial ICM 1653: Time to Progression of CMV Retinitis

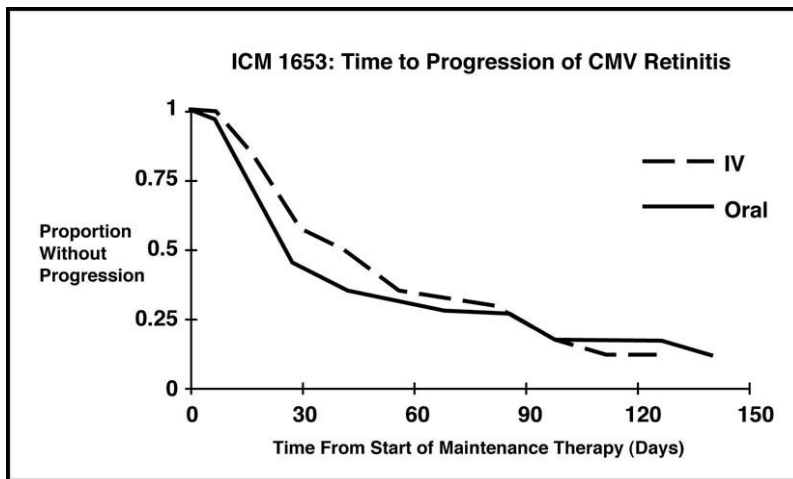


Figure 2 Trial ICM 1774: Time to Progression of CMV Retinitis

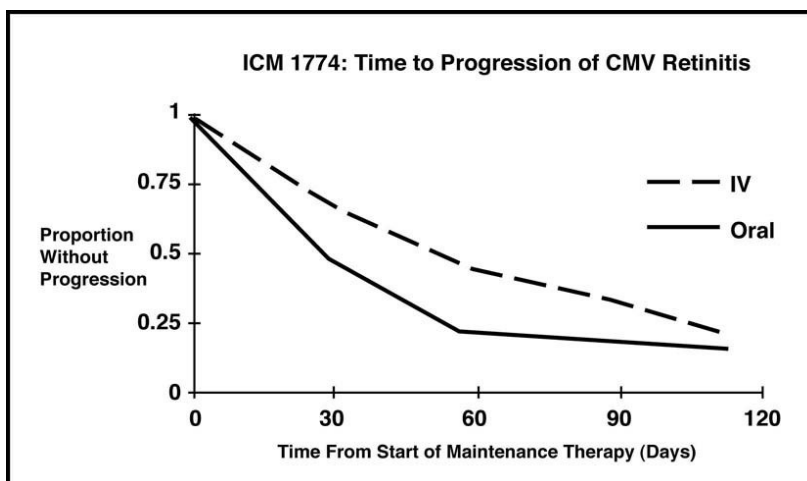
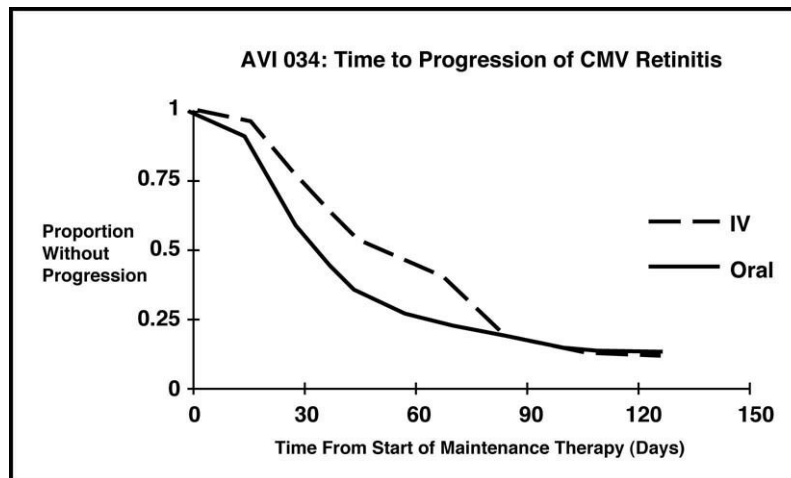


Figure 3

Trial AVI 034: Time to Progression of Retinitis



14.2 Prevention of CMV Disease in Transplant Recipients

Intravenous GANCICLOVIR 500 MG was evaluated in three randomized, controlled trials of prevention of CMV disease in organ transplant recipients.

Trial ICM 1496: In a randomized, double-blind, placebo-controlled study of 149 heart transplant recipients at risk for CMV infection (CMV seropositive or a seronegative recipient of an organ from a CMV seropositive donor), there was a reduction in the overall incidence of CMV disease in patients treated with intravenous GANCICLOVIR 500 MG. Immediately post-transplant, patients received intravenous GANCICLOVIR 500 MG solution 5 mg/kg twice daily for 14 days followed by 6 mg/kg once daily for 5 days/week for an additional 14 days. Twelve of the 76 (16%) patients treated with intravenous GANCICLOVIR 500 MG vs 31 of the 73 (43%) placebo-treated patients developed CMV disease during the 120-day post-transplant observation period. No significant differences in hematologic toxicities were seen between the two treatment groups [see Adverse Reactions (6.1)].

Trial ICM 1689: In a randomized, double-blind, placebo-controlled study of 72 bone marrow transplant recipients with asymptomatic CMV infection (CMV positive culture of urine, throat or blood) there was a reduction in the incidence of CMV disease in patients treated with intravenous GANCICLOVIR 500 MG following successful hematopoietic engraftment. Patients with virologic evidence of CMV infection received intravenous GANCICLOVIR 500 MG solution 5 mg/kg twice daily for 7 days followed by 5 mg/kg once daily through day 100 post-transplant. One of the 37 (3%) patients treated with intravenous GANCICLOVIR 500 MG vs 15 of the 35 (43%) placebo-treated patients developed CMV disease during the study. At 6 months post-transplant, there continued to be a reduction in the incidence of CMV disease in patients treated with intravenous GANCICLOVIR 500 MG. Six of 37 (16%) patients treated with intravenous GANCICLOVIR 500 MG vs 15 of the 35 (43%) placebo-treated patients developed disease through 6 months post-transplant. The overall rate of survival was higher in the group treated with intravenous GANCICLOVIR 500 MG, both at day 100 and day 180 post-transplant. Although the differences in hematologic toxicities were not statistically significant, the incidence of neutropenia was higher in the group treated with intravenous GANCICLOVIR 500 MG [see Adverse Reactions (6.1)].

Trial ICM 1570: This was a randomized, unblinded study that evaluated 40 allogeneic bone marrow transplant recipients at risk for CMV disease. Patients underwent bronchoscopy and bronchoalveolar lavage (BAL) on day 35 post-transplant. Patients with histologic, immunologic or virologic evidence of CMV infection in the lung were then randomized to observation or treatment with intravenous GANCICLOVIR 500 MG solution (5 mg/kg twice daily for 14 days followed by 5 mg/kg once daily 5 days/week until day 120). Four of 20 (20%) patients treated with intravenous GANCICLOVIR 500 MG and 14 of 20 (70%) control patients developed interstitial pneumonia. The incidence of CMV disease was lower in the group treated with intravenous GANCICLOVIR 500 MG, consistent with the results observed in ICM 1689.

15 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

GANCICLOVIR MEDI-MARKET 500 MG (ganciclovir sodium) for injection is supplied in 10 mL clear glass vials with a rubber stopper and aluminium closure with flip-off cap, each containing ganciclovir sodium equivalent to 500 mg of ganciclovir as a white lyophilized powder. The concentration of ganciclovir in the reconstituted solution is 50 mg/mL. 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.

GANCICLOVIR MEDI-MARKET 500 MG is supplied in cartons of 1,5,10 or 25 single dose vials.

Not all package sizes may be marketed.

Shelf-life

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

Use immediately after opening.

Storage

Unopened vial:

Do not store above 30°C.

After reconstitution:

Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated at 20-25°C for no longer than 12 hours. Do not refrigerate or freeze.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user.

Discard any unused portion of the reconstituted solution.

After dilution:

Chemical and physical in-use stability after dilution of the reconstituted solution has been demonstrated at 2° to 8°C for no longer than 24 hours. Do not freeze.

From a microbiological point of view, Ganciclovir should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

MANUFACTURER

HAINAN POLY PHARM CO., LTD., GUILINYANG ECONOMIC DEVELOPMENT AREA, MEILAN DISTRICT, HAIKOU, HAINAN 571127, CHINA

LICENSE HOLDER

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LICENSE NUMBER

173-77-36717-99

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