

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GANCICLOVIR FOR INJECTION safely and effectively. See full prescribing information for GANCICLOVIR FOR INJECTION.

GANCICLOVIR FOR INJECTION, for intravenous use
Initial U.S. Approval: 1989

WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS
See full prescribing information for complete boxed warning.

- Hematologic Toxicity:** Granulocytopenia, anemia, thrombocytopenia, and pancytopenia have been reported in patients treated with Ganciclovir for Injection. (5.1)
- Impairment of Fertility:** Based on animal data and limited human data, Ganciclovir for Injection may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females. (5.3)
- Fetal Toxicity:** Based on animal data, Ganciclovir for Injection has the potential to cause birth defects in humans. (5.4)
- Mutagenesis and Carcinogenesis:** Based on animal data, Ganciclovir for Injection has the potential to cause cancer in humans. (5.5)

INDICATIONS AND USAGE

Ganciclovir for Injection is a deoxynucleoside analogue cytomegalovirus (CMV) DNA polymerase inhibitor indicated for the:

- treatment of CMV retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome (AIDS). (1.1)
- prevention of CMV disease in adult transplant recipients at risk for CMV disease. (1.2)

DOSAGE AND ADMINISTRATION

Ganciclovir for Injection is administered only intravenously. (2.1)

Dosage in Adult Patients with Normal Renal Function	
Treatment of CMV retinitis (2.3)	Induction: 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days. Maintenance: 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week.
Prevention of CMV disease in transplant recipients (2.4)	Induction: 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7 to 14 days. Maintenance: 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily, 7 days per week, or 6 mg/kg once daily, 5 days per week until 100 to 120 days post-transplantation.

Adults with renal impairment: Adjust dosage based on creatinine clearance. (2.5)

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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 Ganciclovir for Injection [see *Warnings and Precautions* (5.1)].
- Impairment of Fertility:** Based on animal data and limited human data, Ganciclovir for Injection 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 for Injection has the potential to cause birth defects in humans [see *Warnings and Precautions* (5.4)].
- Mutagenesis and Carcinogenesis:** Based on animal data, Ganciclovir for Injection has the potential to cause cancers in humans [see *Warnings and Precautions* (5.5)].

1 INDICATIONS AND USAGE

1.1 Treatment of CMV Retinitis

Ganciclovir for Injection is indicated for the treatment of cytomegalovirus (CMV) retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome (AIDS) [see *Clinical Studies* (14.1)].

DOSAGE FORMS AND STRENGTHS

For injection: 500 mg of ganciclovir as lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

Hypersensitivity to ganciclovir or valganciclovir. (4)

WARNINGS AND PRECAUTIONS

Renal Impairment: Increased serum creatinine levels have been observed with the use of Ganciclovir for Injection, particularly in elderly patients and transplant recipients receiving concomitant nephrotoxic drugs. Monitor renal function during therapy with Ganciclovir for Injection, particularly in elderly patients and in patients taking other nephrotoxic drugs, and reduce dosage in patients with renal impairment. (5.2)

ADVERSE REACTIONS

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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Imipenem-cilastatin:** Seizures were reported in patients receiving ganciclovir and imipenem-cilastatin. Concomitant use is not recommended unless the potential benefits outweigh the risks. (7)
- Cyclosporine or amphotericin B:** When coadministered with ganciclovir, the risk of nephrotoxicity may be increased. Monitor renal function. (5.2, 7)
- Mycophenolate mofetil (MMF):** When coadministered with ganciclovir, the risk of hematologic and renal toxicity may be increased. Monitor for ganciclovir and MMF toxicity. (7)
- Other drugs associated with myelosuppression or nephrotoxicity:** Due to potential for increased toxicity, such drugs should be considered for concomitant use with ganciclovir only if the potential benefits are judged to outweigh the risks. (7)
- Didanosine:** Ganciclovir coadministered with didanosine may increase didanosine levels. Monitor for didanosine toxicity (e.g., pancreatitis). (7)
- Probenecid:** May increase ganciclovir levels. Monitor for evidence of ganciclovir toxicity. (7)

USE IN SPECIFIC POPULATIONS

- Lactation:** Breastfeeding is not recommended with use of Ganciclovir for Injection. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2022

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1.2 Prevention of CMV Disease in Transplant Recipients

Ganciclovir for Injection is indicated for the prevention of CMV disease in adult transplant recipients at risk for CMV disease [see *Clinical Studies* (14.2)].

2. DOSAGE AND ADMINISTRATION

2.1 Important Dosing and Administration Information

- To avoid phlebitis/pain at the infusion site, Ganciclovir for Injection must only be administered by intravenous infusion over 1 hour, preferably via plastic cannula, into a vein with adequate blood flow to permit rapid dilution and distribution.
- Do not administer Ganciclovir for Injection by rapid or bolus intravenous injection which may increase toxicity as a result of excessive plasma levels.
- The recommended dosage and infusion rate for Ganciclovir for Injection should not be exceeded.
- Do not administer the reconstituted Ganciclovir for Injection solution intramuscularly or subcutaneously because it may result in severe tissue irritation due to high pH [see *Description* (11)].
- Administration of Ganciclovir for Injection should be accompanied by adequate hydration.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.2 Testing Before and During Treatment

- Females of reproductive potential should undergo pregnancy testing before initiation of treatment with Ganciclovir [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.1, 8.3)].
- Complete blood counts with differential and platelet counts should be performed frequently, especially in patients in whom Ganciclovir for Injection or other nucleoside analogues have previously resulted in cytopenias, or in whom absolute neutrophil counts are less than 1000 cells/ μ L at the beginning of treatment [see *Warnings and Precautions* (5.1)].
- All patients should be monitored for renal function before and during treatment with Ganciclovir for Injection and dose should be adjusted as needed [see *Dosage and Administration* (2.5), *Warnings and Precautions* (5.2)].
- Patients with CMV retinitis should have frequent ophthalmologic examinations during treatment with Ganciclovir for Injection solution to monitor disease status and for other retinal abnormalities [see *Adverse Reactions* (6.1)].

2.3 Recommended Dosage for Treatment of CMV Retinitis in Adult Patients with Normal Renal Function

Induction Dosage: The recommended initial dosage of Ganciclovir for Injection 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 Dosage: Following induction treatment, the recommended maintenance dosage of Ganciclovir for Injection is 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week.

2.4 Recommended Dosage for the Prevention of CMV Disease in Adult Transplant Recipients with Normal Renal Function

Induction Dosage: The recommended initial dosage of Ganciclovir for Injection 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.

Maintenance Dosage: Following induction, the recommended maintenance dosage of Ganciclovir for Injection is 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week until 100 to 120 days post-transplantation.

2.5 Recommended Dosage in Adult Patients with Renal Impairment

For patients with impairment of renal function, refer to Table 1 for recommended doses of Ganciclovir for Injection for induction and maintenance dosage for treatment of CMV retinitis and prevention of CMV disease in transplant recipients. Carefully monitor serum creatinine or creatinine clearance before and during treatment to allow for dosage adjustments in patients with impaired renal function.

Table 1. Recommended Induction and Maintenance Dosage for Adult Patients with Renal Impairment

Creatinine Clearance* (mL/min)	GANCICLOVIR Dose (mg/kg)	Dosing Interval (hours) for Induction	Ganciclovir Maintenance Dose (mg/kg)	Dosing Interval (hours) for Maintenance
Greater than or equal to 70	5	12	5	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
Less than 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.

Creatinine clearance for males = $\frac{140 - \text{age (yrs)}}{72} (\text{body wt (kg)})$

Creatinine clearance for females = $0.85 \times \text{male value}$

Patients Undergoing Hemodialysis

Induction dosing for Ganciclovir for Injection in patients undergoing hemodialysis should not exceed 1.25 mg/kg 3 times per week, and maintenance dosing should not exceed 0.625 mg/kg 3 times per week following each hemodialysis session. Ganciclovir for Injection should be given shortly after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50% [see *Clinical Pharmacology* (13.1)].

2.6 Preparation of Ganciclovir for Injection

Ganciclovir for Injection must be reconstituted and diluted under the supervision of a healthcare provider and administered as intravenous infusion. Each 10 mL clear glass vial contains 543 mg ganciclovir sodium equivalent to 500 mg of ganciclovir. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the vial and the table after reconstitution.

The contents of the vial should be prepared for administration in the following manner:

1. Reconstitution Instructions:
 - Reconstitute lyophilized Ganciclovir for Injection 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 Ganciclovir for Injection and may cause precipitation.
 - Gently swirl the vial in order to ensure complete wetting of the product. Continue swirling until a clear reconstituted solution is obtained.
 - Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion. Discard the vial if particulate matter or discoloration is observed.
 - Reconstituted solution in the vial is stable at room temperature (25°C (77°F)) for 12 hours. Do not refrigerate or freeze. Discard any unused portion of the reconstituted solution.
2. Infusion Instructions:
 - 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 for Injection solution: 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection and Lactated Ringer's Injection, USP.
 - Ganciclovir for Injection, when reconstituted with sterile water for injection (non-bacteriostatic) and further diluted with 0.9% sodium chloride injection or other acceptable infusion fluid as specified above, should be used within 24 hours of dilution to reduce the risk of bacterial contamination. The diluted infusion solution should be refrigerated (2°C to 8°C (36° to 46°F)). Do not freeze.

2.7 Handling and Disposal

Caution should be exercised in the handling and preparation of solutions of Ganciclovir for Injection. Solutions of Ganciclovir for Injection are alkaline (pH 11). Avoid direct contact of the skin or mucous membranes with Ganciclovir for Injection 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.¹ Discard any unused portion of the reconstituted solution [see *How Supplied/Storage and Handling* (16)].

3 DOSAGE FORMS AND STRENGTHS

For injection: Single-dose vial containing 500 mg of ganciclovir as a sterile lyophilized white to off-white powder for reconstitution with 10 mL of preservative-free sterile water for injection, USP for intravenous use. The concentration of ganciclovir in the reconstituted solution is 50 mg/mL [see *Dosage and Administration* (2.6)].

4 CONTRAINDICATIONS

Ganciclovir for Injection is contraindicated in patients who have experienced a clinically significant hypersensitivity reaction (e.g., anaphylaxis) to ganciclovir, valganciclovir, or any component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity

Granulocytopenia (neutropenia), anemia, thrombocytopenia and pancytopenia have been observed in patients treated with Ganciclovir for Injection. The frequency and severity of these events vary widely in different patient populations [see *Adverse Reactions* (6.1)]. Ganciclovir for Injection 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 for Injection 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 Ganciclovir for Injection solution for treatment of CMV retinitis.

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving Ganciclovir for Injection [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 for Injection 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., cyclosporine and amphotericin B). Monitoring renal function during therapy with Ganciclovir for Injection 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 for Injection 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 for Injection [see *Use in Specific Populations* (8.1, 8.3), *Nonclinical Toxicology* (13.1)].

5.4 Fetal Toxicity

Ganciclovir for Injection 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 for Injection. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with Ganciclovir for Injection [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 for Injection should therefore be considered a potential carcinogen in humans [see *Dosage and Administration* (2.7), *Nonclinical Toxicology* (13.1)].

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 Trials 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 Ganciclovir for Injection are summarized below, according to the participating study patient population.

Adverse Reactions in Patients with CMV Retinitis: Three controlled, randomized, phase 3 trials comparing Ganciclovir for Injection and ganciclovir capsules for maintenance treatment of CMV retinitis have been completed. During these trials, Ganciclovir for Injection 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, 1)].

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

Adverse Reaction	Maintenance Treatment Studies	
	Ganciclovir for Injection (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%
Hyperhidrosis	12%	13%
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 Ganciclovir for injection 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*	
	Ganciclovir for Injection† 5 mg/kg/day (N=175) %	Ganciclovir Capsules‡ 3000 mg/day (N=320) %
Neutropenia with Absolute Neutrophil Count (ANC) per μ L:		
<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):		
\geq 2.5	2%	1%
\geq 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

§ 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 Ganciclovir for Injection 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 Ganciclovir for Injection, Placebo, or Control

Laboratory Abnormalities	Ganciclovir for Injection			
	Heart Allograft*		Bone Marrow Allograft†	
	Ganciclovir for Injection (n=76)	Placebo (n=73)	Ganciclovir for Injection (n=57)	Control (n=55)
Neutropenia				
Absolute Neutrophil Count (ANC) per μ L				
<500	4%	3%	12%	6%
500-1000	3%	8%	29%	17%
Total ANC \leq 1000/ μ L	7%	11%	41%	23%
Thrombocytopenia				
Platelet count per μ L				
<25,000	3%	1%	32%	28%
25,000-50,000	5%	3%	25%	37%
Total Platelet Count \leq 50,000/ μ L	8%	4%	57%	65%

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

11 DESCRIPTION
Ganciclovir for Injection, USP contains ganciclovir, in the form of the sodium salt for intravenous injection. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).

8.3 Females and Males of Reproductive Potential Pregnancy Testing
Females of reproductive potential should undergo pregnancy testing before initiation of treatment with Ganciclovir [see Dosage and Administration (2.2), Use in Specific Populations (8.1)].

Contraception
Females
Because of the mutagenic and teratogenic potential of Ganciclovir, females of reproductive potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with Ganciclovir [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 [see Warnings and Precautions (5.4), Nonclinical Toxicology (13.1)].

Infertility
Ganciclovir 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 1.1 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 45 million/mL in the untreated group).

8.4 Pediatric Use
Safety and efficacy of Ganciclovir 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 Ganciclovir 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 mg/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 Ganciclovir 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 Ganciclovir 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 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 should be administered to elderly patients with special attention to 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 to patients with renal impairment [see Dosage and Administration (2.5), Warnings and Precautions (5.2)].

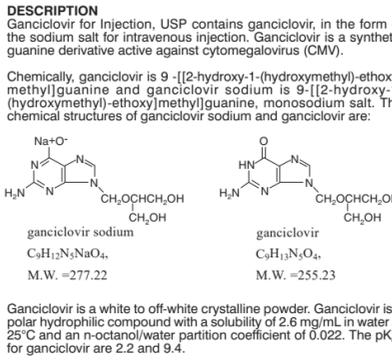
8.7 Hepatic Impairment
The safety and efficacy of Ganciclovir have not been studied in patients with hepatic impairment.

10 OVERDOSAGE
Reports of adverse reactions after overdoses of Ganciclovir, some with fatal outcomes, have been received from clinical trials and during postmarketing surveillance. 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 [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)].

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



Ganciclovir is a white to off-white crystalline 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 for Injection, USP formulated as monosodium salt, using sodium hydroxide as a salt forming agent, is a sterile white to off-white lyophilized powder. The lyophilized powder has an aqueous solubility of greater than 50 mg/mL at 25°C. At physiological pH, ganciclovir sodium exists as the ionized form with a solubility of approximately 6 mg/mL at 37°C.

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

Inactive ingredients may include hydrochloric acid (QS) and sodium hydroxide (QS) added to adjust the pH.

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)].

12.2 Pharmacokinetics
Absorption
At the end of a 1-hour intravenous infusion of 5 mg/kg ganciclovir, total AUC ranged between 22.1 ± 2.2 (n=16) and 26.3 ± 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 ± 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 ± 0.60 mL/min/kg (n=47), accounting for 91 ± 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 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 ± SD	Half-life (hours) Mean ± 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 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.

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
Didanosine 200 mg every 12 hours simultaneously administered with ganciclovir	5 mg/kg IV once daily	11	No effect on ganciclovir PK parameters observed
Probenecid 500 mg every 6 hours	1000 mg orally every 8 hours	10	AUC ↑ 53 ± 91% (range: -14% to 299%) Ganciclovir renal clearance ↓ 22 ± 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 cyclosporine 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 cyclosporine 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 ↑ 70 ± 40% (range: 3% to 121%) C _{max} ↑ 49 ± 48% (range: -28% to 125%)
Didanosine 200 mg every 12 hours	5 mg/kg IV once daily	11	AUC ₀₋₁₂ ↓ 50 ± 26% (range: 22% to 110%) C _{max} ↓ 36 ± 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 of 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, (M480V/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

	L465P, A40W, M480V/I/T, V466G/M, C518Y, H520Q, P521L, del 590-593, A610V/D, C592G, A594E/G/T/V/P, L595F/S/T/W, del 595, del 595-603, E598D/G/Y, K599E/M, del 600-601, del 597-600, del 601-603, C603W/R/S/Y, C607F/S/Y, I610T, A613V
pUL97	
	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, O578H/L, D588E/N, G628S, S665T, I726T/V, E758K, L773V, V781I, V787L, L802M, A809V, T813S, T821I, A834P, G841A/S, D879G, A872V, 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 Ganciclovir. 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 23 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 pUL97 confer cross-resistance to ganciclovir and cidofovir or 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, F488R, L501I, T503I, K513E/N, L516R/W, I521T, P522A/L/S, V526L, C539G/H, L545S/W, Q578H, D588N, I726T/V, E758K, 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 mouse 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 micro nucleus 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 embryolethality 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 doses of 10 mg/kg (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.

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 Ganciclovir 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 Ganciclovir 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 Ganciclovir 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 Ganciclovir for injection 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) Range	38 24–62	37 22–56	39 23–62
Sex	Males 116 (96%) Females 5 (4%)	222 (99%) 3 (1%)	148 (93%) 10 (6%)
Ethnicity	Asian 3 (3%) Black 11 (9%) Caucasian 98 (81%) Other 9 (7%)	5 (2%) 9 (4%) 186 (83%) 25 (11%)	7 (4%) 3 (2%) 140 (88%) 8 (5%)
Median CD ₄ Count Range	9.5 0–141	7.0 0–80	10.0 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 Ganciclovir 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 Ganciclovir 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 Ganciclovir solution were randomized to receive maintenance treatment with Ganciclovir 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 Ganciclovir, 5 mg/kg twice daily, were randomized to receive 20 weeks of maintenance treatment with either ganciclovir capsules, 500 mg 6 times daily, or Ganciclovir 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

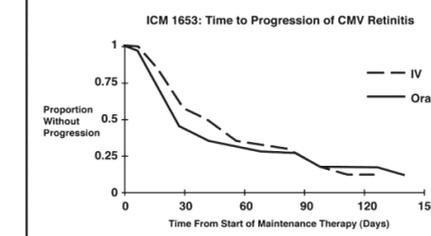


Figure 2 Trial ICM 1774: Time to Progression of CMV Retinitis

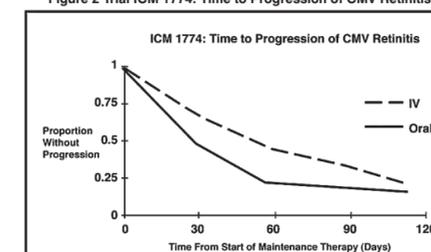
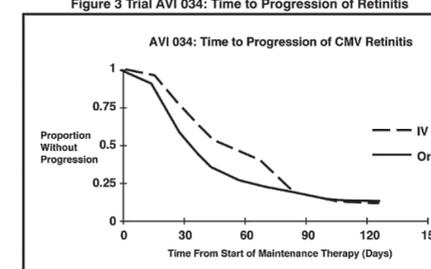


Figure 3 Trial AVI 034: Time to Progression of Retinitis



14.2 Prevention of CMV Disease in Transplant Recipients

Ganciclovir 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 Ganciclovir. Immediately post-transplant, patients received Ganciclovir 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 Ganciclovir 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 Ganciclovir following successful hematopoietic engraftment. Patients with virologic evidence of CMV infection received Ganciclovir 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