Boehringer Ingelheim
Ben Venue Laboratories

Ben Venue Laboratories, Inc.

Dockets Management Branch, Room 1-23
Food and Drug Administation
12420 Parklawn Drive
Rockville, MD 20857

September 24, 2001

RE: Citizen Petition, Ganciclovir Sodium Injection, 500mg/10 mL

Dear Sir or Madam:

The attached petition requests a determination that Ganciclovir Sodium Injection, as a ready to use solution for injection, is suitable for submission as an Abbreviated New Drug Application.

If there are any further questions/comments, do not hesitate to call the undersigned at (440) 201-3576.

Sincerely,

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

300 Northfield Road
P.O. Box 46568
Bedford, Ohio 44146-0568
Telephone (440) 232-3320
Telefax (440) 232-2772

OIP-0440

CP1

Citizen Petition

The undersigned submits this petition under section 505(j)(2)(C) of the Federal Food Drug, and Cosmetic Act and 21 CFR 314.93, and 10.30 to request the Commissioner of Food and Drugs to grant the Petitioner permission to file an Abbreviated New Drug Application (ANDA) for the Petitioner's Ganciclovir Sodium Injection, 500 mg / 10 mL vials in a ready to use solution for injection.

A. Action Required

This petition seeks a determination that the proposed Ganciclovir Sodium Injection, 500 mg / 10 mL, in a ready to use solution for injection is suitable for evaluation under an ANDA. This Petition further requests a waiver from the need to conduct clinical studies in pediatric patients, as described in the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs an Biological Products in Pediatric Patients; Final Rule published, December 2, 1998, in the Federal Register (Pediatric rule)(63 FR 66632); and the Pediatric Use Information CFR314.55.

B. Statement of Grounds

The reference listed drug, Cytovene®-IV, (Ganciclovir Sodium Injection, 500 mg per vial) by Roche Laboratories is a lyophilized product that requires reconstitution prior to use. The proposed product, Ganciclovir Sodium Injection, 500 mg / 10 mL vials is a ready to use solution.

The proposed product is equivalent in use, dosage, and route of administration to the listed drug Cytovene®-IV, and the concentration of the proposed solution product is in accordance with the FDA approved labeling for Cytovene®-IV (Attachment I). For these reasons, the proposed drug product is expected to have the same therapeutic effect as the reference listed drug when administered to patients.

The formulations of Cytovene®-IV and the proposed Ganciclovir Sodium Injection are presented in Table 1.

Table 1.
Comparison of the Reference Listed Drug and the Proposed Drug Product

Ingredient	Amount per vial	
	Cytovene®-IV	Proposed Drug Product
Ganciclovir	Equivalent of 500 mg ganciclovir per vial as the ganciclovir sodium salt	Equivalent of 500 mg ganciclovir per vial as the ganciclovir sodium salt
Water for Injection, USP	N/A	10 mL

The proposed drug product will also eliminate the need for reconstitution and mixing prior to use. This will avoid the possibility of improper reconstitution and mixing of the powder and minimize aseptic manipulations of the product, thereby, reducing the chance of contamination.

The petitioner also requests a waiver from the need to conduct clinical studies in pediatric patients in support of this petition to change dosage form. Under the regulations cited in Part A of this petition, waivers are granted if: (1) The product (a) did not represent a meaningful therapeutic benefit over existing treatments, and (b) was not likely to be used in substantial number of one or more pediatric subpopulations; (2) The necessary studies are impossible or highly impractical; (3) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

The petitioner submits that the requested change in dosage form described above satisfies the requirements for a waiver from the need for clinical studies in the pediatric population for the following reasons:

a). The change in the dosage form from lyophilized ganciclovir sodium powder to a ready to use aqueous form of ganciclovir sodium is a pharmaceutical change only. The proposed drug product contains same amount of ganciclovir (as the sodium salt) as the reference listed drug. This change does not represent a meaningful therapeutic benefit over the reference product.

b). Due to the probability of reproductive toxicity, impairment of fertility, and long-term carcinogenicity, as reported in the Reference Listed Drug package insert, this product is deemed to be unsafe for general use in the pediatric population.

For the above listed reasons, it is believed that the proposed Ganciclovir Sodium Injection, 500 mg / 10 mL vials is suitable for evaluation under an ANDA.

C. Environment Impact

Action on an ANDA is categorically excluded from the requirements of an environmental assessment or impact statement under 21 CFR 25.31 (a).

D. Economic Impact

Not Applicable

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all the information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,

Molly Rapp
Supervisor Regulatory Affairs
Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, OH 44146
Phone: 440-201-3576
Fax: 440-232-2772

Roche

CYTOVENE®-IV
(ganciclovir sodium for injection)

FOR INTRAVENOUS INFUSION ONLY

CYTOVENE®
(ganciclovir capsules)

FOR ORAL ADMINISTRATION

WARNING: THE CLINICAL TOXICITY OF CYTOVENE AND CYTOVENE-IV INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

CYTOVENE-IV IS INDICATED FOR USE *ONLY* IN THE TREATMENT OF CYTOMEGALOVIRUS (CMV) RETINITIS IN IMMUNOCOMPROMISED PATIENTS AND FOR THE PREVENTION OF CMV DISEASE IN TRANSPLANT PATIENTS AT RISK FOR CMV DISEASE.

CYTOVENE CAPSULES ARE INDICATED *ONLY* FOR PREVENTION OF CMV DISEASE IN PATIENTS WITH ADVANCED HIV INFECTION AT RISK FOR CMV DISEASE, FOR MAINTENANCE TREATMENT OF CMV RETINITIS IN IMMUNOCOMPROMISED PATIENTS, AND FOR PREVENTION OF CMV DISEASE IN SOLID ORGAN TRANSPLANT RECIPIENTS (see INDICATIONS AND USAGE).

BECAUSE CYTOVENE CAPSULES ARE ASSOCIATED WITH A RISK OF MORE RAPID RATE OF CMV RETINITIS PROGRESSION, THEY SHOULD BE USED AS MAINTENANCE TREATMENT ONLY IN THOSE PATIENTS FOR WHOM THIS RISK IS BALANCED BY THE BENEFIT ASSOCIATED WITH AVOIDING DAILY INTRAVENOUS INFUSIONS.

DESCRIPTION: Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV). CYTOVENE-IV and CYTOVENE are the brand names for ganciclovir sodium for injection and ganciclovir capsules, respectively.

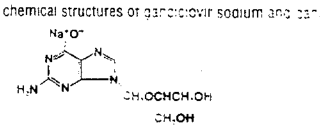
CYTOVENE-IV is available as sterile lyophilized powder in strength of 500 mg per vial for intravenous administration only. Each vial of CYTOVENE-IV contains the equivalent of 500 mg ganciclovir as the sodium salt (46 mg sodium). Reconstitution with 10 mL of Sterile Water for Injection, USP, yields a solution with pH 11 and a ganciclovir concentration of approximately 50 mg/mL. Further dilution in an appropriate intravenous solution must be performed before infusion (see DOSAGE AND ADMINISTRATION).

CYTOVENE is available as 250 mg and 500 mg capsules. Each capsule contains 250 mg or 500 mg ganciclovir, respectively, and inactive ingredients croscarmellose sodium, magnesium stearate and povidone. Both hard gelatin shells consist of gelatin, titanium dioxide, yellow iron oxide and FD&C Blue No. 2.

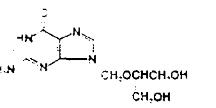
Ganciclovir is a white to off-white crystalline powder with a molecular formula of $C_9H_{13}N_5O_4$ and a molecular weight of 255.23. The chemical name for ganciclovir is 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine. Ganciclovir is a polar hydrophilic compound with a solubility of 2.6 mg/mL 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, when formulated as monosodium salt in the IV dosage form, is a white to off-white lyophilized powder with a molecular formula of $C_9H_{12}N_5NaO_4$ and a molecular weight of 277.22. The chemical name for ganciclovir sodium is 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine, monosodium salt. The lyophilized powder has an aqueous solubility of greater than 50 mg/mL at 25°C. At physiological pH, ganciclovir sodium exists as the un-ionized form with a solubility of approximately 6 mg/mL at 37°C.

The chemical structures of ganciclovir sodium and ganciclovir are:



ganciclovir sodium



ganciclovir

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

VIROLOGY: *Mechanism of Action:* Ganciclovir is an acyclic nucleoside analogue of 2'-deoxyguanosine that inhibits replication of herpes viruses. Ganciclovir has been shown to be active against cytomegalovirus (CMV) and herpes simplex virus (HSV) in human clinical studies.

To achieve anti-CMV activity, ganciclovir is phosphorylated first to the monophosphate form by a CMV-encoded (UL97 gene) protein kinase homologue, then to the di- and triphosphate forms by cellular kinases. Ganciclovir triphosphate concentrations may be 100-fold greater in CMV-infected than in uninfected cells, indicating preferential phosphorylation in infected cells. Ganciclovir triphosphate, once formed, persists for days in the CMV-infected cell. Ganciclovir triphosphate is believed to inhibit viral DNA synthesis by (1) competitive inhibition of viral DNA polymerases; and (2) incorporation into viral DNA, resulting in eventual termination of viral DNA elongation.

Antiviral Activity: The median concentration of ganciclovir that inhibits CMV replication (IC_{50}) in vitro (laboratory strains or clinical isolates) has ranged from 0.02 to 3.48 µg/mL. Ganciclovir inhibits mammalian cell proliferation (IC_{50}) in vitro at higher concentrations ranging from 30 to 725 µg/mL. Bone marrow-derived colony-forming cells are more sensitive (IC_{50} 0.028 to 0.7 µg/mL). The relationship of in vitro sensitivity of CMV to ganciclovir and clinical response has not been established.

Clinical Antiviral Effect of CYTOVENE-IV and CYTOVENE Capsules: CYTOVENE-IV: In a study of CYTOVENE-IV treatment of life- or sight-threatening CMV disease in immunocompromised patients, 121 of 314 patients had CMV cultured within 7 days prior to treatment and sequential posttreatment viral cultures of urine, blood, throat and/or semen. As judged by conversion to culture negativity, or a greater than 100-fold decrease in in vitro CMV titer, at least [illegible] of patients had a virologic response with a median response time of 7 to 15 days.

Antiviral activity of CYTOVENE-IV was demonstrated in two randomized studies for the prevention of CMV disease in transplant recipients (see table below).

Patients With Positive CMV Cultures

	Heart Allograft* (n=[illegible])		Bone Marrow Allograft (n=72)	
	[illegible]	[illegible]	CYTOVENE-IV	[illegible]
Pretreatment	[illegible]	[illegible] 64 [illegible]	37 (100%)	[illegible] (100%)
Week 2	[illegible]	[illegible] 67 [illegible]	[illegible]	[illegible]
Week 4	[illegible]	[illegible] 66 [illegible]	[illegible]	[illegible]

* CMV seropositive or receiving graft from seropositive donor
† 5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for 14 days
‡ 5 mg/kg bid for 7 days followed by 5 mg/kg qd until day 100 posttransplant

CYTOVENE Capsules: In trials comparing CYTOVENE-IV with CYTOVENE capsules for the maintenance treatment of CMV retinitis in patients with AIDS, serial urine cultures and other available cultures (semen, biopsy specimens, blood and others) showed that a small proportion of patients remained culture-positive during maintenance therapy with no statistically significant differences in CMV isolation rates between treatment groups.

A study of CYTOVENE capsules (1000 mg q8h) for prevention of CMV disease in individuals with advanced HIV infection (ICM 1654) evaluated antiviral activity as measured by CMV isolation in culture; most cultures were from urine. At baseline, 40% (176/436) and 44% (92/210) of ganciclovir and placebo recipients, respectively, had positive cultures (urine or blood). After 2 months on treatment, 10% vs 44% of ganciclovir vs placebo recipients had positive cultures.

Viral Resistance: The current working definition of CMV resistance to ganciclovir in in vitro assays is IC_{50} >3.0 µg/mL (12.0 µM). 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 CYTOVENE-IV. In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.

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

CLINICAL PHARMACOLOGY: *Pharmacokinetics:*

BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR CYTOVENE-IV AND SHOULD BE CONSIDERED FOR CYTOVENE CAPSULES. FOR DOSING INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.

Absorption: The absolute bioavailability of oral ganciclovir under fasting conditions was approximately 5% (n=6) and following food was 6% to 9% (n=32). When ganciclovir was administered orally with food at a total daily dosage of 3 g/day (500 mg q3h, 6 times daily and 1000 mg tid), the steady-state absorption as measured by area under the serum concentration vs time curve (AUC) over 24 hours and maximum serum concentrations (C_{max}) were similar following both regimens with an AUC_{0-24} of 15.9 ± 4.2 (mean ± SD) and 15.4 ± 4.3 µg·hr/mL and C_{max} of 1.02 ± 0.24 and 1.18 ± 0.36 µg/mL, respectively (n=16).

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 µg·hr/mL (n=16) and C_{max} ranged between 8.27 ± 1.02 (n=16) and 9.0 ± [illegible] µg/mL (n=16).

Food Effects: When CYTOVENE capsules were given with a meal containing 602 calories and 46.5% fat at a dosage of 1000 mg every 8 hours to 20 HIV-positive subjects, the steady-state AUC increased by 22 ± 22% (range: -6% to 68%) and there was a significant prolongation of time to peak serum concentrations (T_{max}) from 1.8 ± 0.8 to 3.0 ± 0.6 hours and a higher C_{max} (0.85 ± 0.25 vs 0.96 ± 0.27 µg/mL) (n=20).

Distribution: The steady-state volume of distribution of ganciclovir after intravenous administration was 0.74 ± 0.15 L/kg (n=98). For CYTOVENE capsules, no correlation was observed between AUC and reciprocal weight (range: 55 to 128 kg); oral dosing according to weight is not required. Cerebrospinal fluid concentrations obtained 0.25 to 5.67 hours postdose in 3 patients who received 2.5 mg/kg ganciclovir intravenously q8h or q12h ranged from 0.31 to 0.68 µg/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 µg/mL.

Metabolism: Following oral administration of a single 1000 mg dose of ^{14}C-labeled ganciclovir, 86 ± 3% of the administered dose was recovered in the feces and 5 ± 1% was recovered in the urine (n=4). No metabolite accounted for more than 1% to 2% of the radioactivity recovered in urine or feces.

Elimination: When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6 to 5.0 mg/kg and when administered orally, it exhibits linear kinetics up to a total daily dose of 4 g/day. 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 ± 0.80 mL/min/kg (n=47), accounting for 91 ± 11% of the systemic clearance (n=47). After oral administration of ganciclovir, steady-state is achieved within 24 hours. Renal clearance following oral administration was 3.1 ± 1.2 mL/min/kg (n=22). Half-life was 3.5 ± [illegible] hours (n=98) following IV administration and 4.8 ± 0.9 hours (n=39) following oral administration.

Special Populations: *Renal Impairment:* The pharmacokinetics following intravenous administration of CYTOVENE-IV solution were evaluated in 10 immunocompromised patients with renal impairment who received doses ranging from 1.25 to 5.0 mg/kg.

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

The pharmacokinetics of ganciclovir following oral administration of CYTOVENE capsules were evaluated in 44 patients, who were either solid organ transplant recipients or HIV positive. Apparent oral clearance of ganciclovir decreased and AUC_{0-24} increased with diminishing renal function (as expressed by creatinine clearance). Based on these observations, it is necessary to modify the dosage of ganciclovir in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both intravenous and oral administration.

Race/Ethnicity and Gender: The effects of race/ethnicity and gender were studied in subjects receiving a dose regimen of 1000 mg every 8 hours. Although the numbers of blacks (16%) and Hispanics (20%) were small, there appeared to be a trend towards a lower steady-state C_{max} and AUC_{0-8} in these subpopulations as compared to Caucasians. No definitive conclusions regarding gender differences could be made because of the small number of females (12%); however, no differences between males and females were observed.

Pediatrics: Ganciclovir pharmacokinetics were studied in 27 neonates, aged 2 to 49 days. At an intravenous dose of 4 mg/kg (n=14) or 6 mg/kg (n=13), the pharmacokinetic parameters were, respectively, C_{max} of 5.5 ± 1.6 and 7.0 ± 1.6 µg/mL, systemic clearance of 3.14 ± 1.75 and 3.56 ± 1.27 mL/min/kg, and $t_{1/2}$ of 2.4 hours (harmonic mean) for both.

Ganciclovir pharmacokinetics were also studied in 10 pediatric patients, aged 9 months to 12 years. The pharmacokinetic characteristics of ganciclovir were the same after single and multiple (q12h) 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 µg/mL, systemic clearance was 4.7 ± 2.2 mL/min/kg, and $t_{1/2}$ was 2.4 ± 0.7 hours. The pharmacokinetics of intravenous ganciclovir in pediatric patients are similar to those observed in adults.

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

INDICATIONS AND USAGE: CYTOVENE-IV is indicated for the treatment of CMV retinitis in immunocompromised patients, [illegible] CYTOVENE-IV is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease (see CLINICAL TRIALS).

CYTOVENE capsules are indicated for the prevention of CMV disease in solid organ transplant recipients and in individuals with advanced HIV infection at risk for developing CMV disease. CYTOVENE capsules are also indicated as an alternative to the intravenous formulation for maintenance treatment of CMV retinitis in immunocompromised patients, including patients with AIDS, in whom retinitis is stable following appropriate induction therapy and for whom the risk of more rapid progression is balanced by the benefit associated with avoiding daily IV infusions (see CLINICAL TRIALS).

SAFETY AND EFFICACY OF **CYTOVENE-IV** AND **CYTOVENE** 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. THE SAFETY AND EFFICACY OF **CYTOVENE** CAPSULES HAVE NOT BEEN ESTABLISHED FOR TREATING ANY MANIFESTATION OF CMV DISEASE OTHER THAN MAINTENANCE TREATMENT OF CMV RETINITIS.

CLINICAL TRIALS:

1. *Treatment of CMV Retinitis*

The diagnosis of CMV retinitis should be made by indirect ophthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis include candidiasis, toxoplasmosis, histoplasmosis, retinal scars and cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason it is essential that the diagnosis of CMV be established by an ophthalmologist familiar with the retinal presentation of these conditions. The diagnosis of CMV retinitis may be supported by culture of CMV from urine, blood, throat or other sites, but a negative CMV culture does not rule out CMV retinitis.

Studies With CYTOVENE-IV: 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 CYTOVENE-IV solution resulted in a significant 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 CYTOVENE-IV 5 mg/kg bid 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 (see DOSAGE AND ADMINISTRATION).

In a controlled, randomized study conducted between February 1989 and December 1990,[1] *immediate treatment with CYTOVENE-IV 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.

Studies Comparing CYTOVENE Capsules to CYTOVENE-IV:

Population Characteristics in Studies ICM 1653, ICM 1774 and AVI 034

		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%)	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%)
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)

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 CYTOVENE-IV solution, 5 mg/kg bid for 14 days followed by 5 mg/kg once daily for 1 additional week.[2] Following the 21-day intravenous induction course, patients with stable CMV *retinitis were randomized to receive 20 weeks of maintenance treatment with either CYTOVENE-IV* solution, 5 mg/kg once daily, or CYTOVENE 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.

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 CYTOVENE-IV solution were randomized to receive maintenance treatment with CYTOVENE-IV solution, 5 mg/kg once daily, CYTOVENE capsules, 500 mg 6 times daily, or CYTOVENE capsules, 1000 mg tid 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.

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 CYTOVENE-IV, 5 mg/kg twice daily, were randomized to receive 20 weeks of maintenance treatment with either CYTOVENE capsules, 500 mg 6 times daily or CYTOVENE-IV solution, 5 mg/kg/day.[3] 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 - ICM 1653

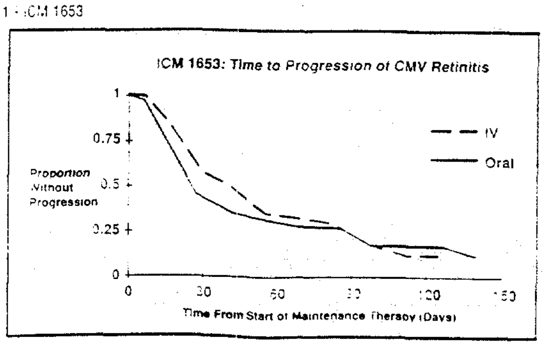


Figure 2 - ICM 1774

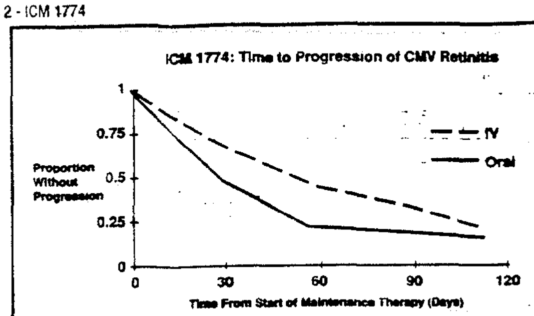
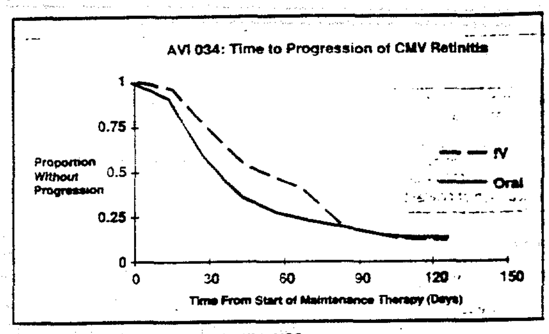


Figure 3 - AVI 034



2. *Prevention of CMV Disease in Subjects With AIDS*

ICM 1654: In a double-blind study conducted between November 1992 and July 1994, 725 subjects with AIDS, who were CMV seropositive and/or culture positive, were randomized to receive *CYTOVENE capsules, 1000 mg, every 8 hours, or placebo.*[4] The study population had a median age of 38 years (range: 21 to 69); were 99% male; were 82% Caucasian, 10% Hispanic, 7% African-American and 1% Asian; and had a median CD_4 count of 21 (range: 0 to 100). The mean observation time was 351 days (range: 5 to 621). As shown in the following table, significantly more placebo recipients developed CMV disease.

Incidence of CMV Disease at 6, 12 and 18 Months After Enrollment (Kaplan-Meier Estimates)

	Incidence (Number Still at Risk)	
	CMV Disease	
	Ganciclovir	**Placebo**
6 months	8% (397)	**11% (190)**
12 months	14% (225)	**26% (92)**
18 months	20% (27)	**39% (9)**

3. ***Prevention of CMV Disease in Transplant Recipients***

CYTOVENE-IV: CYTOVENE-IV was evaluated in three randomized, controlled trials of prevention of CMV disease in organ transplant recipients.

ICM 1496: In a randomized, double-blind, placebo-controlled study of 149 heart transplant recipients[5] at risk for CMV infection (CMV seropositive or a seronegative recipient of an organ from a CMV seropositive donor), there was a statistically significant reduction in the overall incidence of CMV disease in patients treated with CYTOVENE-IV. Immediately posttransplant, patients received CYTOVENE-IV solution 5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for an additional 14 days. Twelve of the 76 (16%) patients treated with CYTOVENE-IV vs 31 of the 73 (43%) placebo-treated patients developed CMV disease during the 120-day posttransplant observation period. No significant differences in hematologic toxicities were seen between the two treatment groups (refer to table in ADVERSE EVENTS).

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

ICM 1570: A second, randomized, unblinded study evaluated 40 allogeneic bone marrow transplant recipients at risk for CMV disease.[7] Patients underwent bronchoscopy and bronchoalveolar lavage (BAL) on day 35 posttransplant. Patients with histologic, immunologic or virologic evidence of CMV infection in the lung were then randomized to observation or treatment with CYTOVENE-IV solution (5 mg/kg bid for 14 days followed by 5 mg/kg qd 5 days/week until day 120). Four of 20 (20%) patients treated with CYTOVENE-IV and 14 of 20 (70%) control patients developed interstitial pneumonia. *The incidence of CMV disease was significantly lower in the group treated with* CYTOVENE-IV, consistent with the results observed in ICM 1689.

CYTOVENE Capsules: *GAN040:* CYTOVENE capsules were evaluated in a randomized, double-blind, placebo-controlled study of 304 orthotopic liver transplant recipients who were CMV seropositive or recipients of an organ from a seropositive donor. Administration of CYTOVENE capsules (1000 mg three times daily) or matching placebo commenced as soon as patients were able to take medication by mouth, but no later than 10 days following transplantation, and continued through 14 weeks after transplantation. Dosing was adjusted for patients with an estimated creatinine clearance <50 mL/min. The incidence of CMV disease at 6 months is summarized in the table below:

Incidence of CMV Disease at 6 Months (Kaplan-Meier Estimates)

CMV Disease at 6 months			
	Ganciclovir (n=150)	Placebo (n=154)	Relative Risk (95% CI)
CMV Disease[1]	7 (4.8%)	29 (18.9%)	0.22 (0.10, 0.5[illegible])
CMV syndrome[2]	[illegible] (4.1%)	19 (12.4%)	
CMV hepatitis	1 (0.7%)	9 (5.9%)	
CMV GI disease	[illegible] (0%)	[illegible]	
CMV lung disease	[illegible] (0%)	4 (2.6%)	

[1] One or more CMV endpoints
[2] CMV syndrome: CMV viremia and unexplained fever accompanied by malaise and/or neutropenia.

CYTOVENE capsules significantly reduced the 6-month incidence of CMV disease in patients at

increased risk of CMV disease, including seronegative recipients of organs from seropositive donors (15% [3/21] with CYTOVENE capsules vs 44% [11/25] with placebo), and patients receiving antilymphocyte antibodies (5% [2/44] with CYTOVENE capsules vs 33% [12/37] with placebo). The incidence of HSV infection at 6 months was 4% (5/150) in ganciclovir vs 24% (36/154) in placebo recipients (relative risk: 0.13; 95% CI: 0.05, 0.32).

CONTRAINDICATIONS: CYTOVENE-IV and CYTOVENE are contraindicated in patients with hypersensitivity to ganciclovir or acyclovir.

WARNINGS: ***Hematologic:*** **CYTOVENE-IV and CYTOVENE should not be administered if the absolute neutrophil count is less than 500 cells/μL or the platelet count is less than 25,000 cells/μL.** Granulocytopenia (neutropenia), anemia and thrombocytopenia have been observed in patients treated with CYTOVENE-IV and CYTOVENE. The frequency and severity of these events vary widely in different patient populations (see ADVERSE EVENTS).

CYTOVENE-IV and CYTOVENE should, therefore, be used with caution in patients with pre-existing cytopenias or with a history of cytopenic reactions to other drugs, chemicals or irradiation. Granulocytopenia 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 of discontinuing drug. Colony-stimulating factors have been shown to increase neutrophil and white blood cell counts in patients receiving CYTOVENE-IV solution for treatment of CMV retinitis.

Impairment of Fertility: Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS: *Carcinogenesis, Mutagenesis* and *Impairment of Fertility*). Although data in humans have not been obtained regarding this effect, it is considered probable that ganciclovir at the recommended doses causes temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

Teratogenesis: Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with CYTOVENE-IV or CYTOVENE (see *Pregnancy:* Category C).

PRECAUTIONS: ***General:*** In clinical studies with CYTOVENE-IV, the maximum single dose administered was 6 mg/kg by intravenous infusion over 1 hour. Larger doses have resulted in increased toxicity. It is likely that more rapid infusions would also result in increased toxicity (see OVERDOSAGE). Administration of CYTOVENE-IV solution should be accompanied by adequate hydration.

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

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR CYTOVENE-IV AND SHOULD BE CONSIDERED FOR CYTOVENE CAPSULES. Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION).

Information for Patients: All patients should be informed that the major toxicities of ganciclovir are granulocytopenia (neutropenia), anemia and thrombocytopenia and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized. Patients should be informed that ganciclovir has been associated with elevations in serum creatinine.

Patients should be instructed to take CYTOVENE capsules with food to maximize bioavailability.

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause infertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment with CYTOVENE-IV or CYTOVENE. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with CYTOVENE-IV or CYTOVENE.

Patients should be advised that ganciclovir causes tumors in animals. Although there is no information from human studies, ganciclovir should be considered a potential carcinogen.

All HIV+ Patients: These patients may be receiving zidovudine (Retrovir®*). Patients should be counseled that treatment with both ganciclovir and zidovudine simultaneously may not be tolerated by some patients and may result in severe granulocytopenia (neutropenia). Patients with AIDS may be receiving didanosine (Videx®‡). Patients should be counseled that concomitant treatment with both ganciclovir and didanosine can cause didanosine serum concentrations to be significantly increased.

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

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

Laboratory Testing: Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving CYTOVENE-IV and CYTOVENE (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 leukopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment. Increased serum creatinine levels have been observed in trials evaluating both CYTOVENE-IV and CYTOVENE. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION).

Drug Interactions: *Didanosine:* At an oral dose of 1000 mg of CYTOVENE every 8 hours and didanosine, 200 mg every 12 hours, the steady-state didanosine $AUC_{0\text{-}12}$ increased 111 ± 114% (range: 10% to 493%) when didanosine was administered either 2 hours prior to or concurrent with administration of CYTOVENE (n=12 patients, 23 observations). A decrease in steady-state ganciclovir AUC of 21 ± 17% (range: -44% to 5%) was observed when didanosine was administered 2 hours prior to administration of CYTOVENE, but ganciclovir AUC was not affected by the presence of didanosine when the two drugs were administered simultaneously (n=12). There were no significant changes in renal clearance for either drug.

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

Zidovudine: At an oral dose of 1000 mg of CYTOVENE every 8 hours, mean steady-state ganciclovir $AUC_{0\text{-}8}$ decreased 17 ± 25% (range: -52% to 23%) in the presence of zidovudine, 100 mg every 4 hours (n=12). Steady-state zidovudine $AUC_{0\text{-}4}$ increased 19 ± 27% (range: -11% to 74%) in the presence of ganciclovir.

Since both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy with these drugs at full dosage.

Probenecid: At an oral dose of 1000 mg of CYTOVENE every 8 hours (n=10), ganciclovir $AUC_{0\text{-}8}$ increased 53 ± 91% (range: -14% to 299%) in the presence of probenecid, 500 mg every 6 hours. Renal clearance of ganciclovir decreased 22 ± 20% (range: -54% to -4%), which is consistent with an interaction involving competition for renal tubular secretion.

Imipenem-cilastatin: Generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Other Medications: It is possible that drugs that inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia and germinal layers of skin and gastrointestinal mucosa may have additive toxicity when administered concomitantly with ganciclovir. Therefore, drugs such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B,

CYTOVENE®-IV (ganciclovir sodium for injection) and CYTOVENE® (ganciclovir capsules)

trimethoprim/sulfamethoxazole combinations or other nucleoside analogues, should be considered for concomitant use with ganciclovir only if the potential benefits are judged to outweigh the risks.

No formal drug interaction studies of CYTOVENE-IV or CYTOVENE and drugs commonly used in transplant recipients have been conducted. Increases in serum creatinine were observed in patients treated with CYTOVENE-IV plus either cyclosporine or amphotericin B, drugs with known potential for nephrotoxicity (see ADVERSE EVENTS). In a retrospective analysis of 93 liver allograft recipients receiving ganciclovir (5 mg/kg infused over 1 hour every 12 hours) and oral cyclosporine (at therapeutic doses), there was no evidence of an effect on cyclosporine whole blood concentrations.

Carcinogenesis; Mutagenesis[1]: Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve (AUC) comparisons). At the dose of 1000 mg/kg/day 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, 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 (estimated as 0.01x the human dose based on AUC comparison). 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 (IV) (2.8 to 10x human exposure based on AUC) but not 50 mg/kg (exposure approximately comparable to the human based on AUC). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 µg/mL.

Impairment of Fertility[1]: Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryoletHality in female mice following intravenous doses of 90 mg/kg/day (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons). 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 0.1x the AUC of the recommended human intravenous dose.

Pregnancy: **Category C[1]:** Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

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

Ganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. CYTOVENE-IV or CYTOVENE should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

[1]***Footnote:*** All dose comparisons presented in the ***Carcinogenesis, Mutagenesis, Impairment of Fertility,*** and ***Pregnancy*** subsections are based on the human AUC following administration of a single 5 mg/kg intravenous infusion of CYTOVENE-IV as used during the maintenance phase of treatment. Compared with the single 5 mg/kg intravenous infusion, human exposure is doubled during the intravenous induction phase (5 mg/kg bid) and approximately halved during maintenance treatment with CYTOVENE capsules (1000 mg tid). The cross-species dose comparisons should be divided by 2 for intravenous induction treatment with CYTOVENE-IV and multiplied by 2 for CYTOVENE capsules.

Nursing Mothers: It is not known whether ganciclovir is excreted in human milk. However, many drugs are excreted in human milk and, because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely (see *Pregnancy*: Category C). Mothers should be instructed to discontinue nursing if they are receiving CYTOVENE-IV or CYTOVENE. The minimum interval before nursing can safely be resumed after the last dose of CYTOVENE-IV or CYTOVENE is unknown.

Pediatric Use: **SAFETY AND EFFICACY OF CYTOVENE-IV AND CYTOVENE IN PEDIATRIC PATIENTS HAVE NOT BEEN ESTABLISHED. THE USE OF CYTOVENE-IV OR CYTOVENE IN THE PEDIATRIC POPULATION WARRANTS EXTREME CAUTION DUE TO THE PROBABILITY OF LONG-TERM CARCINOGENICITY AND REPRODUCTIVE TOXICITY. ADMINISTRATION TO PEDIATRIC PATIENTS SHOULD BE UNDERTAKEN ONLY AFTER CAREFUL EVALUATION AND ONLY IF THE POTENTIAL BENEFITS OF TREATMENT OUTWEIGH THE RISKS.**

The spectrum of adverse events reported in 120 immunocompromised pediatric clinical trial participants with serious CMV infections receiving CYTOVENE-IV solution were similar to those reported in adults. Granulocytopenia (17%) and thrombocytopenia (10%) were the most common adverse events reported.

Sixteen pediatric patients (8 months to 15 years of age) with life- or sight-threatening CMV infections were evaluated in an open-label, CYTOVENE-IV solution, pharmacokinetics study. Adverse events reported for more than one pediatric patient were as follows: hypokalemia (4/16, 25%), abnormal kidney function (3/16, 19%), sepsis (3/16, 19%), thrombocytopenia (3/16, 19%), leukopenia (2/16, 13%), coagulation disorder (2/16, 13%), hypertension (2/16, 13%), pneumonia (2/16, 13%) and immune system disorder (2/16, 13%).

There has been very limited clinical experience using CYTOVENE-IV for the treatment of CMV retinitis in patients under the age of 12 years. Two pediatric patients (ages 9 and 5 years) showed improvement or stabilization of retinitis for 23 and 9 months, respectively. These pediatric patients received induction treatment with 2.5 mg/kg tid followed by maintenance therapy with 6 to 6.5 mg/kg once per day, 5 to 7 days per week. When retinitis progressed during once-daily maintenance therapy, both pediatric patients were treated with the 5 mg/kg qd regimen. Two other pediatric patients (ages 2.5 and 4 years) who received similar induction regimens showed only partial or no response to treatment. Another pediatric patient, a 6-year-old with T-cell dysfunction, showed stabilization of retinitis for 3 months while receiving continuous infusions of CYTOVENE-IV at doses of 2 to 5 mg/kg/24 hours. Continuous infusion treatment was discontinued due to granulocytopenia.

Eleven of the 72 patients in the placebo-controlled trial in bone marrow transplant recipients were pediatric patients, ranging in age from 3 to 13 years (5 treated with CYTOVENE-IV and 6 with placebo). Five of the pediatric patients treated with CYTOVENE-IV received 5 mg/kg intravenously bid for up to 7 days; 4 patients went on to receive 5 mg/kg qd up to day 100 posttransplant. Results were similar to those observed in adult transplant recipients treated with CYTOVENE-IV. Two of the 6 placebo-treated pediatric patients developed CMV pneumonia vs none of the 5 patients treated with CYTOVENE-IV. The spectrum of adverse events in the pediatric group was similar to that observed in the adult patients.

CYTOVENE capsules have not been studied in pediatric patients under age 13.

Geriatric Use: The pharmacokinetic profiles of CYTOVENE-IV and CYTOVENE in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of CYTOVENE-IV or CYTOVENE (see DOSAGE AND ADMINISTRATION).

Clinical studies of CYTOVENE-IV and CYTOVENE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Use in Patients With Renal Impairment: CYTOVENE-IV and CYTOVENE 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 (see DOSAGE AND ADMINISTRATION and ADVERSE EVENTS). Renal function

Hemodialysis has been shown to reduce plasma levels of ganciclovir approximately 50%.

ADVERSE EVENTS: Adverse events that occurred during clinical trials of CYTOVENE-IV solution and CYTOVENE capsules are summarized below, according to the participating study subject population.

Subjects With AIDS: Three controlled, randomized, phase 3 trials comparing CYTOVENE-IV and CYTOVENE capsules for maintenance treatment of CMV retinitis have been completed. During these trials, CYTOVENE-IV or CYTOVENE capsules were prematurely discontinued in 9% of subjects because of adverse events. In a placebo-controlled, randomized, phase 3 trial of CYTOVENE capsules for prevention of CMV disease in AIDS, treatment was prematurely discontinued because of adverse events, new or worsening intercurrent illness, or laboratory abnormalities in 19.5% of subjects treated with CYTOVENE capsules and 16% of subjects receiving placebo. Laboratory data and adverse events reported during the conduct of these controlled trials are summarized below.

Laboratory Data:

Selected Laboratory Abnormalities in Trials for Treatment of CMV Retinitis and Prevention of CMV Disease

	CMV Retinitis Treatment*		CMV Disease Prevention‡	
Treatment	CYTOVENE Capsules† 3000 mg/day	CYTOVENE-IV§ 5 mg/kg/day	CYTOVENE Capsules¶ 3000 mg/day	Placebo¶
Subjects, number	320	175	478	234
Neutropenia:				
<500 ANC/µL	18%	25%	10%	6%
500 – <749	17%	14%	16%	7%
750 – <1000	19%	26%	22%	16%
Anemia:				
Hemoglobin:				
<6.5 g/dL	2%	5%	1%	<1%
6.5 – <8.0	10%	16%	5%	3%
8.0 – <9.5	25%	26%	15%	16%
Maximum Serum Creatinine:				
≥2.5 mg/dL	1%	2%	1%	2%
≥1.5 – <2.5	12%	14%	19%	11%

* Pooled data from Treatment Studies, ICM 1653, Study ICM 1774 and Study AVI 034
† Mean time on therapy = 91 days, including allowed reinduction treatment periods
‡ Mean time on therapy = 103 days, including allowed reinduction treatment periods
§ Data from Prevention Study, ICM 1654
¶ Mean time on ganciclovir = 269 days
¶ Mean time on placebo = 240 days
(See discussion of clinical trials under INDICATIONS AND USAGE.)

Adverse Events: The following table shows selected adverse events reported in 5% or more of the subjects in three controlled clinical trials during treatment with either CYTOVENE-IV solution (5 mg/kg/day) or CYTOVENE capsules (3000 mg/day), and in one controlled clinical trial in which CYTOVENE capsules (3000 mg/day) were compared to placebo for the prevention of CMV disease.

Selected Adverse Events Reported in ≥ 5% of Subjects in Three Randomized Phase 3 Studies Comparing CYTOVENE Capsules to CYTOVENE-IV Solution for Maintenance Treatment of CMV Retinitis and in One Phase 3 Randomized Study Comparing CYTOVENE Capsules to Placebo for Prevention of CMV Disease

		Maintenance Treatment Studies*		Prevention Study	
Body System	Adverse Event	Capsules (n=326)	IV (n=179)	Capsules (n=478)	Placebo (n=234)
Body as a Whole	Fever	38%	48%	35%	33%
	Infection	9%	13%	8%	4%
	Chills	7%	10%	7%	4%
	Sepsis	4%	15%	3%	2%
Digestive System	Diarrhea	41%	44%	48%	42%
	Anorexia	15%	14%	19%	16%
	Vomiting	13%	13%	14%	11%
Hemic and Lymphatic System	Leukopenia	29%	41%	17%	9%
	Anemia	19%	25%	9%	7%
	Thrombocytopenia	6%	6%	3%	1%
Nervous System	Neuropathy	8%	9%	21%	15%
Other	Sweating	11%	12%	14%	12%
	Pruritus	6%	5%	10%	9%
Catheter Related†	Total Catheter Events	6%	22%	–	–
	Catheter Infection	4%	9%	–	–
	Catheter Sepsis	1%	8%	–	–

* Some of these events also appear under other body systems.

The following events were frequently observed in clinical trials but occurred with equal or greater frequency in placebo-treated subjects: abdominal pain, nausea, flatulence, pneumonia, paresthesia, rash.

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 CYTOVENE-IV solution and in 9% of patients treated with CYTOVENE capsules. Patients with CMV retinitis should have frequent ophthalmologic evaluations to monitor the status of their retinitis and to detect any other retinal pathology.

Transplant Recipients: There have been three controlled clinical trials of CYTOVENE-IV solution and one controlled clinical trial of CYTOVENE capsules for the prevention of CMV disease in transplant recipients. Laboratory data and adverse events reported during these trials are summarized below.

Laboratory Data: The following table shows the frequency of granulocytopenia (neutropenia) and thrombocytopenia observed:

Controlled Trials – Transplant Recipients

	CYTOVENE-IV				CYTOVENE Capsules	
	Heart Allograft*		Bone Marrow Allograft*		Liver Allograft†	
	CYTOVENE-IV (n=76)	Placebo (n=73)	CYTOVENE-IV (n=57)	Control (n=55)	CYTOVENE Capsules (n=150)	Placebo (n=154)
Neutropenia						
Minimum ANC <500/µL	4%	3%	12%	9%	3%	1%
Minimum ANC 500-1000/µL	3%	8%	29%	17%	3%	3%
TOTAL ANC <1000/µL	7%	11%	41%	26%	6%	3%
Thrombocytopenia						
Platelet count <25,000/µL	0%	1%	16%	13%	1%	1%
Platelet count 25,000-50,000/µL	3%	3%	25%	37%	5%	2%
TOTAL Platelet <50,000/µL	3%	4%	41%	50%	6%	3%

* Study ICM 1496, Mean duration of treatment = 28 days
Study ICM 1570 and ICM 1689, Mean duration of treatment = 45 days
† Study GAN040, Mean duration of ganciclovir treatment = 82 days
See discussion of clinical trials under INDICATIONS AND USAGE.)

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

Controlled Trials – Transplant Recipients

	CYTOVENE-IV						CYTOVENE Capsules	
	Heart Allograft ICM 1496		Bone Marrow Allograft ICM 1570		Bone Marrow Allograft ICM 1689		Liver Allograft Study 040	
Maximum Serum Creatinine Levels	CYTOVENE-IV (n=76)	Placebo (n=73)	CYTOVENE-IV (n=20)	Control (n=20)	CYTOVENE-IV (n=37)	Placebo (n=35)	CYTOVENE Capsules (n=150)	Placebo (n=154)
Serum Creatinine ≥ 2.5 mg/dL	18%	4%	20%	0%	0%	0%	16%	10%
Serum Creatinine ≥1.5 – <2.5 mg/dL	58%	69%	50%	35%	43%	44%	39%	42%

In 3 out of 4 trials, patients receiving either CYTOVENE-IV solution or CYTOVENE capsules had elevated serum creatinine levels when compared to those receiving placebo. Most patients in these studies also received cyclosporine. The mechanism of impairment of renal function is not known. However, careful monitoring of renal function during therapy with CYTOVENE-IV solution or CYTOVENE capsules is essential, especially for those patients receiving concomitant agents that may cause nephrotoxicity.

General: Other adverse events that were thought to be "probably" or "possibly" related to CYTOVENE-IV solution or CYTOVENE capsules in controlled clinical studies in either subjects with AIDS or transplant recipients are listed below. These events all occurred in at least 3 subjects.

Body as a Whole: abdomen enlarged, asthenia, chest pain, edema, headache, injection site inflammation, malaise, pain

Digestive System: abnormal liver function test, aphthous stomatitis, constipation, dyspepsia, eructation

Hemic and Lymphatic System: pancytopenia

Respiratory System: cough increased, dyspnea

Nervous System: abnormal dreams, anxiety, confusion, depression, dizziness, dry mouth, insomnia, seizures, somnolence, thinking abnormal, tremor

Skin and Appendages: alopecia, dry skin

Special Senses: abnormal vision, taste perversion, tinnitus, vitreous disorder

Metabolic and Nutritional Disorders: creatinine increased, SGOT increased, SGPT increased, weight loss

Cardiovascular System: hypertension, phlebitis, vasodilatation

Urogenital System: creatinine clearance decreased, kidney failure, kidney function abnormal, urinary frequency

Musculoskeletal System: arthralgia, leg cramps, myalgia, myasthenia

The following adverse events reported in patients receiving ganciclovir may be potentially fatal: gastrointestinal perforation, multiple organ failure, pancreatitis and sepsis.

Adverse Events Reported During Postmarketing Experience With CYTOVENE-IV and CYTOVENE Capsules: The following events have been identified during postapproval use of the drug. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either the seriousness, frequency of reporting, the apparent causal connection or a combination of these factors:

acidosis, allergic reaction, anaphylactic reaction, arthritis, bronchospasm, cardiac arrest, cardiac conduction abnormality, cataracts, cholelithiasis, cholestasis, congenital anomaly, dry eyes, dysesthesia, dysphasia, elevated triglyceride levels, encephalopathy, exfoliative dermatitis, extrapyramidal reaction, facial palsy, hallucinations, hemolytic anemia, hemolytic uremic syndrome, hepatic failure, hepatitis, hypercalcemia, hyponatremia, inappropriate serum ADH, infertility, intestinal ulceration, intracranial hypertension, irritability, loss of memory, loss of sense of smell, myelopathy, oculomotor nerve paralysis, peripheral ischemia, pulmonary fibrosis, renal tubular disorder, rhabdomyolysis, Stevens-Johnson syndrome, stroke, testicular hypotrophy, Torsades de Pointes, vasculitis, ventricular tachycardia

OVERDOSAGE: *CYTOVENE-IV:* Overdosage with CYTOVENE-IV has been reported in 17 patients (13 adults and 4 children under 2 years of age). Five patients experienced no adverse events following overdosage at the following doses: 7 doses of 11 mg/kg over a 3-day period (adult), single dose of 3500 mg (adult), single dose of 500 mg (72.5 mg/kg) followed by 48 hours of peritoneal dialysis (4-month-old), single dose of approximately 60 mg/kg followed by exchange transfusion (18-month-old), 2 doses of 500 mg instead of 31 mg (21-month-old).

Irreversible pancytopenia developed in 1 adult with AIDS and CMV colitis after receiving 3000 mg of CYTOVENE-IV solution on each of 2 consecutive days. He experienced worsening GI symptoms and acute renal failure that required short-term dialysis. Pancytopenia developed and persisted until his death from a malignancy several months later. Other adverse events reported following overdosage included: persistent bone marrow suppression (1 adult with neutropenia and thrombocytopenia after a single dose of 6000 mg), reversible neutropenia or granulocytopenia (4 adults, overdoses ranging from 8 mg/kg daily for 4 days to a single dose of 25 mg/kg), hepatitis (1 adult receiving 10 mg/kg daily, and one 2 kg infant after a single 40 mg dose), renal toxicity (1 adult with transient worsening of hematuria after a single 500 mg dose, and 1 adult with elevated creatinine (5.2 mg/dL) after a single 5000 to 7000 mg dose), and seizure (1 adult with known seizure disorder after 3 days of 9 mg/kg). In addition, 1 adult received 0.4 mL (instead of 0.1 mL) CYTOVENE-IV solution by intravitreal injection, and experienced temporary loss of vision and central retinal artery occlusion secondary to increased intraocular pressure related to the injected fluid volume.

CYTOVENE Capsules: There have been no reports of overdosage with CYTOVENE capsules. Doses as high as 6000 mg/day, given either as 1000 mg 6 times daily or as 2000 mg tid, did not result in overt toxicity other than transient neutropenia. Daily doses of more than 6000 mg have not been studied.

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered.

DOSAGE AND ADMINISTRATION: CAUTION – DO NOT ADMINISTER CYTOVENE-IV SOLUTION BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF CYTOVENE-IV MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS.

CAUTION – INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF RECONSTITUTED CYTOVENE-IV SOLUTION MAY RESULT IN SEVERE TISSUE IRRITATION DUE TO HIGH pH (11).

Dosage: THE RECOMMENDED DOSE FOR CYTOVENE-IV SOLUTION AND CYTOVENE CAPSULES SHOULD NOT BE EXCEEDED. THE RECOMMENDED INFUSION RATE FOR CYTOVENE-IV SOLUTION SHOULD NOT BE EXCEEDED.

For Treatment of CMV Retinitis in Patients With Normal Renal Function:

1. *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. CYTOVENE capsules should not be used for induction treatment.

2. *Maintenance Treatment*

CYTOVENE-IV: Following induction treatment, the recommended maintenance dosage of CYTOVENE-IV 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.

CYTOVENE Capsules: Following induction treatment, the recommended maintenance dosage of CYTOVENE capsules is 1000 mg tid with food. Alternatively, the dosing regimen of 500 mg 6 times daily every 3 hours with food, during waking hours, may be used.

For patients who experience progression of CMV retinitis while receiving maintenance treatment with [illegible] ganciclovir [illegible]

For the Prevention of CMV Disease in Patients With Advanced HIV Infection and Normal Renal Function:

CYTOVENE Capsules: The recommended prophylactic dosage of CYTOVENE capsules is 1000 mg tid with food.

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

CYTOVENE-IV: The recommended initial dosage of CYTOVENE-IV 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.

CYTOVENE Capsules: The recommended prophylactic dosage of CYTOVENE capsules is 1000 mg tid with food.

The duration of treatment with CYTOVENE-IV solution and CYTOVENE capsules in transplant recipients is dependent upon the duration and degree of immunosuppression. In controlled clinical trials in bone marrow allograft recipients, treatment with CYTOVENE-IV was continued until day 100 to 120 posttransplantation. CMV disease occurred in several patients who discontinued treatment with CYTOVENE-IV solution prematurely. In heart allograft recipients, the onset of newly diagnosed CMV disease occurred after treatment with CYTOVENE-IV was stopped at day 28 posttransplant, suggesting that continued dosing may be necessary to prevent late occurrence of CMV disease in this patient population. In a controlled clinical trial of liver allograft recipients, treatment with CYTOVENE capsules was continued through week 14 posttransplantation (see INDICATIONS AND USAGE section for a more detailed discussion).

Renal Impairment:

CYTOVENE-IV: For patients with impairment of renal function, refer to the table below for recommended doses of CYTOVENE-IV solution and adjust the dosing interval as indicated:

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

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

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

CYTOVENE Capsules: In patients with renal impairment, the dose of CYTOVENE capsules should be modified as shown below:

Creatinine Clearance* mL/min	CYTOVENE Capsule Dosages
≥70	1000 mg tid or 500 mg q3h, 6x/day
50-69	1500 mg qd or 500 mg tid
25-49	1000 mg qd or 500 mg bid
10-24	500 mg qd
<10	500 mg 3 times per week, following hemodialysis

*Creatinine clearance can be related to serum creatinine by the following formulas:

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

Creatinine clearance for females = 0.85 x male value

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

1. *Reconstituted Solution:*

a. Reconstitute lyophilized CYTOVENE-IV 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 CYTOVENE-IV AND MAY CAUSE PRECIPITATION.

b. Shake the vial to dissolve the drug.

c. Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion solution. Discard the vial if particulate matter or discoloration is observed.

d. Reconstituted solution in the vial is stable at room temperature for 12 hours. It should not be refrigerated.

2. *Infusion Solution:*

Based on patient weight, the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) should be removed from the vial and added to an acceptable (see below) 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 CYTOVENE-IV solution: 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection and Lactated Ringer's Injection, USP.

CYTOVENE-IV, when reconstituted with sterile water for injection, further diluted with 0.9% sodium chloride injection, and stored refrigerated at 5°C in polyvinyl chloride (PVC) bags, remains physically and chemically stable for 14 days.

However, because CYTOVENE-IV is reconstituted with nonbacteriostatic sterile water, it is recommended that the infusion solution be used within 24 hours of dilution to reduce the risk of bacterial contamination. The infusion should be refrigerated. Freezing is not recommended.

Handling and Disposal: Caution should be exercised in the handling and preparation of solutions of CYTOVENE-IV and in the handling of CYTOVENE capsules. Solutions of CYTOVENE-IV are alkaline (pH 11). Avoid direct contact with the skin or mucous membranes of the powder contained in CYTOVENE capsules or of CYTOVENE-IV solutions. If such contact occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. CYTOVENE capsules should not be opened or crushed.

Because ganciclovir shares some of the properties of antitumor agents (ie, carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. Several guidelines on this subject have been published.[3-8]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED: CYTOVENE®-IV (ganciclovir sodium for injection) is supplied in 10 mL sterile vials, each containing ganciclovir sodium equivalent to 500 mg of ganciclovir, in cartons of 25 (NDC 0004-6940-03).

Store vials at temperatures below 40°C (104°F).

CYTOVENE® (ganciclovir capsules) 250 mg are two-pieced, size No. 1, opaque green hard gelatin capsules with ROCHE and CYTOVENE 250 mg imprinted on the capsules in dark blue ink and with two blue lines partially encircling the capsule body. Each capsule contains 250 mg of ganciclovir as a [illegible] (NDC 0004-0269-[illegible]).

CYTOVENE® (ganciclovir capsules) 500 mg are two-pieced, size No. 0 elongated, opaque yellow/opaque green hard gelatin capsules with ROCHE and CYTOVENE 500 mg imprinted on the capsules in dark blue ink and with two blue lines partially encircling the capsule body. Each capsule contains 500 mg of ganciclovir as a white to off-white powder. CYTOVENE capsules are supplied as follows: Bottles of 180 capsules (NDC 0004-0278-48).

Store between 5° and 25°C (41° and 77°F).

*Retrovir is a registered trademark of Glaxo Wellcome.

*Videx is a registered trademark of Bristol-Myers Squibb.

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BEDFORD LABORATORIES™

GNC-AQ-P00A

GANCICLOVIR SODIUM INJECTION

FOR INTRAVENOUS INFUSION ONLY

Rx ONLY.

WARNING

THE CLINICAL TOXICITY OF GANCICLOVIR INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

GANCICLOVIR IS INDICATED FOR USE *ONLY* IN THE TREATMENT OF CYTOMEGALOVIRUS (CMV) RETINITIS IN IMMUNOCOMPROMISED PATIENTS AND FOR THE PREVENTION OF CMV DISEASE IN TRANSPLANT PATIENTS AT RISK FOR CMV DISEASE.

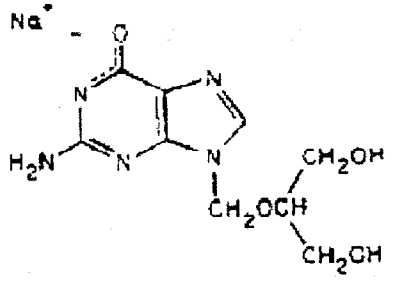
DESCRIPTION

Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).

Ganciclovir Sodium Injection is available as sterile solution in strength of 50 mg/mL for intravenous administration only. Each mL contains the equivalent of 50 mg ganciclovir as the sodium salt (4.6 mg sodium), sodium hydroxide to adjust pH to 11, and water for injection, qs. Further dilution in an appropriate intravenous solution must be performed before infusion (see **DOSAGE AND ADMINISTRATION**).

Ganciclovir, when formulated as monosodium salt, is a clear, colorless solution with a molecular formula of $C_9H_{12}N_5NaO_4$ and a molecular weight of 277.21. The chemical name for ganciclovir sodium is 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy] methyl] guanine, monosodium salt. At physiological pH, ganciclovir sodium exists as the un-ionized form with a solubility of approximately 6 mg/mL at 37°C.

The chemical structure of ganciclovir sodium is:



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

VIROLOGY

Mechanism of Action: Ganciclovir is an acyclic nucleoside analogue of 2'-deoxyguanosine that inhibits replication of herpes viruses. Ganciclovir has been shown to be active against cytomegalovirus (CMV) and herpes simplex virus (HSV) in human clinical studies.

To achieve anti-CMV activity, ganciclovir is phosphorylated first to the monophosphate form by a CMV-encoded (UL97 gene) protein kinase homologue, then to the di- and triphosphate forms by cellular kinases. Ganciclovir triphosphate concentrations may be 100-fold greater in CMV-infected than in uninfected cells, indicating preferential phosphorylation in infected cells. Ganciclovir triphosphate, once formed, persists for days in the CMV-infected cell. Ganciclovir triphosphate is believed to inhibit viral DNA synthesis by (1) competitive inhibition of viral DNA polymerases; and (2) incorporation into viral DNA, resulting in eventual termination of viral DNA elongation.

Antiviral Activity: The median concentration of ganciclovir that inhibits CMV replication (IC_{50}) *in vitro* (laboratory strains or clinical isolates) has ranged from 0.02 to 3.48 mcg/mL. Ganciclovir inhibits mammalian cell proliferation (CIC_{50}) *in vitro* at higher concentrations ranging from 30 to 725 mcg/mL. Bone marrow-derived colony-forming cells are more sensitive (CIC_{50} 0.028 to 0.7 mcg/mL). The relationship of *in vitro* sensitivity of CMV to ganciclovir and clinical response has not been established.

Clinical Antiviral Effect of Ganciclovir: In a study of ganciclovir treatment of life- or sight-threatening CMV disease in immunocompromised patients, 121 of 314 patients had CMV cultured within 7 days prior to treatment and sequential posttreatment viral cultures of urine, blood, throat and/or semen. As judged by conversion to culture negativity, or a greater than 100-fold decrease in *in vitro* CMV titer, at least 83% of patients had a virologic response with a median response time of 7 to 15 days.

Antiviral activity of ganciclovir was demonstrated in two randomized studies for the prevention of CMV disease in transplant recipients (see table below).

Patients With Positive CMV Cultures

	Heart Allograft* (n=147)		Bone Marrow Allograft (n=72)	
Time	Ganciclovir†	Placebo	Ganciclovir‡	Placebo
Pretreatment	1/67 (2%)	5/64 (8%)	37/37 (100%)	35/35 (100%)
Week 2	2/75 (3%)	11/67(16%)	2/31 (6%)	19/28 (68%)
Week 4	3/66(5%)	28/66(43%)	0/24 (0%)	16/20(80%)

* CMV seropositive or receiving graft from seropositive donor

† 5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for 14 days

‡ 5 mg/kg bid for 7 days followed by 5 mg/kg qd until day 100 posttransplant

Viral Resistance: The current working definition of CMV resistance to ganciclovir in *in vitro* assays is IC_{50} >3.0 mcg/mL (12.0 mcM). 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.

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

CLINICAL PHARMACOLOGY

Pharmacokinetics: **BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR GANCICLOVIR. FOR DOSING INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.**

Absorption: At the end of a 1-hour intravenous infusion of 5 mg/kg ganciclovir, total area under the serum concentration vs time curve (AUC) ranged between 22.1 ± 3.2 (n=16) and 26.8 ± 6.1 mcg-hr/mL (n=16) and maximum serum concentrations (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). Cerebrospinal fluid concentrations obtained 0.25 to 5.67 hours postdose in 3 patients who received 2.5 mg/kg ganciclovir intravenously q8h or q12h 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 and when administered orally, it exhibits linear kinetics up to a total daily dose of 4 g/day. 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 ± 0.80 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 IV administration.

Special Populations: *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.

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

The pharmacokinetics of ganciclovir following oral administration of ganciclovir capsules were evaluated in 44 patients, who were either solid organ transplant recipients or HIV positive. Apparent oral clearance of ganciclovir decreased and $AUC_{0\text{-}24h}$ increased with diminishing renal function (as expressed by creatinine clearance). Based on these observations, it is necessary to modify the dosage of ganciclovir in patients with renal impairment (see **DOSAGE AND ADMINISTRATION**).

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both intravenous and oral administration.

Race/Ethnicity and Gender: The effects of race/ethnicity and gender were studied in subjects receiving a dose regimen of 1000 mg every 8 hours. Although the numbers of blacks (16%) and Hispanics (20%) were small, there appeared to be a trend towards a lower steady-state C_{max} and $AUC_{0\text{-}8}$ in these subpopulations as compared to Caucasians. No definitive conclusions regarding gender differences could be made because of the small number of females (12%); however, no differences between males and females were observed.

Pediatrics: Ganciclovir pharmacokinetics were studied in 27 neonates, aged 2 to 49 days. At an intravenous dose of 4 mg/kg (n=14) or 6 mg/kg (n=13), the pharmacokinetic parameters were, respectively, C_{max} of 5.5 ± 1.6 and 7.0 ± 1.6 mcg/mL, systemic clearance of 3.14 ± 1.75 and 3.56 ± 1.27 mL/min/kg, and $t_{1/2}$ of 2.4 hours (harmonic mean) for both.

Ganciclovir pharmacokinetics were also studied in 10 pediatric patients, aged 9 months to 12 years. The pharmacokinetic characteristics of ganciclovir were the same after single and multiple (q12h) 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. The pharmacokinetics of intravenous ganciclovir in pediatric patients are similar to those observed in adults.

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

INDICATIONS AND USAGE

Ganciclovir is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). Ganciclovir is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease (see ***CLINICAL TRIALS***).

SAFETY AND EFFICACY OF **GANCICLOVIR** 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.

CLINICAL TRIALS

1. Treatment of CMV Retinitis

The diagnosis of CMV retinitis should be made by indirect ophthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis include candidiasis, toxoplasmosis, histoplasmosis, retinal scars and cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason it is essential that the diagnosis of CMV be established by an ophthalmologist familiar with the retinal presentation of these conditions. The diagnosis of CMV retinitis may be supported by culture of CMV from urine, blood, throat or other sites, but a negative CMV culture does not rule out CMV retinitis.

Studies With Ganciclovir: 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 significant 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 bid 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 (see **DOSAGE AND ADMINISTRATION**).

In a controlled, randomized study conducted between February 1989 and December 1990,[1] 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.

Studies Comparing Ganciclovir Capsules to Ganciclovir IV:

Population Characteristics in Studies ICM 1653, ICM 1774 and AVI 034

		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%)	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%)
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)

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 bid for 14 days followed by 5 mg/kg once daily for 1 additional week.[2] 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.

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 tid 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.

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.[3] 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 - ICM 1653

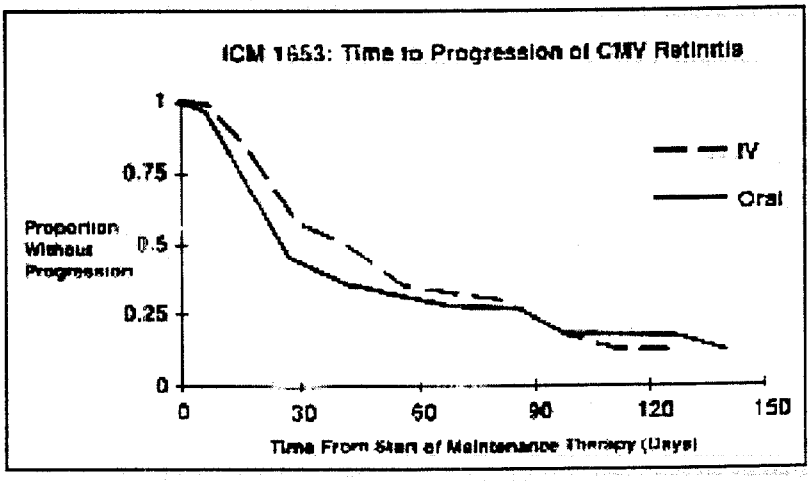


Figure 2 – ICM 1774

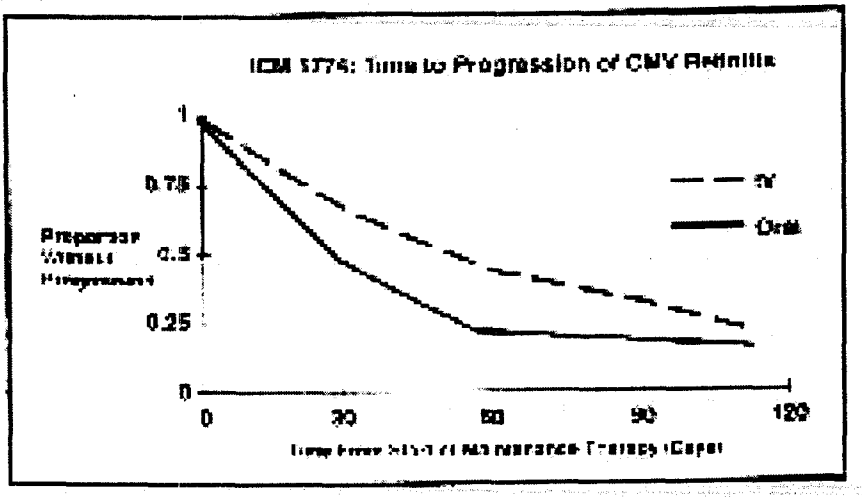
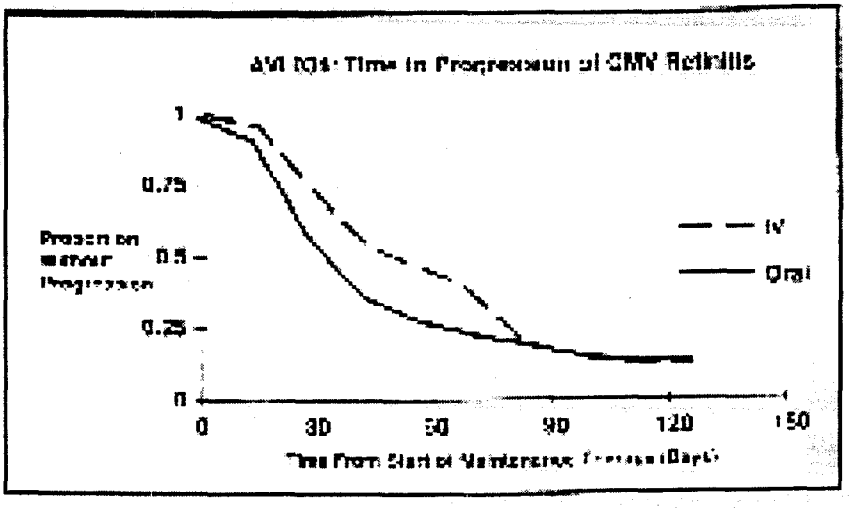


Figure 3 – AVI 034



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.

ICM 1496: In a randomized, double-blind, placebo-controlled study of 149 heart transplant recipients[5] at risk for CMV infection (CMV seropositive or a seronegative recipient of an organ from a CMV seropositive donor), there was a statistically significant reduction in the overall incidence of CMV disease in patients treated with

ganciclovir. Immediately posttransplant, patients received ganciclovir solution 5 mg/kg bid for 14 days followed by 6 mg/kg qd 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 posttransplant observation period. No significant differences in hematologic toxicities were seen between the two treatment groups (refer to table in **ADVERSE REACTIONS**).

ICM 1689: In a randomized, double-blind, placebo-controlled study of 72 bone marrow transplant recipients[6] with asymptomatic CMV infection (CMV positive culture of urine, throat or blood) there was a statistically significant 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 bid for 7 days followed by 5 mg/kg qd through day 100 posttransplant. One of the 37 (3%) patients treated with ganciclovir vs 15 of the 35 (43%) placebo-treated patients developed CMV disease during the study. At 6 months posttransplant, there continued to be a statistically significant reduction in the incidence of CMV disease in patients treated with ganciclovir. Six of 37 (16%) patients treated with ganciclovir vs 15 of the 35 (43%) placebo-treated patients developed disease through 6 months posttransplant. The overall rate of survival was statistically significantly higher in the group treated with ganciclovir, both at day 100 and day 180 posttransplant. Although the differences in hematologic toxicities were not statistically significant, the incidence of neutropenia was higher in the group treated with ganciclovir (refer to table in **ADVERSE REACTIONS**).

ICM 1570: A second, randomized, unblinded study evaluated 40 allogeneic bone marrow transplant recipients at risk for CMV disease.[7] Patients underwent bronchoscopy and bronchoalveolar lavage (BAL) on day 35 posttransplant. Patients with histologic, immunologic or virologic evidence of CMV infection in the lung were then randomized to observation or treatment with ganciclovir solution (5 mg/kg bid for 14 days followed by 5 mg/kg qd 5 days/week until day 120). Four of 20 (20%) patients treated with ganciclovir and 14 of 20 (70%) control patients developed interstitial

pneumonia. The incidence of CMV disease was significantly lower in the group treated with ganciclovir, consistent with the results observed in ICM 1689.

CONTRAINDICATIONS

Ganciclovir is contraindicated in patients with hypersensitivity to ganciclovir or acyclovir.

WARNINGS

***Hematologic*: Ganciclovir should not be administered if the absolute neutrophil count is less than 500 cells/mcL or the platelet count is less than 25,000 cells/mcL.** Granulocytopenia, (neutropenia), anemia and thrombocytopenia have been observed in patients treated with ganciclovir. The frequency and severity of these events vary widely in different patient populations (see **ADVERSE REACTIONS**).

Ganciclovir should, therefore, be used with caution in patients with pre-existing cytopenias or with a history of cytopenic reactions to other drugs, chemicals or irradiation. Granulocytopenia 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 of discontinuing drug. Colony-stimulating factors have been shown to increase neutrophil and white blood cell counts in patients receiving ganciclovir solution for treatment of CMV retinitis.

Impairment of Fertility: Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see **PRECAUTIONS: *Carcinogenesis, Mutagenesis, Impairment of Fertility***). Although data in humans have not been obtained regarding this effect, it is considered probable that ganciclovir at the recommended doses causes temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

Teratogenesis: Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir (see ***Pregnancy: Teratogenic Effects: Pregnancy Category C***).

PRECAUTIONS

General: In clinical studies with ganciclovir, the maximum single dose administered was 6 mg/kg by intravenous infusion over 1 hour. Larger doses have resulted in increased toxicity. It is likely that more rapid infusions would also result in increased toxicity (see **OVERDOSAGE**). Administration of ganciclovir solution should be accompanied by adequate hydration.

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

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR GANCICLOVIR. Such adjustments should be based on measured or estimated creatinine clearance values (see **DOSAGE AND ADMINISTRATION**).

Information for Patients: All patients should be informed that the major toxicities of ganciclovir are granulocytopenia (neutropenia), anemia and thrombocytopenia and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized. Patients should be informed that ganciclovir has been associated with elevations in serum creatinine.

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause infertility in humans. Women of childbearing potential

should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment with ganciclovir. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir.

Patients should be advised that ganciclovir causes tumors in animals. Although there is no information from human studies, ganciclovir should be considered a potential carcinogen.

All HIV+ Patients: These patients may be receiving zidovudine (Retrovir®*). Patients should be counseled that treatment with both ganciclovir and zidovudine simultaneously may not be tolerated by some patients and may result in severe granulocytopenia (neutropenia). Patients with AIDS may be receiving didanosine (Videx®†). Patients should be counseled that concomitant treatment with both ganciclovir and didanosine can cause didanosine serum concentrations to be significantly increased.

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

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

Laboratory Testing: Due to the frequency of neutropenia, anemia and thrombocytopenia in patents receiving ganciclovir (see **ADVERSE REACTIONS**), 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 leukopenia, or in whom neutrophil counts are less than 1000 cells/mcL at the beginning of treatment. Increased serum creatinine levels have been observed in trials evaluating ganciclovir. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patents (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions: *Didanosine:* At an oral dose of 1000 mg of ganciclovir every 8 hours and didanosine, 200 mg every 12 hours, the steady-state didanosine AUC_{0-12} increased 111 ± 114% (range: 10% to 493%) when didanosine was administered either 2 hours prior to or concurrent with administration of ganciclovir (n=12 patients, 23 observations). A decrease in steady-state ganciclovir AUC of 21 ± 17% (range: -44% to 5%) was observed when didanosine was administered 2 hours prior to administration of ganciclovir, but ganciclovir AUC was not affected by the presence of didanosine when the two drugs were administered simultaneously (n=12). There were no significant changes renal clearance for either drug.

When the standard intravenous ganciclovir induction dose (5 mg/kg infused over 1 hour every 12 hours) was coadministered with didanosine at a dose of 200 mg orally every 12 hours, the steady-state didanosine AUC_{0-12} increased 70 ± 40% (range: 3% to 121%, n=11) and C_{max} increased 49 ± 48% (range: -28% to 125%). In a separate study, when the standard intravenous ganciclovir maintenance dose (5 mg/kg infused over 1 hour every 24 hours) was coadministered with didanosine at a dose of 200 mg orally every 12 hours, didanosine AUC_{0-12} increased 50 ± 26% (range: 22% to 110%, n=11) and C_{max} increased 36 ± 36% (range: -27% to 94%) over the first didanosine dosing interval. Didanosine plasma concentrations (AUC_{12-24}) were unchanged during the dosing intervals when ganciclovir was not coadministered. Ganciclovir

pharmacokinetics were not affected by didanosine. In neither study were there significant changes in the renal clearance of either drug.

Zidovudine: At an oral dose of 1000 mg of ganciclovir every 8 hours, mean steady-state ganciclovir AUC_{0-8} decreased 17 ± 25% (range: -52% to 23%) in the presence of zidovudine, 100 mg every 4 hours (n=12). Steady-state zidovudine AUC_{0-4} increased 19 ± 27% (range: -11% to 74%) in the presence of ganciclovir.

Since both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy with these drugs at full dosage.

Probenecid: At an oral dose of 1000 mg of ganciclovir every 8 hours (n=10), ganciclovir AUC_{0-8} increased 53 ± 91% (range: -14% to 299%) in the presence of probenecid, 500 mg every 6 hours. Renal clearance of ganciclovir decreased 22 ± 20% (range: -54% to -4%), which is consistent with an interaction involving competition for renal tubular secretion.

Imipenem-cilastatin: Generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Other Medications: It is possible that drugs that inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia and germinal layers of skin and gastrointestinal mucosa may have additive toxicity when administered concomitantly with ganciclovir. Therefore, drugs such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulfamethoxazole combinations or other nucleoside analogues, should be considered for concomitant use with ganciclovir only if the potential benefits are judged to outweigh the risks.

No formal drug interaction studies of ganciclovir and drugs commonly used in transplant recipients have been conducted. Increases in serum creatinine were

observed in patients treated with ganciclovir plus either cyclosporine or amphotericin B, drugs with known potential for nephrotoxicity (see **ADVERSE REACTIONS**). In a retrospective analysis of 93 liver allograft recipients receiving ganciclovir (5 mg/kg infused over 1 hour every 12 hours) and oral cyclosporine (at therapeutic doses), there was no evidence of an effect on cyclosporine whole blood concentrations.

Carcinogenesis, Mutagenesis†, Impairment of Fertility: Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve [AUC] comparisons). At the dose of 1000 mg/kg/day 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, 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 (estimated as 0.01x the human dose based on AUC comparison). Except for histiocytic sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestornach 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 mcg/mL, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (IV) (2.8 to 10x human exposure based on AUC) but not 50 mg/kg (exposure approximately comparable to the human based on AUC). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 mcg/mL.

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons). 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 0.1x the AUC of the recommended human intravenous dose.

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

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

Ganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. Ganciclovir should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

†Footnote: All dose comparisons presented in the ***Carcinogenesis, Mutagenesis, Impairment of Fertility,*** and ***Pregnancy*** subsections are based on the human AUC following administration of a single 5 mg/kg intravenous infusion of ganciclovir as used during the maintenance phase of treatment. Compared with the single 5 mg/kg intravenous infusion, human exposure is doubled during the intravenous induction phase (5 mg/kg bid) and approximately halved during maintenance treatment with ganciclovir capsules (1000 mg tid). The cross-species dose comparisons should be divided by 2 for intravenous induction treatment with ganciclovir IV and multiplied by 2 for ganciclovir capsules.

Nursing Mothers: It is not known whether ganciclovir is excreted in human milk. However, many drugs are excreted in human milk and, because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely (see ***Pregnancy: Teratogenic Effects; Pregnancy Category C***). Mothers should be instructed to discontinue nursing if they are receiving ganciclovir. The minimum interval before nursing can safely be resumed after the last dose of ganciclovir is unknown.

Pediatric Use: **SAFETY AND EFFICACY OF GANCICLOVIR IN PEDIATRIC PATIENTS HAVE NOT BEEN ESTABLISHED. THE USE OF GANCICLOVIR IN THE PEDIATRIC POPULATION WARRANTS EXTREME CAUTION DUE TO THE PROBABILITY OF LONG-TERM CARCINOGENICITY AND REPRODUCTIVE TOXICITY. ADMINISTRATION TO PEDIATRIC PATIENTS SHOULD BE UNDERTAKEN ONLY AFTER CAREFUL EVALUATION AND ONLY IF THE POTENTIAL BENEFITS OF TREATMENT OUTWEIGH THE RISKS.**

The spectrum of adverse events reported in 120 immunocompromised pediatric clinical trial participants with serious CMV infections receiving ganciclovir solution were similar to those reported in adults. Granulocytopenia (17%) and thrombocytopenia (10%) were the most common adverse events reported.

Sixteen pediatric patients (8 months to 15 years of age) with life- or sight-threatening CMV infections were evaluated in an open-label, ganciclovir solution, pharmacokinetics study. Adverse events reported for more than one pediatric patient were as follows: hypokalemia (4/16, 25%), abnormal kidney function (3/16, 19%), sepsis (3/16, 19%), thrombocytopenia (3/16, 19%), leukopenia (2/16, 13%), coagulation disorder (2/16, 13%), hypertension (2/16, 13%), pneumonia (2/16, 13%) and immune system disorder (2/16, 13%).

There has been very limited clinical experience using ganciclovir for the treatment of CMV retinitis in patients under the age of 12 years. Two pediatric patients (ages 9 and 5 years) showed improvement or stabilization of retinitis for 23 and 9 months, respectively. These pediatric patients received induction treatment with 2.5 mg/kg tid followed by maintenance therapy with 6 to 6.5 mg/kg once per day, 5 to 7 days per week. When retinitis progressed during once-daily maintenance therapy, both pediatric patients were treated with the 5 mg/kg bid regimen. Two other pediatric patients (ages 2.5 and 4 years) who received similar induction regimens showed only partial or no response to treatment. Another pediatric patient, a 6-year-old with T-cell dysfunction, showed stabilization of retinitis for 3 months while receiving continuous infusions of ganciclovir at doses of 2 to 5 mg/kg/24 hours. Continuous infusion treatment was discontinued due to granulocytopenia.

Eleven of the 72 patients in the placebo-controlled trial in bone marrow transplant recipients were pediatric patients, ranging in age from 3 to 10 years (5 treated with ganciclovir and 6 with placebo). Five of the pediatric patients treated with ganciclovir received 5 mg/kg intravenously bid for up to 7 days; 4 patients went on to receive 5 mg/kg qd up to day 100 posttransplant. Results were similar to those observed in adult transplant recipients treated with ganciclovir. Two of the 6 placebo-treated pediatric patients developed CMV pneumonia vs none of the 5 patients treated with ganciclovir. The spectrum of adverse events in the pediatric group was similar to that observed in the adult patients.

Geriatric Use: The pharmacokinetic profiles of ganciclovir in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of ganciclovir (see **DOSAGE AND ADMINISTRATION**).

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 elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly. (See **PRECAUTIONS:** ***General:*** *Renal Impairment* and **DOSAGE AND ADMINISTRATION**).

Use in Patients With Renal Impairment: Ganciclovir and 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 (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS:** ***Renal Toxicity***).

Hemodialysis has been shown to reduce plasma levels of ganciclovir by approximately 50%.

ADVERSE REACTIONS

Adverse events that occurred during clinical trials of ganciclovir solution are summarized below, according to the participating study subject population.

Subjects with AIDS: Three controlled, randomized, phase 3 trials comparing ganciclovir and ganciclovir capsules for maintenance treatment of CMV retinitis have

been completed. During these trials, ganciclovir or ganciclovir capsules were prematurely discontinued in 9% of subjects because of adverse events. Laboratory data and adverse events reported during the conduct of these controlled trials are summarized below.

Laboratory Data:

Selected Laboratory Abnormalities in Trials for Treatment of CMV Retinitis

	CMV Retinitis Treatment*	
Treatment	Ganciclovir Capsules† 3000 mg/day	Ganciclovir IV‡ 5 mg/kg/day
Subjects, number	320	175
Neutropenia:		
<500 ANC/mcL	18%	25%
500 - <749	17%	14%
750 - <1000	19%	26%
Anemia:		
Hemoglobin:		
<6.5 g/dL	2%	5%
6.5 - <8.0	10%	16%
8.0 - <9.5	25%	26%
Maximum Serum Creatinine:		
≥2.5 mg/dL	1%	2%
≥1.5 - <2.5	12%	14%

*Pooled data from Treatment Studies, ICM 1653, Study ICM 1774 and Study AVI 034
†Mean time on therapy = 91 days, including allowed reinduction treatment periods
‡Mean time on therapy = 103 days, including allowed reinduction treatment periods
(See discussion of clinical trials under **INDICATIONS AND USAGE**.)

Adverse Events: The following table shows selected adverse events reported in 5% or more of the subjects in three controlled clinical trials during treatment with either ganciclovir solution 5 mg/kg/day) or ganciclovir capsules (3000 mg/day).

Selected Adverse Events Reported in ≥ 5% of Subjects in Three Randomized Phase 3 Studies Comparing Ganciclovir Capsules to Ganciclovir Solution for Maintenance Treatment of CMV Retinitis

		Maintenance Treatment Studies	
Body System	Adverse Event	Capsules (n=326)	IV (n=179)
Body as a Whole	Fever	38%	48%
	Infection	9%	13%
	Chills	7%	10%
	Sepsis	4%	15%
Digestive System	Diarrhea	41%	44%
	Anorexia	15%	14%
	Vomiting	13%	13%
Hemic and Lymphatic System	Leukopenia	29%	41%
	Anemia	19%	25%
	Thrombocytopenia	6%	6%
Nervous System	Neuropathy	8%	9%
Other	Sweating	11%	12%
	Pruritus	6%	5%
Catheter Related*	Total Catheter Events		
	Catheter Infection	6%	22%
	Catheter Sepsis	4%	9%
		1%	8%
* Some of these events also appear under other body systems			

The following events were frequently observed in clinical trials but occurred with equal or greater frequency in placebo-treated subjects: abdominal pain, nausea, flatulence, pneumonia, paresthesia, rash.

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 solution and in 8% of patients treated with ganciclovir capsules. Patients with CMV retinitis should have frequent ophthalmologic evaluations to monitor the status of their retinitis and to detect any other retinal pathology.

Transplant Recipients: There have been three controlled clinical trials of ganciclovir solution for the prevention of CMV disease in transplant recipients. Laboratory data and adverse events reported during these trials are summarized below.

Laboratory Data: The following table shows the frequency of granulocytopenia (neutropenia) and thrombocytopenia observed:

Controlled Trials - Transplant Recipients				
	Ganciclovir			
	Heart Allograft*		Bone Marrow Allograft†	
	Ganciclovir (n=76)	Placebo (n=73)	Ganciclovir (n=57)	Control (n=55)
Neutropenia				
Minimum ANC <500/mcL	4%	3%	12%	6%
Minimum ANC 500 - 1000/mcL	3%	8%	29%	17%
TOTAL ANC ≤1000/mcL	7%	11%	41%	23%
Thrombocytopenia				
Platelet count <25,000/mcL	3%	1%	32%	28%
Platelet count 25,000 - 50,000/mcL	5%	3%	25%	37%
TOTAL Platelet ≤50,000/mcL	8%	4%	57%	65%

* Study ICM 1496. Mean duration of treatment = 28 days
† Study ICM 1570 and ICM 1689. Mean duration of treatment = 82 days
(See discussion of clinical trials under **INDICATIONS AND USAGE**)

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

Controlled Trials – Transplant Recipients						
	Ganciclovir					
	Heart Allograft ICM 1496		Bone Marrow Allograft ICM 1570		Bone Marrow Allograft ICM1689	
Maximum						

Serum Creatinine Levels	Ganciclovir (n=76)	Placebo (n=73)	Ganciclovir (n=20)	Control (n=20)	Ganciclovir (n=37)	Placebo (n=35)
Serum Creatinine ≥ 2.5 mg/dL	18%	4%	20%	0%	0%	0%
Serum Creatinine ≥1.5 - <2.5 mg/dL	58%	69%	50%	35%	43%	44%

In 3 out of 4 trials, patients receiving either ganciclovir solution or ganciclovir capsules had elevated serum creatinine levels when compared to those receiving placebo. Most patients in these studies also received cyclosporine. The mechanism of impairment of renal function is not known. However, careful monitoring of renal function during therapy with ganciclovir solution or ganciclovir capsules is essential, especially for those patients receiving concomitant agents that may cause nephrotoxicity.

General: Other adverse events that were thought to be "probably" or "possibly" related to ganciclovir solution or ganciclovir capsules in controlled clinical studies in either subjects with AIDS or transplant recipients are listed below. These events all occurred in at least 3 subjects.

Body as a Whole: abdomen enlarged, asthenia, chest pain, edema, headache, injection site inflammation, malaise, pain

Digestive System: abnormal liver function test, aphthous stomatitis, constipation, dyspepsia, eructation

Hemic and Lymphatic System: pancytopenia

Respiratory System: cough increased, dyspnea

Nervous System: abnormal dreams, anxiety, confusion, depression, dizziness, dry mouth, insomnia, seizures, somnolence, thinking abnormal, tremor

Skin and Appendages: alopecia, dry skin

Special Senses: abnormal vision, taste perversion, tinnitus, vitreous disorder

Metabolic and Nutritional Disorders: creatinine increased, SGOT increased, SGPT increased, weight loss

Cardiovascular System: hypertension, phlebitis, vasodilatation

Urogenital System: creatinine clearance decreased, kidney failure, kidney function abnormal, urinary frequency

Musculoskeletal System: arthralgia, leg cramps, myalgia, myasthenia

The following adverse events reported in patients receiving ganciclovir may be potentially fatal: gastrointestinal perforation, multiple organ failure, pancreatitis and sepsis.

Adverse Events Reported During Postmarketing Experience With Ganciclovir: The following events have been identified during postapproval use of the drug. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either the seriousness, frequency of reporting, the apparent causal connection or a combination of these factors:

acidosis, allergic reaction, anaphylactic reaction, arthritis, bronchospasm, cardiac arrest, cardiac conduction abnormality, cataracts, cholelithiasis, cholestasis, congenital anomaly, dry eyes, dysesthesia, dysphasia, elevated triglyceride levels, encephalopathy, exfoliative dermatitis, extrapyramidal reaction, facial palsy, hallucinations, hemolytic anemia, hemolytic uremic syndrome, hepatic failure, hepatitis, hypercalcemia, hyponatremia, inappropriate serum ADH, infertility, intestinal

ulceration, intracranial hypertension, irritability, loss of memory, loss of sense of smell, myelopathy, oculomotor nerve paralysis, peripheral ischemia, pulmonary fibrosis, renal tubular disorder, rhabdomyolysis, Stevens-Johnson syndrome, stroke, testicular hypotrophy, Torsades de Pointes, vasculitis, ventricular tachycardia

OVERDOSAGE

Overdosage with ganciclovir has been reported in 17 patients (13 adults and 4 children under 2 years of age). Five patients experienced no adverse events following overdosage at the following doses: 7 doses of 11 mg/kg over a 3-day period (adult), single dose of 3500 mg (adult), single dose of 500 mg (72.5 mg/kg) followed by 48 hours of peritoneal dialysis (4-month-old), single dose of approximately 60 mg/kg followed by exchange transfusion (18-month-old), 2 doses of 500 mg instead of 31 mg (21-month-old).

Irreversible pancytopenia developed in 1 adult with AIDS and CMV colitis after receiving 3000 mg of ganciclovir solution on each of 2 consecutive days. He experienced worsening GI symptoms and acute renal failure that required short-term dialysis. Pancytopenia developed and persisted until his death from a malignancy several months later. Other adverse events reported following overdosage included: persistent bone marrow suppression (1 adult with neutropenia and thrombocytopenia after a single dose of 6000 mg), reversible neutropenia or granulocytopenia (4 adults, overdoses ranging from 8 mg/kg daily for 4 days to a single dose of 25 mg/kg), hepatitis (1 adult receiving 10 mg/kg daily, and one 2 kg infant after a single 40 mg dose), renal toxicity (1 adult with transient worsening of hematuria after a single 500 mg dose, and 1 adult with elevated creatinine (5.2 mg/dL) after a single 5000 to 7000 mg dose), and seizure (1 adult with known seizure disorder after 3 days of 9 mg/kg). In addition, 1 adult received 0.4 mL (instead of 0.1 mL) ganciclovir solution by intravitreal injection, and experienced temporary loss of vision and central retinal artery occlusion secondary to increased intraocular pressure related to the injected fluid volume.

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered.

DOSAGE AND ADMINISTRATION

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

CAUTION – INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF GANCICLOVIR SOLUTION MAY RESULT IN SEVERE TISSUE IRRITATION DUE TO HIGH pH (11).

Dosage: THE RECOMMENDED DOSE FOR GANCICLOVIR SOLUTION SHOULD NOT BE EXCEEDED. THE RECOMMENDED INFUSION RATE FOR GANCICLOVIR SOLUTION SHOULD NOT BE EXCEEDED.

For Treatment of CMV Retinitis in Patients With Normal Renal Function:

1. 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.

2. Maintenance Treatment

Following induction treatment, the recommended maintenance dosage of ganciclovir 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, reinduction treatment is recommended.

For the Prevention of CMV Disease in Transplant Recipients With Normal Renal

Function: The recommended initial dosage of ganciclovir 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 solution in transplant recipients is dependent upon the duration and degree of immunosuppression. In controlled clinical trials in bone marrow allograft recipients, treatment with ganciclovir was continued until day 100 to 120 posttransplantation. CMV disease occurred in several patients who discontinued treatment with ganciclovir solution prematurely. In heart allograft recipients, the onset of newly diagnosed CMV disease occurred after treatment with ganciclovir 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 the table below for recommended doses of ganciclovir solution and adjust the dosing interval as indicated:

Creatinine Clearance* (mL/min)	Ganciclovir Induction Dose (mg/kg)	Dosing Interval (hours)	Ganciclovir Maintenance Dose (mg/kg)	Dosing Interval (hours)
≥70	5.5	12	5.0	24
50-69	2.5	12	2.5	24
25-49	2.5	24	1.25	24
10-24	1.25	24	0.625	24
<10	1.25	3 times per week following hemodialysis	0.625	3 times per week following hemodialysis

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

Dosing for patients undergoing hemodialysis should not exceed 1.25 mg/kg 3 times per week, following each hemodialysis session. Ganciclovir should be given shortly

after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50%.

*Creatinine clearance can be related to serum creatinine by the following formulas:

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

Creatinine clearance for females = 0.85 x male value

Patient Monitoring: Due to the frequency of granulocytopenia, anemia and thrombocytopenia in patients receiving ganciclovir (see **ADVERSE REACTIONS**), 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/mcL 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 (see ***Renal Impairment).*** Dosage reductions should also be considered for those with neutropenia, anemia and/or thrombocytopenia (see **ADVERSE REACTIONS).** Ganciclovir should not be administered in patients with severe neutropenia (ANC less than 500/mcL) or severe thrombocytopenia (platelets less than 25,000/mcL).

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

Infusion Solution:

Based on patient weight, the appropriate volume of the solution (ganciclovir concentration 50 mg/mL) should be removed from the vial and added to an acceptable (see below) 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 solution: 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection and Lactated Ringer's Injection, USP.

Ganciclovir, when further diluted with 0.9% sodium chloride injection, and stored refrigerated at 5°C in polyvinyl chloride (PVC) bags, remains physically and chemically stable for 14 days.

However, it is recommended that the infusion solution of ganciclovir be used within 24 hours of dilution to reduce the risk of bacterial contamination. The infusion should be refrigerated. Freezing is not recommended.

Handling and Disposal: Caution should be exercised in the handling and preparation of solutions of ganciclovir. Solutions of ganciclovir are alkaline (pH 11). Avoid direct contact with the skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water.

Because ganciclovir shares some of the properties of antitumor agents (ie, carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued antineoplastic drugs. Several guidelines on this subject have been published.[8-10]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Ganciclovir Sodium Injection is supplied in 10 mL sterile vials, each containing ganciclovir sodium equivalent to 500 mg of ganciclovir, 50 mg/mL in cartons of 10 (**NDC 55390-024-10**).

Store at room temperature 15° to 30°C (59° to 86°F). [See USP].

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