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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 \pm SD) and 15.4 ± 4.3 μ g-hr/mL and C_{max} of 1.02 ± 0.24 and 1.18 ± 0.36 μ g/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 μ g-hr/mL (n=16) and C_{max} ranged between 8.27 ± 1.02 (n=16) and 9.0 ± 1.4 μ g/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 $22 \pm 22\%$ (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 μ g/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 μ g/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 μ g/mL.

Metabolism: Following oral administration of a single 1000 mg dose of 14 C-labeled ganciclovir, $86 \pm 3\%$ of the administered dose was recovered in the feces and $5 \pm 1\%$ 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, $91.3 \pm 5.0\%$ (n=4) of intravenously administered ganciclovir was recovered unmetabolized in the urine. Systemic clearance of intravenously administered ganciclovir was 3.52 ± 0.80 mL/min/kg (n=98) while renal clearance was 3.20 ± 0.80 mL/min/kg (n=47), accounting for $91 \pm 11\%$ of the systemic clearance (n=47). 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

	ICM 1653 (n=121)	ICM 1774 (n=225)	A
Median age (years)	38	37	
Range	24-62	22-56	
Sex	Males	116 (96%)	14
	Females	5 (4%)	1
Ethnicity	Asian	3 (3%)	7
	Black	11 (9%)	3
	Caucasian	98 (81%)	140
	Other	9 (7%)	8
Median CD ₄ Count	9.5	7.0	
Range	0 - 141	0 - 80	0
Mean (SD)			
Observation Time (days)	107.9 (43.0)	97.6 (42.5)	80.5

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,* N (%)	7 (4.8%)	29 (18.9%)	0.22 (0.10, 0.48)
CMV syndrome†	6 (4.1%)	19 (12.4%)	
CMV hepatitis	1 (0.7%)	9 (5.9%)	
CMV GI disease	0 (0.0%)	3 (2.0%)	
CMV lung disease	0 (0.0%)	4 (2.6%)	

* One or more CMV endpoints

† CMV syndrome: CMV viremia and unexplained fever, accompanied by malaise and/or neutropenia.

was 3.5 ± 0.9 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.

[See second table above]

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_{0-24h} 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_{0-24} 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 μ g/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 pediatric patients, aged 9 months to 12 years. The pharmacokinetic characteristics of ganciclovir were the same in single and multiple (q12h) intravenous doses (5 steady-state volume of distribution was 0.64 ± 0.12 L/kg, C_{max} was 7.9 ± 3.9 μ g/mL, systemic clearance was 3.1 ± 1.2 mL/min/kg, and $t_{1/2}$ was 2.4 ± 0.7 hours. The pharmacokinetics of intravenous ganciclovir in pediatric patients were similar to those observed in adults.

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

INDICATIONS AND USAGE

CYTOVENE-IV is indicated for the treatment of CMV retinitis in immunocompromised patients, including those with acquired immunodeficiency syndrome. 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 recipient individuals with advanced HIV infection at risk for CMV disease. CYTOVENE capsules are also indicated as an alternative to the intravenous formulation for the maintenance treatment of CMV retinitis in immunocompromised patients, including patients with AIDS, in 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 CAPSULES IN CHILDREN AND NEONATAL CMV DISEASE: THE TREATMENT OF ESTABLISHED CMV RETINITIS, NOR FOR USE IN IMMUNOCOMPROMISED INDIVIDUALS. THE SAFETY AND EFFICACY OF CYTOVENE CAPSULES IN CHILDREN AND NEONATAL CMV DISEASE, EXH. 1024, p. 0004

FOR TREATING ANY MANIFESTED DISEASE OTHER THAN MAINTENANCE OF CMV RETINITIS.

Retinitis

retinitis should be made by indirect conditions in the differential diagnosis include candidiasis, toxoplasmosis, histiocytes and cotton wool spots, any of retinal appearance similar to CMV. Essential that the diagnosis of CMV be made by a hematologist familiar with the retinal conditions. The diagnosis of CMV retinitis is confirmed by culture of CMV from urine, vitreous, or aqueous humor, but a negative CMV culture does not rule out CMV retinitis.

NE-IV: In a retrospective, non-randomized analysis of 41 patients with AIDS diagnosed by ophthalmologic examination in March 1988 and April 1988, treatment with NE-IV resulted in a significant delay in first retinitis progression compared to observation (105 [71] days from diagnosis vs 35 [21] days). Patients in this series received CYTOVENE-IV 5 mg/kg bid for 14 to 21 days followed by 5 mg/kg once daily, 5 mg/kg once weekly, or 6 mg/kg once daily, 5 mg/kg once weekly.

ICM 1689: In a randomized, double-blind study conducted between February 1990, immediate treatment with NE-IV compared to delayed treatment in 42 patients with peripheral CMV retinitis; 35 of the immediate-treatment group and 22 in the delayed-treatment group were included in the analysis. Based on masked assessments, the mean [95% CI] and median progression of retinitis were 66 days [51, 84], respectively, in the immediate-treatment group and 13.5 days [11, 27] and 13.5 days [11, 27] in the delayed-treatment group.

TOVENE Capsules to CYTOVENE-IV: In a randomized, open-label, parallel group study conducted between March 1991 and November 1992, newly diagnosed CMV retinitis patients were randomized to receive CYTOVENE-IV solution or TOVENE capsules. Following the 21-day intravenous induction phase, patients with stable CMV retinitis were randomized to receive maintenance treatment with TOVENE capsules or CYTOVENE-IV solution, 5 mg/kg once daily, or 500 mg 6 times daily (3000 mg/day). The mean [95% CI] and median [95% CI] time to progression of retinitis, as assessed by fundus photographs, were 57 days [44, 73], respectively, for patients on oral TOVENE capsules and 49 days [29, 61], respectively, for patients on intravenous CYTOVENE-IV solution. The difference in time to progression between the two therapies (oral - IV) was -5 days [-22, 12].

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. 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 CD4 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.

rates among these endpoints, these studies are underpowered to rule out significant differences in these endpoints.

Figure 1 - ICM 1689

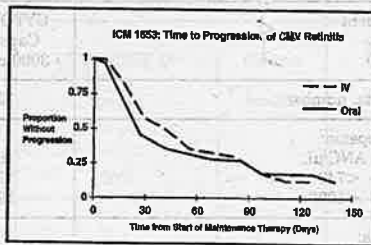


Figure 2 - ICM 1774

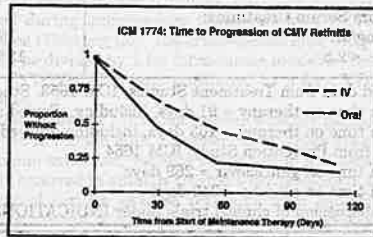
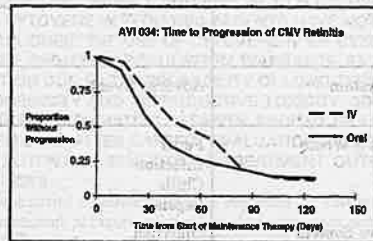


Figure 3 - AVI 034



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. 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 CD4 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)

poietic 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 post-transplant. 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 post-transplant. 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. 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.

[See fourth table on previous page]
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/ μ L or the platelet count is less than 25,000 cells/ μ L. 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 admin-

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