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# PHYSICIANS TOTAL

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# DOCKET A L A R X

Cept Oral Suspension can be administered c tube with a minimum size of 8 French m interior diameter).

uspension at that CellCept Oral Suspension be constiurmacist prior to dispensing to the patient. 
anofetil has demonstrated teratogenic effects 
bits. There are no adequate and well-conpregnant women (see WARNINGS, PREVERSE REACTIONS, and HANDLING). Care should be taken to avoid inhalation 
with skin or mucous membranes of the dry 
onstituted suspension. If such contact ocughly with soap and water; rinse eyes with

bottle several times to loosen the powder. L of water in a graduated cylinder.

ately half the total amount of water for cons bottle and shake the closed bottle well for

inder of water and shake the closed bottle

nild-resistant cap and push bottle adapter

ith child-resistant cap tightly. This will asr seating of the bottle adapter in the bottle tant status of the cap.

tient instruction sheet and oral dispensers. d to write the date of expiration of the conon on the bottle label. (The shelf-life of the msion is 60 days.)

1 the oral suspension contains 200 mg/mL nofetil. Store constituted suspension at ursions permitted to 15° to 30°C (59° to a refrigerator at 2° to 8°C (36° to 46°F) is rd any unused portion 60 days after con-

ious: CellCept Intravenous is an alternato CellCept capsules, tablets and oral susended for patients unable to take oral pt Intravenous should be administered following transplantation. CellCept Intradministered for up to 14 days; patients ad to oral CellCept as soon as they can toltion.

nous must be reconstituted and diluted to a ing/mL using 5% Dextrose Injection USP. nous is incompatible with other intraveutions. Following reconstitution, CellCept be administered by slow intravenous inod of NO LESS THAN 2 HOURS by either tral vein.

LICEPT INTRAVENOUS SOLUTION R BE ADMINISTERED BY RAPID OR ENOUS INJECTION.

fusion Solution (6 mg/mL):

e exercised in the handling and preparaf CellCept Intravenous. Avoid skin contact such contact occurs, wash thoroughly with rinse eyes with plain water (see WARN-TIONS, ADVERSE REACTIONS, and ) DISPOSAL).

lous does not contain an antibacterial prere, reconstitution and dilution of the prodrmed under aseptic conditions.

tous infusion solution must be prepared in st step is a reconstitution step with 5% a, USP and the second step is a dilution rose Injection, USP. A detailed description is given below:

of CellCept Intravenous are used for pre-1 g dose, whereas three (3) vials are ich 1.5 g dose. Reconstitute the contents of injecting 14 mL of 5% Dextrose Injection,

the vial to dissolve the drug.

be avoided. These patients should also be carefully observed. No dose adjustments are needed in renal transplant patients experiencing delayed graft function postoperatively (see CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: General).

No data are available for cardiac transplant patients with severe chronic renal impairment. CellCept may be used for cardiac transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

If neutropenia develops (ANC  $<1.3\times10^3/\mu$ L), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see WARNINGS, ADVERSE REACTIONS, and PRECAUTIONS: Laboratory Tests).

HANDLING AND DISPOSAL: Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits. CellCept tablets should not be crushed and CellCept capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in CellCept capsules and CellCept Oral Suspension (before or after constitution). If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. Should a spill occur wipe up using paper towels wetted with water to remove spilled powder or suspension. Caution should be exercised in the handling and preparation of solutions of CellCept Intravenous. Avoid skin contact of the solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

### HOW SUPPLIED

CellCept (mycophenolate mofetil capsules)

250 mg

Blue-brown, two-piece hard gelatin capsules, printed in black with "CellCept 250" on the blue cap and "Roche" on the brown body. Supplied in the following presentations:

 NDC Number
 Size

 NDC 0004-0259-01
 Bottle of 100

 NDC 0004-0259-43
 Bottle of 500

Storage: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

CellCept (mycophenolate mofetil tablets)

Lavender-colored, caplet-shaped, film-coated tablets printed in black with "CellCept 500" on one side and "Roche" on the other. Supplied in the following presentations:

 NDC Number
 Size

 NDC 0004-0260-01
 Bottle of 100

 NDC 0004-0260-43
 Bottle of 500

Storage and Dispensing Information: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in light-resistant containers, such as the manufacturer's original containers.

CellCept Oral Suspension (mycophenolate mofetil for oral suspension)

Supplied as a white to off-white powder blend for constitution to a white to off-white mixed-fruit flavor suspension. Supplied in the following presentation:

NDC Number Size NDC 0004-0261-29 225 mL bottle with bottle adapter

and 2 oral dispensers

Storage: Store dry powder at 25°C (77°F); excursions permitted to 15° to 30°C (50° to 86°F). Store constituted suspension at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) for up to 60 days. Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable. Do not freeze.

CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)

Supplied in a 20 mL, sterile vial containing the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt in cartons of 4 vials:

NDC Number

NDC 0004-0298-09

Storage: Tall 01 III BANDING YES ROUGHS VI-SVENTO

Store powder and reconstituted/infusion solutions at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). CAUTION: Federal (USA) law prohibits dispensing with-

out a prescription.

CellCent capsules and tablets manufactured by Syntay

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 INTERIORS

### 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 consules, respectively.

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-hydroxyl-(hydroxymethyl)lethoxy]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\_s for ganciclovir are 2.2 and 9.4.

dosage form, is a white to off-white lyophilized powder with a molecular formula of  $C_3H_{12}N_6NaO_4$ , and a molecular weight of 277.22. The chemical name for ganciclovir sodium is 9-[[2-bydroxy-1-chydroxymethyl) 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. 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 ganciclosis

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 GAN-CICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR CY-TOVENE-IV AND SHOULD BE CONSIDERED FOR CY-TOVENE CAPSULES. FOR DOSING INSTRUCTIONS IN PA-TIENTS 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<sub>0-24</sub> of 15.9 ± 4.2 (mean ± SD) and 15.4  $\pm$  4.3 µg·hr/mL and C<sub>max</sub> of 1.02  $\pm$  0.24 and  $1.18 \pm 0.36 \, \mu \text{g/mL}$ , 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  $26.8 \pm 6.1 \, \mu g \cdot hr/mL (n=16)$  and  $C_{max}$  ranged between  $8.27 \pm$ 

1.02 (n=16) and  $9.0 \pm 1.4 \mu g/mL (n=16)$ .

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 ± 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)

Distribution: The steady-state volume of distribution of ganciclovir after intravenous administration was 0.74  $\pm$ 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  $\pm$  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

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

or of California in the in	ICM 1653 (n=121)	ICM 1774 (n=225)	A (1
Median age (years)		37 22–56	in three days income tooks
Males	116 (96%)	222 (99%)	14
Females	5 (4%)	3 (1%)	10
Asian	3 (3%)	5 (2%)	rium ma 7
Ethnicity Black Caucasian	11 (9%)	9 (4%)	3
	98 (81%)	186 (83%)	140
Other	9 (7%)	25 (11%)	8
	9.5 0 - 141	7.0 0 – 80	0
ys) The Old The Co	107.9 (43.0)	97.6 (42.5)	80.9
	Males Females Asian Black Caucasian Other	(n=121)  38 24-62  Males  116 (96%)  Females  5 (4%)  Asian  3 (3%)  Black  11 (9%)  Caucasian  98 (81%)  Other  9.5 0-141	(n=121)     (n=225)       38 24-62     37 22-56       Males     116 (96%)     222 (99%)       Females     5 (4%)     3 (1%)       Asian     3 (3%)     5 (2%)       Black     11 (9%)     9 (4%)       Caucasian     98 (81%)     186 (83%)       Other     9 (7%)     25 (11%)       9.5 7.0 0 - 141     0 - 80

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

CMV Disease at 6 months

DOMESTICAL STREET	Ganciclovir (n=150)	Placebo (n=154)	Relative Risk (
CMV Disease,* N (%)	7 (4.8%)	29 (18.9%)	0.22 (0.10, 0
CMV syndrome†	6 (4.1%)	19 (12.4%)	Prof. No. 27 and a Contract of the Contract of
CMV hepatitis	1 (0.7%)	9 (5.9%)	market bett
CMV GI disease	0 (0.0%)	3 (2.0%)	KENCA PROTEIN
CMV lung disease	0 (0.0%)	4 (2.6%)	trais our syst

\* One or more CMV endpoints

was 3.5 ± 0.9 hours (n=98) following IV administration and  $4.8 \pm 0.9$  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 AUC0-24h 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 DOS-AGE AND ADMINISTRATION).

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both intravenous and oral administra-

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 Cmay and AUCons 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 ob-

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  $\pm$  1.6 and 7.0  $\pm$  1.6  $\mu g/mL$ , systemic clearance of 3.14  $\pm$  1.75 and 3.56  $\pm$  1.27 mL/min/kg, and to of 2.4 hours (harmonic mean) for both.

Ganciclovir phrmacokinetics were also studied ric patients, aged 9 months to 12 years. The netic characteristics of ganciclovir were the sa gle and multiple (q12h) intravenous doses (5 steady-state volume of distribution was 0.64 Cmax was 7.9 ± 3.9 µg/mL, systemic clearance w mL/min/kg, and tis was 2.4 ± 0.7 hours. The netics of intravenous ganciclovir in pediatric similar to those observed in adults.

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

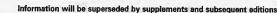
### INDICATIONS AND USAGE

CYTOVENE-IV is indicated for the treatment of nitis in immunocompromised patients, includi with acquired immunodeficiency syndron CYTOVENE-IV is also indicated for the prevent disease in transplant recipients at risk for CMV CLINICAL TRIALS).

CYTOVENE capsules are indicated for the pr CMV disease in solid organ transplant recipient dividuals with advanced HIV infection at risk ing CMV disease. CYTOVENE capsules are als as an alternative to the intravenous formulation tenance treatment of CMV retinitis in immunoco patients, including patients with AIDS, in whom stable following appropriate induction thera whom the risk of more rapid progression is bala benefit associated with avoiding daily IV infi CLINICAL TRIALS).

SAFETY AND EFFICACY OF CYTOVEN CYTOVENE HAVE NOT BEEN ESTABLISHED GENITAL OR NEONATAL CMV DISEASE; THE TREATMENT OF ESTABLISHED CMV OTHER THAN RETINITIS: NOR FOR USE IN MUNOCOMPROMISED INDIVIDUALS. THE

AND EFFICACY OF CYTOVENE CAPSULES F ALVOGEN, Exh. 1024, p. 0004



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

FOR TREATING ANY MANIFES-SEASE OTHER THAN MAINTE-OF CMV RETINITIS.

### letinitis

retinitis should be made by indirect conditions in the differential diagnolude candidiasis, toxoplasmosis, hiscars and cotton wool spots, any of retinal appearance similar to CMV. sential that the diagnosis of CMV be halmologist familiar with the retinal onditions. The diagnosis of CMV reted by culture of CMV from urine, sites, but a negative CMV culture retinitis.

NE-IV: In a retrospective, non-rananalysis of 41 patients with AIDS gnosed by ophthalmologic examina-983 and April 1988, treatment with n resulted in a significant delay in first retinitis progression compared 105 (71) days from diagnosis vs 35 is]. Patients in this series received CYTOVENE-IV 5 mg/kg bid for 14 to aintenance treatment with either 5 s per week or 6 mg/kg once daily, 5 SAGE AND ADMINISTRATION).

nized study conducted between Feber 1990,1 immediate treatment with mpared to delayed treatment in 42 1 peripheral CMV retinitis; 35 of 42 mediate-treatment group and 22 in group) were included in the analysis gression. Based on masked assessraphs, the mean [95% CI] and meprogression of retinitis were 66 days , 84), respectively, in the immediatered to 19 days [11, 27] and 13.5 days the delayed-treatment group.

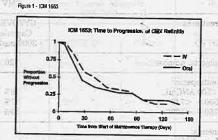
**TOVENE Capsules to CYTOVENE-IV:** 

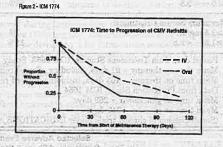
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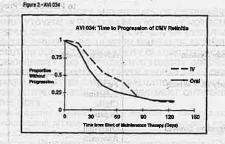
domized, open-label, parallel group n March 1991 and November 1992. I newly diagnosed CMV retinitis reion course of CYTOVENE-IV soludays followed by 5 mg/kg once daily Following the 21-day intravenous inwith stable CMV retinitis were raneeks of maintenance treatment with solution, 5 mg/kg once daily, or 500 mg 6 times daily (3000 mg/day). the mean [95% CI] and median [95% m of CMV retinitis, as assessed by dus photographs, were 57 days [44, 3], respectively, for patients on oral days [50, 73] and 49 days [29, 61], s on intravenous therapy. The differan time to progression between the erapies (oral - IV) was -5 days [-22, omparison of the proportion of paprogression over time.

e-arm, randomized; open-label, parted between June 1991 and August OS and stable CMV retinitis followo 4: months of treatment with a were randomized to receive main-CYTOVENE-IV solution; 5 mg/kg capsules, 500 mg 6 times daily, or 1000 mg tid for 20 weeks. The study 95% CI] and median [95% CI] times retinitis, as assessed by masked graphs, were 54 days [48, 60] and 42 ly, for patients on oral therapy com-3] and 54 days [41, 69], respectively, ous therapy. The difference [95% CI]

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







CYTOYENE W Salution for M

and in Societain's Rund

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 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)

at the state of	Incidence (Number CMV D	
Benchill Into	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 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 significan't 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%) placebotreated 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 AD-VERSE 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.

[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.

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 admin-

## DOCKET

### Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

### **Real-Time Litigation Alerts**



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

### **Advanced Docket Research**



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

### **Analytics At Your Fingertips**



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

### API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

### **LAW FIRMS**

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

### **FINANCIAL INSTITUTIONS**

Litigation and bankruptcy checks for companies and debtors.

### **E-DISCOVERY AND LEGAL VENDORS**

Sync your system to PACER to automate legal marketing.

