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PHYSICIANS' DESK REFERENCE®

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PHYSICIANS' DESK REFERENCE®

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Cept Oral Suspension can be administered
ic tube with a minimum size of 8 French
m interior diameter).
uspension
ed that CellCept Oral Suspension be consti-
rmacist prior to dispensing to the patient.
nofetil has demonstrated teratogenic effects
bits. There are no adequate and well-con-
pregnant women (see WARNINGS, PRE-
VERSE REACTIONS, and HANDLING
). Care should be taken to avoid inhalation
with skin or mucous membranes of the dry
onstituted suspension. If such contact oc-
ughly 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 con-
e bottle and shake the closed bottle well for
e.
inder of water and shake the closed bottle
1 minute.
ild-resistant cap and push bottle adapter
ttle.
ith child-resistant cap tightly. This will as-
r 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 con-
on on the bottle label. (The shelf-life of the
nsion is 60 days.)
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-

ous: CellCept Intravenous is an alterna-
to CellCept capsules, tablets and oral sus-
ended for patients unable to take oral
pt Intravenous should be administered
following transplantation. CellCept Intra-
dministered for up to 14 days; patients
d to oral CellCept as soon as they can tol-
tion.
ous must be reconstituted and diluted to a
mg/mL using 5% Dextrose Injection USP.
nous is incompatible with other intrave-
utions. Following reconstitution, CellCept
t be administered by slow intravenous in-
od of NO LESS THAN 2 HOURS by either
tral vein.
LLCEPT INTRAVENOUS SOLUTION
R BE ADMINISTERED BY RAPID OR
ENOUS INJECTION.
fusion Solution (6 mg/mL):
e exercised in the handling and prepara-
f CellCept Intravenous. Avoid skin contact
such contact occurs, wash thoroughly with
rinse eyes with plain water (see WARN-
TIONS, ADVERSE REACTIONS, and
) DISPOSAL).
ous does not contain an antibacterial pre-
re, reconstitution and dilution of the prod-
rmed under aseptic conditions.
ous infusion solution must be prepared in
st step is a reconstitution step with 5%
n, 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
ch 1.5 g dose. Reconstitute the contents of
injecting 14 mL of 5% Dextrose Injection,

the vial to dissolve the drug.
esulting slightly yellow solution for partic-

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 $<1.3 \times 10^3/\mu L$), 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)
500 mg
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 (59° 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:
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 without a prescription.

CellCept capsules and tablets manufactured by: Syntex

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.

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

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 ± 1.4 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 ± 0.9 hours (n=98) following IV administration and 4.8 ± 0.9 hours (n=39) following oral administration.

		ICM 1653 (n=121)	ICM 1774 (n=225)	A (n
Median age (years) Range		38 24–62	37 22–56	2
Sex	Males	116 (96%)	222 (99%)	14
	Females	5 (4%)	3 (1%)	1
Ethnicity	Asian	3 (3%)	5 (2%)	7
	Black	11 (9%)	9 (4%)	3
	Caucasian	98 (81%)	186 (83%)	14
	Other	9 (7%)	25 (11%)	8
Median CD_4 Count Range		9.5 0 – 141	7.0 0 – 80	0
Mean (SD) Observation Time (days)		107.9 (43.0)	97.6 (42.5)	80.9

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

CMV Disease at 6 months

	Ganciclovir (n=150)	Placebo (n=154)	Relative Risk (9
CMV Disease,* N (%)	7 (4.8%)	29 (18.9%)	0.22 (0.10, 0
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.

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_{0-8} 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
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
C_{max} was 7.9 ± 3.9 μg/mL, systemic clearance w
mL/min/kg, and $t_{1/2}$ 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
nitis in immunocompromised patients, includi
with acquired immunodeficiency syndro
CYTOVENE-IV is also indicated for the preve
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 al
as an alternative to the intravenous formulatio
tenance treatment of CMV retinitis in immunoc
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 inf
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 I
MUNOCOMPROMISED INDIVIDUALS. THE
AND EFFICACY OF **CYTOVENE** CAPSULES F

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

letinitis

retinitis should be made by indirect
conditions in the differential diagno-
lude candidiasis, toxoplasmosis, his-
cars 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 ret-
ed by culture of CMV from urine,
sites, but a negative CMV culture
retinitis.

NE-IV: In a retrospective, non-ran-
analysis 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).
ized study conducted between Feb-
er 1990,[1] immediate treatment with
mpared to delayed treatment in 42
l peripheral CMV retinitis; 35 of 42
mediate-treatment group and 22 in
group) were included in the analysis
gression. Based on masked assess-
raphs, the mean [95% CI] and me-
progression of retinitis were 66 days
, 84], respectively, in the immediate-
red to 19 days [11, 27] and 13.5 days
the delayed-treatment group.

TOVENE Capsules to CYTOVENE-IV:

rious page]

domized, open-label, parallel group
n March 1991 and November 1992,
l newly diagnosed CMV retinitis re-
ion course of CYTOVENE-IV solu-
days followed by 5 mg/kg once daily
Following the 21-day intravenous in-
with stable CMV retinitis were ran-
eeks 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%
n of CMV retinitis, as assessed by
lus photographs, were 57 days [44,
3], respectively, for patients on oral
2 days [50, 73] and 49 days [29, 61],
s on intravenous therapy. The differ-
ean time to progression between the
herapies (oral - IV) was -5 days [-22,
omparison of the proportion of pa-
progression over time.
e-arm, randomized, open-label, par-
ted between June 1991 and August
DS and stable CMV retinitis follow-
o 4 months of treatment with
n were randomized to receive main-
n 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.

Figure 1 - ICM 1653

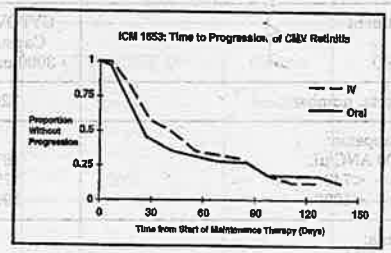


Figure 2 - ICM 1774

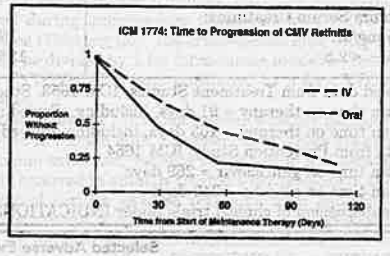
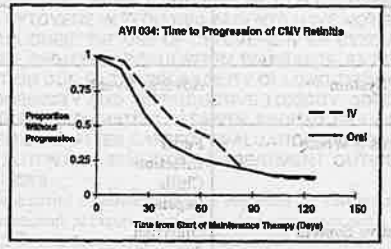


Figure 3 - AVI 034



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)

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 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.

[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/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-

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