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CYTOVENE®-IV
(ganciclovir sodium for injection)
FOR INTRAVENOUS INFUSION ONLY

5 **Rx only**

6 **WARNING**

7 **THE CLINICAL TOXICITY OF CYTOVENE-IV INCLUDES**
8 **GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL**
9 **STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND**
10 **CAUSED ASPERMATOGENESIS.**

11 **CYTOVENE-IV IS INDICATED FOR USE ONLY IN THE TREATMENT OF**
12 **CYTOMEGALOVIRUS (CMV) RETINITIS IN IMMUNOCOMPROMISED**
13 **PATIENTS AND FOR THE PREVENTION OF CMV DISEASE IN TRANSPLANT**
14 **PATIENTS AT RISK FOR CMV DISEASE (see [INDICATIONS AND USAGE](#)).**

15 **DESCRIPTION**

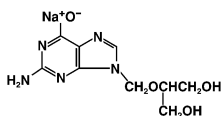
16 Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).
17 CYTOVENE-IV is the brand name for ganciclovir sodium for injection.

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

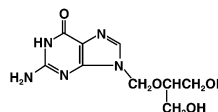
24 Ganciclovir is a white to off-white crystalline powder with a molecular formula of
25 C₉H₁₃N₅O₄ and a molecular weight of 255.23. The chemical name for ganciclovir is 9-[[2-
26 hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine. Ganciclovir is a polar hydrophilic
27 compound with a solubility of 2.6 mg/mL in water at 25°C and an n-octanol/water partition
28 coefficient of 0.022. The pK_as for ganciclovir are 2.2 and 9.4.

29 Ganciclovir, when formulated as monosodium salt in the IV dosage form, is a white to off-
30 white lyophilized powder with the molecular formula of C₉H₁₂N₅NaO₄, and a molecular
31 weight of 277.22. The chemical name for ganciclovir sodium is 9-[[2-hydroxy-1-
32 (hydroxymethyl)-ethoxy]methyl]guanine, monosodium salt. The lyophilized powder has an
33 aqueous solubility of greater than 50 mg/mL at 25°C. At physiological pH, ganciclovir
34 sodium exists as the un-ionized form with a solubility of approximately 6 mg/mL at 37°C.

35 The chemical structures of ganciclovir sodium and ganciclovir are:



ganciclovir sodium



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

39 **VIROLOGY**

40 **Mechanism of Action**

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

44 To achieve anti-CMV activity, ganciclovir is phosphorylated first to the monophosphate
45 form by a CMV-encoded (UL97 gene) protein kinase homologue, then to the di- and
46 triphosphate forms by cellular kinases. Ganciclovir triphosphate concentrations may be
47 100-fold greater in CMV-infected than in uninfected cells, indicating preferential
48 phosphorylation in infected cells. Ganciclovir triphosphate, once formed, persists for days
49 in the CMV-infected cell. Ganciclovir triphosphate is believed to inhibit viral DNA
50 synthesis by (1) competitive inhibition of viral DNA polymerases; and (2) incorporation
51 into viral DNA, resulting in eventual termination of viral DNA elongation.

52 **Antiviral Activity**

53 The median concentration of ganciclovir that inhibits CMV replication (IC_{50}) in vitro
54 (laboratory strains or clinical isolates) has ranged from 0.02 to 3.48 $\mu\text{g/mL}$. Ganciclovir
55 inhibits mammalian cell proliferation (CIC_{50}) in vitro at higher concentrations ranging from
56 30 to 725 $\mu\text{g/mL}$. Bone marrow-derived colony-forming cells are more sensitive (CIC_{50}
57 0.028 to 0.7 $\mu\text{g/mL}$). The relationship of in vitro sensitivity of CMV to ganciclovir and
58 clinical response has not been established.

59 **Clinical Antiviral Effect of CYTOVENE-IV and Ganciclovir Capsules**

60 **CYTOVENE-IV**

61 In a study of CYTOVENE-IV treatment of life- or sight-threatening CMV disease in
62 immunocompromised patients, 121 of 314 patients had CMV cultured within 7 days prior
63 to treatment and sequential posttreatment viral cultures of urine, blood, throat and/or
64 semen. As judged by conversion to culture negativity, or a greater than 100-fold decrease in
65 in vitro CMV titer, at least 83% of patients had a virologic response with a median response
66 time of 7 to 15 days.

67 Antiviral activity of CYTOVENE-IV was demonstrated in two randomized studies for the
68 prevention of CMV disease in transplant recipients (see **Table 1**).

69 **Table 1 Patients With Positive CMV Cultures**

Time	Heart Allograft* (n = 147)		Bone Marrow Allograft (n = 72)	
	CYTOVENE-IV†	Placebo	CYTOVENE-IV‡	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%)

70 * CMV seropositive or receiving graft from seropositive donor

71 † 5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for 14 days

72 ‡ 5 mg/kg bid for 7 days followed by 5 mg/kg qd until day 100 posttransplant

73 **Ganciclovir Capsules**

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

79 **Viral Resistance**

80 The current working definition of CMV resistance to ganciclovir in in vitro assays is IC₅₀
 81 >3.0 µg/mL (12.0 µM). CMV resistance to ganciclovir has been observed in individuals
 82 with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance
 83 has also been observed in patients receiving prolonged treatment for CMV retinitis with
 84 CYTOVENE-IV. In a controlled study of oral ganciclovir for prevention of AIDS-
 85 associated CMV disease, 364 individuals had one or more cultures performed after at least
 86 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last
 87 available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were
 88 found to be resistant to ganciclovir. These resistant isolates were associated with
 89 subsequent treatment failure for retinitis.

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

96 **CLINICAL PHARMACOLOGY**

97 **Pharmacokinetics**

98 **BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS**
 99 **RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE**
 100 **ARE REQUIRED FOR CYTOVENE-IV. FOR DOSING INSTRUCTIONS IN**
 101 **PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND**
 102 **ADMINISTRATION.**

103 **Absorption**

104 At the end of a 1-hour intravenous infusion of 5 mg/kg ganciclovir, total AUC ranged
105 between 22.1 ± 3.2 (n=16) and 26.8 ± 6.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (n=16) and C_{max} ranged between
106 8.27 ± 1.02 (n=16) and 9.0 ± 1.4 $\mu\text{g}/\text{mL}$ (n=16).

107 **Distribution**

108 The steady-state volume of distribution of ganciclovir after intravenous administration was
109 0.74 ± 0.15 L/kg (n=98). Cerebrospinal fluid concentrations obtained 0.25 to 5.67 hours
110 postdose in 3 patients who received 2.5 mg/kg ganciclovir intravenously q8h or q12h
111 ranged from 0.31 to 0.68 $\mu\text{g}/\text{mL}$ representing 24% to 70% of the respective plasma
112 concentrations. Binding to plasma proteins was 1% to 2% over ganciclovir concentrations
113 of 0.5 and 51 $\mu\text{g}/\text{mL}$.

114 **Elimination**

115 When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the
116 range of 1.6 to 5.0 mg/kg and when administered orally, it exhibits linear kinetics up to a
117 total daily dose of 4 g/day. Renal excretion of unchanged drug by glomerular filtration and
118 active tubular secretion is the major route of elimination of ganciclovir. In patients with
119 normal renal function, $91.3 \pm 5.0\%$ (n=4) of intravenously administered ganciclovir was
120 recovered unmetabolized in the urine. Systemic clearance of intravenously administered
121 ganciclovir was 3.52 ± 0.80 mL/min/kg (n=98) while renal clearance was 3.20 ± 0.80
122 mL/min/kg (n=47), accounting for $91 \pm 11\%$ of the systemic clearance (n=47). Half-life
123 was 3.5 ± 0.9 hours (n=98) following IV administration and 4.8 ± 0.9 hours (n=39)
124 following oral administration.

125 **Special Populations**

126 **Renal Impairment**

127 The pharmacokinetics following intravenous administration of CYTOVENE-IV solution
128 were evaluated in 10 immunocompromised patients with renal impairment who received
129 doses ranging from 1.25 to 5.0 mg/kg.

130 **Table 2 Pharmacokinetics of Patients with Renal Impairment**

Estimated Creatinine Clearance (mL/min)	n	Dose	Clearance (mL/min) Mean \pm SD	Half-life (hours) Mean \pm 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

131 Based on these observations, it is necessary to modify the dosage of ganciclovir in patients
132 with renal impairment (see **DOSAGE AND ADMINISTRATION**).

133 Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after intravenous
134 administration.

135 **Race/Ethnicity and Gender**

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

142 **Pediatrics**

143 Ganciclovir pharmacokinetics were studied in 27 neonates, aged 2 to 49 days. At an
144 intravenous dose of 4 mg/kg (n=14) or 6 mg/kg (n=13), the pharmacokinetic parameters
145 were, respectively, C_{max} of 5.5 ± 1.6 and 7.0 ± 1.6 $\mu\text{g/mL}$, systemic clearance of
146 3.14 ± 1.75 and 3.56 ± 1.27 mL/min/kg, and $t_{1/2}$ of 2.4 hours (harmonic mean) for both.

147 Ganciclovir pharmacokinetics were also studied in 10 pediatric patients, aged 9 months to
148 12 years. The pharmacokinetic characteristics of ganciclovir were the same after single and
149 multiple (q12h) intravenous doses (5 mg/kg). The steady-state volume of distribution was
150 0.64 ± 0.22 L/kg, C_{max} was 7.9 ± 3.9 $\mu\text{g/mL}$, systemic clearance was 4.7 ± 2.2 mL/min/kg,
151 and $t_{1/2}$ was 2.4 ± 0.7 hours. The pharmacokinetics of intravenous ganciclovir in pediatric
152 patients are similar to those observed in adults.

153 **Elderly**

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

155 **INDICATIONS AND USAGE**

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

160 SAFETY AND EFFICACY OF **CYTOVENE-IV** HAVE NOT BEEN ESTABLISHED
161 FOR CONGENITAL OR NEONATAL CMV DISEASE; NOR FOR THE TREATMENT
162 OF ESTABLISHED CMV DISEASE OTHER THAN RETINITIS; NOR FOR USE IN
163 NON-IMMUNOCOMPROMISED INDIVIDUALS.

164 **CLINICAL TRIALS**

165 **1. Treatment of CMV Retinitis**

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

173 **Studies With CYTOVENE-IV**

174 In a retrospective, non-randomized, single-center analysis of 41 patients with AIDS and
 175 CMV retinitis diagnosed by ophthalmologic examination between August 1983 and April
 176 1988, treatment with CYTOVENE-IV solution resulted in a significant delay in mean
 177 (median) time to first retinitis progression compared to untreated controls [105 (71) days
 178 from diagnosis vs 35 (29) days from diagnosis]. Patients in this series received induction
 179 treatment of CYTOVENE-IV 5 mg/kg bid for 14 to 21 days followed by maintenance
 180 treatment with either 5 mg/kg once daily, 7 days per week or 6 mg/kg once daily, 5 days per
 181 week (see **DOSAGE AND ADMINISTRATION**).

182 In a controlled, randomized study conducted between February 1989 and December 1990,¹
 183 immediate treatment with CYTOVENE-IV was compared to delayed treatment in 42
 184 patients with AIDS and peripheral CMV retinitis; 35 of 42 patients (13 in the immediate-
 185 treatment group and 22 in the delayed-treatment group) were included in the analysis of
 186 time to retinitis progression. Based on masked assessment of fundus photographs, the mean
 187 [95% CI] and median [95% CI] times to progression of retinitis were 66 days [39, 94] and
 188 50 days [40, 84], respectively, in the immediate-treatment group compared to 19 days [11,
 189 27] and 13.5 days [8, 18], respectively, in the delayed-treatment group.

190 **Studies Comparing Ganciclovir Capsules to CYTOVENE-IV**

191 **Table 3 Population Characteristics in Studies ICM 1653, ICM 1774**
 192 **and AVI 034**

		ICM 1653 (n=121)	ICM 1774 (n=225)	AVI 034 (n=159)
Median age (years)		38	37	39
Range		24-62	22-56	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		9.5	7.0	10.0
Range		0-141	0-80	0-320
Mean (SD)				
Observation Time (days)		107.9 (43.0)	97.6 (42.5)	80.9 (47.0)

193
 194 *ICM 1653*: In this randomized, open-label, parallel group trial, conducted between March
 195 1991 and November 1992, patients with AIDS and newly diagnosed CMV retinitis
 196 received a 3-week induction course of CYTOVENE-IV solution, 5 mg/kg bid for 14 days
 197 followed by 5 mg/kg once daily for 1 additional week.² Following the 21-day intravenous
 198 induction course, patients with stable CMV retinitis were randomized to receive 20 weeks
 199 of maintenance treatment with either CYTOVENE-IV solution, 5 mg/kg once daily, or
 200 ganciclovir capsules, 500 mg 6 times daily (3000 mg/day). The study showed that the
 201 mean [95% CI] and median [95% CI] times to progression of CMV retinitis, as assessed

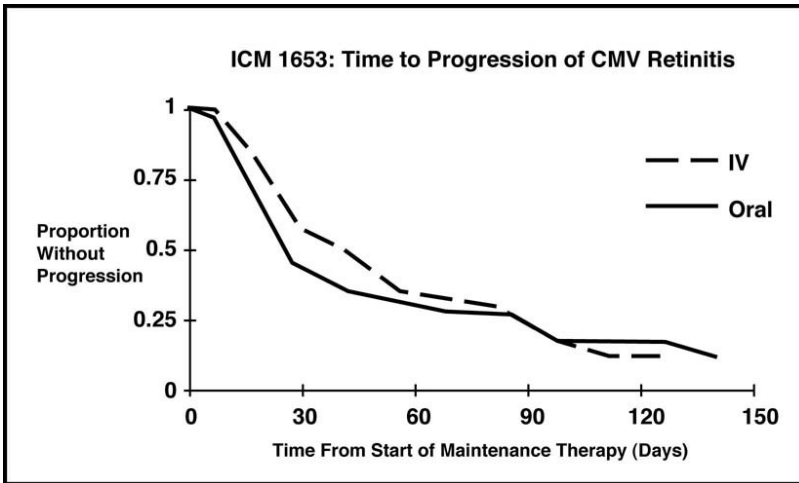
202 by masked reading of fundus photographs, were 57 days [44, 70] and 29 days [28, 43],
203 respectively, for patients on oral therapy compared to 62 days [50, 73] and 49 days [29,
204 61], respectively, for patients on intravenous therapy. The difference [95% CI] in the
205 mean time to progression between the oral and intravenous therapies (oral - IV) was -5
206 days [-22, 12]. See **Figure 1** for comparison of the proportion of patients remaining free
207 of progression over time.

208 *ICM 1774*: In this three-arm, randomized, open-label, parallel group trial, conducted
209 between June 1991 and August 1993, patients with AIDS and stable CMV retinitis
210 following from 4 weeks to 4 months of treatment with CYTOVENE-IV solution were
211 randomized to receive maintenance treatment with CYTOVENE-IV solution, 5 mg/kg
212 once daily, ganciclovir capsules, 500 mg 6 times daily, or ganciclovir capsules, 1000 mg
213 tid for 20 weeks. The study showed that the mean [95% CI] and median [95% CI] times
214 to progression of CMV retinitis, as assessed by masked reading of fundus photographs,
215 were 54 days [48, 60] and 42 days [31, 54], respectively, for patients on oral therapy
216 compared to 66 days [56, 76] and 54 days [41, 69], respectively, for patients on
217 intravenous therapy. The difference [95% CI] in the mean time to progression between
218 the oral and intravenous therapies (oral - IV) was -12 days [-24, 0]. See **Figure 2** for
219 comparison of the proportion of patients remaining free of progression over time.

220 *AVI 034*: In this randomized, open-label, parallel group trial, conducted between June
221 1991 and February 1993, patients with AIDS and newly diagnosed (81%) or previously
222 treated (19%) CMV retinitis who had tolerated 10 to 21 days of induction treatment with
223 CYTOVENE-IV, 5 mg/kg twice daily, were randomized to receive 20 weeks of
224 maintenance treatment with either ganciclovir capsules, 500 mg 6 times daily or
225 CYTOVENE-IV solution, 5 mg/kg/day.³ The mean [95% CI] and median [95% CI] times
226 to progression of CMV retinitis, as assessed by masked reading of fundus photographs,
227 were 51 days [44, 57] and 41 days [31, 45], respectively, for patients on oral therapy
228 compared to 62 days [52, 72] and 60 days [42, 83], respectively, for patients on
229 intravenous therapy. The difference [95% CI] in the mean time to progression between
230 the oral and intravenous therapies (oral - IV) was -11 days [-24, 1]. See **Figure 3** for
231 comparison of the proportion of patients remaining free of progression over time.

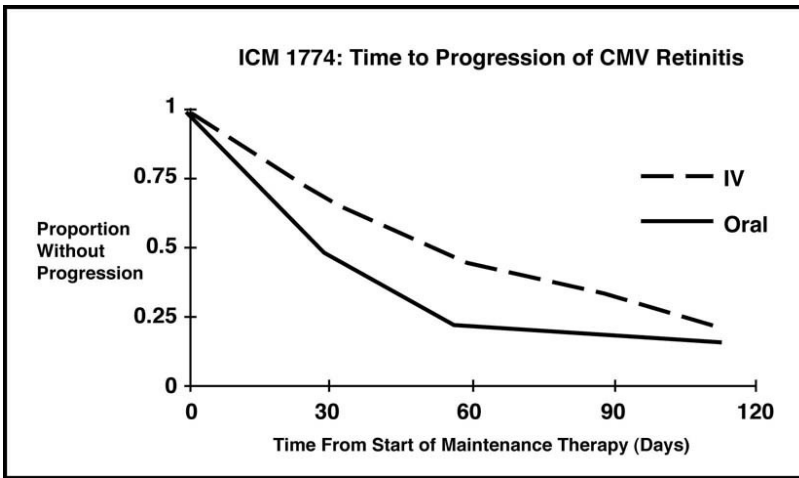
232 Comparison of other CMV retinitis outcomes between oral and IV formulations
233 (development of bilateral retinitis, progression into Zone 1, and deterioration of visual
234 acuity), while not definitive, showed no marked differences between treatment groups in
235 these studies. Because of low event rates among these endpoints, these studies are
236 underpowered to rule out significant differences in these endpoints.

237 **Figure 1 ICM 1653**



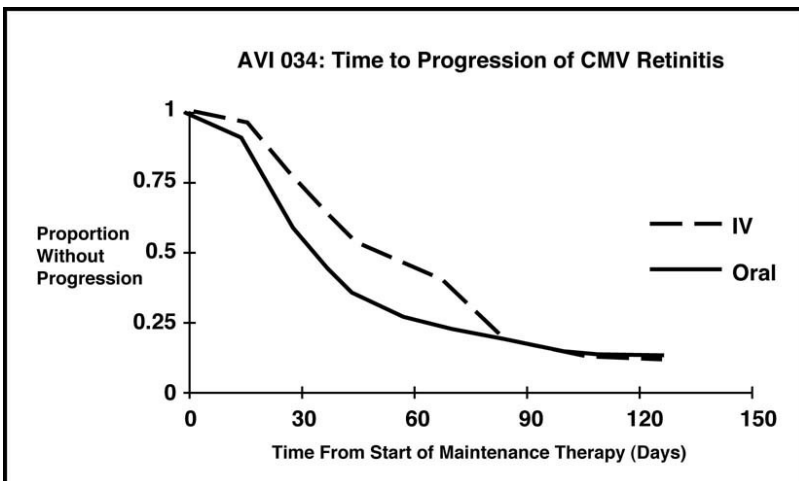
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239 **Figure 2 ICM 1774**



240

241 **Figure 3 AVI 034**



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243

244 **2. Prevention of CMV Disease in Transplant Recipients**

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

247 *ICM 1496:* In a randomized, double-blind, placebo-controlled study of 149 heart transplant
248 recipients⁴ at risk for CMV infection (CMV seropositive or a seronegative recipient of an
249 organ from a CMV seropositive donor), there was a statistically significant reduction in the
250 overall incidence of CMV disease in patients treated with CYTOVENE-IV. Immediately
251 posttransplant, patients received CYTOVENE-IV solution 5 mg/kg bid for 14 days
252 followed by 6 mg/kg qd for 5 days/week for an additional 14 days. Twelve of the 76 (16%)
253 patients treated with CYTOVENE-IV vs 31 of the 73 (43%) placebo-treated patients
254 developed CMV disease during the 120-day posttransplant observation period. No
255 significant differences in hematologic toxicities were seen between the two treatment
256 groups (refer to **Table 6** in **ADVERSE EVENTS**).

257 *ICM 1689:* In a randomized, double-blind, placebo-controlled study of 72 bone marrow
258 transplant recipients⁵ with asymptomatic CMV infection (CMV positive culture of urine,
259 throat or blood) there was a statistically significant reduction in the incidence of CMV
260 disease in patients treated with CYTOVENE-IV following successful hematopoietic
261 engraftment. Patients with virologic evidence of CMV infection received CYTOVENE-
262 IV solution 5 mg/kg bid for 7 days followed by 5 mg/kg qd through day 100
263 posttransplant. One of the 37 (3%) patients treated with CYTOVENE-IV vs 15 of the 35
264 (43%) placebo-treated patients developed CMV disease during the study. At 6 months
265 posttransplant, there continued to be a statistically significant reduction in the incidence
266 of CMV disease in patients treated with CYTOVENE-IV. Six of 37 (16%) patients treated
267 with CYTOVENE-IV vs 15 of the 35 (43%) placebo-treated patients developed disease
268 through 6 months posttransplant. The overall rate of survival was statistically
269 significantly higher in the group treated with CYTOVENE-IV, both at day 100 and day
270 180 posttransplant. Although the differences in hematologic toxicities were not
271 statistically significant, the incidence of neutropenia was higher in the group treated with
272 CYTOVENE-IV (refer to **Table 6** in **ADVERSE EVENTS**).

273 *ICM 1570:* A second, randomized, unblinded study evaluated 40 allogeneic bone marrow
274 transplant recipients at risk for CMV disease.⁶ Patients underwent bronchoscopy and
275 bronchoalveolar lavage (BAL) on day 35 posttransplant. Patients with histologic,
276 immunologic or virologic evidence of CMV infection in the lung were then randomized to
277 observation or treatment with CYTOVENE-IV solution (5 mg/kg bid for 14 days followed
278 by 5 mg/kg qd 5 days/week until day 120). Four of 20 (20%) patients treated with
279 CYTOVENE-IV and 14 of 20 (70%) control patients developed interstitial pneumonia. The
280 incidence of CMV disease was significantly lower in the group treated with CYTOVENE-
281 IV, consistent with the results observed in ICM 1689.

282 **CONTRAINDICATIONS**

283 CYTOVENE-IV is contraindicated in patients with hypersensitivity to ganciclovir or
284 acyclovir.

285 **WARNINGS**

286 **Hematologic**

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

292 CYTOVENE-IV should, therefore, be used with caution in patients with pre-existing
293 cytopenias or with a history of cytopenic reactions to other drugs, chemicals or irradiation.
294 Granulocytopenia usually occurs during the first or second week of treatment but may
295 occur at any time during treatment. Cell counts usually begin to recover within 3 to 7 days
296 of discontinuing drug. Colony-stimulating factors have been shown to increase neutrophil
297 and white blood cell counts in patients receiving CYTOVENE-IV solution for treatment of
298 CMV retinitis.

299 **Impairment of Fertility**

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

307 **Teratogenesis**

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

312 **PRECAUTIONS**

313 **General**

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

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

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

328 **Information for Patients**

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

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

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

343 **All HIV+ Patients**

344 These patients may be receiving zidovudine. Patients should be counseled that treatment
345 with both ganciclovir and zidovudine simultaneously may not be tolerated by some patients
346 and may result in severe granulocytopenia (neutropenia). Patients with AIDS may be
347 receiving didanosine. Patients should be counseled that concomitant treatment with both
348 ganciclovir and didanosine can cause didanosine serum concentrations to be significantly
349 increased.

350 **HIV+ Patients With CMV Retinitis**

351 Ganciclovir is not a cure for CMV retinitis, and immunocompromised patients may
352 continue to experience progression of retinitis during or following treatment. Patients
353 should be advised to have ophthalmologic follow-up examinations at a minimum of every
354 4 to 6 weeks while being treated with CYTOVENE-IV. Some patients will require more
355 frequent follow-up.

356 **Transplant Recipients**

357 Transplant recipients should be counseled regarding the high frequency of impaired renal
358 function in transplant recipients who received CYTOVENE-IV solution in controlled
359 clinical trials, particularly in patients receiving concomitant administration of nephrotoxic
360 agents such as cyclosporine and amphotericin B. Although the specific mechanism of this
361 toxicity, which in most cases was reversible, has not been determined, the higher rate of
362 renal impairment in patients receiving CYTOVENE-IV solution compared with those who

363 received placebo in the same trials may indicate that CYTOVENE-IV played a significant
364 role.

365 **Laboratory Testing**

366 Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving
367 CYTOVENE-IV (see **ADVERSE EVENTS**), it is recommended that complete blood
368 counts and platelet counts be performed frequently, especially in patients in whom
369 ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in
370 whom neutrophil counts are less than 1000 cells/ μ L at the beginning of treatment.
371 Increased serum creatinine levels have been observed in trials evaluating CYTOVENE-IV.
372 Patients should have serum creatinine or creatinine clearance values monitored carefully to
373 allow for dosage adjustments in renally impaired patients (see **DOSAGE AND**
374 **ADMINISTRATION**).

375 **Drug Interactions**

376 **Didanosine**

377 When the standard intravenous ganciclovir induction dose (5 mg/kg infused over 1 hour
378 every 12 hours) was coadministered with didanosine at a dose of 200 mg orally every 12
379 hours, the steady-state didanosine AUC_{0-12} increased $70 \pm 40\%$ (range: 3% to 121%, n=11)
380 and C_{max} increased $49 \pm 48\%$ (range: -28% to 125%). In a separate study, when the
381 standard intravenous ganciclovir maintenance dose (5 mg/kg infused over 1 hour every 24
382 hours) was coadministered with didanosine at a dose of 200 mg orally every 12 hours,
383 didanosine AUC_{0-12} increased $50 \pm 26\%$ (range: 22% to 110%, n=11) and C_{max} increased 36
384 $\pm 36\%$ (range: -27% to 94%) over the first didanosine dosing interval. Didanosine plasma
385 concentrations (AUC_{12-24}) were unchanged during the dosing intervals when ganciclovir
386 was not coadministered. Ganciclovir pharmacokinetics were not affected by didanosine. In
387 neither study were there significant changes in the renal clearance of either drug.

388 **Zidovudine**

389 At an oral dose of 1000 mg of ganciclovir every 8 hours, mean steady-state ganciclovir
390 AUC_{0-8} decreased $17 \pm 25\%$ (range: -52% to 23%) in the presence of zidovudine, 100 mg
391 every 4 hours (n=12). Steady-state zidovudine AUC_{0-4} increased $19 \pm 27\%$ (range: -11% to
392 74%) in the presence of ganciclovir. No drug-drug interaction studies have been conducted
393 with IV ganciclovir and zidovudine.

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

396 **Probenecid**

397 At an oral dose of 1000 mg of ganciclovir every 8 hours (n=10), ganciclovir AUC_{0-8}
398 increased $53 \pm 91\%$ (range: -14% to 299%) in the presence of probenecid, 500 mg every 6
399 hours. Renal clearance of ganciclovir decreased $22 \pm 20\%$ (range: -54% to -4%), which is
400 consistent with an interaction involving competition for renal tubular secretion. No drug-
401 drug interaction studies have been conducted with IV ganciclovir and probenecid.

402 Imipenem-cilastatin

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

406 Other Medications

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

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

421 **Carcinogenesis, Mutagenesis[†]**

422 Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day
423 (approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following
424 the recommended intravenous dose of 5 mg/kg, based on area under the plasma
425 concentration curve [AUC] comparisons). At the dose of 1000 mg/kg/day there was a
426 significant increase in the incidence of tumors of the preputial gland in males, forestomach
427 (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus,
428 mammary gland, clitoral gland and vagina) and liver in females. At the dose of 20
429 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and
430 harderian glands in males, forestomach in males and females, and liver in females. No
431 carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day
432 (estimated as 0.01x the human dose based on AUC comparison). Except for histiocytic
433 sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular
434 origin. Although the preputial and clitoral glands, forestomach and harderian glands of
435 mice do not have human counterparts, ganciclovir should be considered a potential
436 carcinogen in humans.

437 Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human
438 lymphocytes in vitro at concentrations between 50 to 500 and 250 to 2000 µg/mL,
439 respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150
440 and 500 mg/kg (IV) (2.8 to 10x human exposure based on AUC) but not 50 mg/kg
441 (exposure approximately comparable to the human based on AUC). Ganciclovir was not
442 mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 µg/mL.

443 **Impairment of Fertility[‡]**

444 Ganciclovir caused decreased mating behavior, decreased fertility, and an increased
445 incidence of embryoletality in female mice following intravenous doses of 90 mg/kg/day
446 (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg,
447 based on AUC comparisons). Ganciclovir caused decreased fertility in male mice and
448 hypospermatogenesis in mice and dogs following daily oral or intravenous administration
449 of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose
450 showing toxicity in each species ranged from 0.03 to 0.1x the AUC of the recommended
451 human intravenous dose.

452 **Pregnancy[‡]**

453 **Category C**

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

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

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

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

478 **Nursing Mothers**

479 It is not known whether ganciclovir is excreted in human milk. However, many drugs are
480 excreted in human milk and, because carcinogenic and teratogenic effects occurred in
481 animals treated with ganciclovir, the possibility of serious adverse reactions from
482 ganciclovir in nursing infants is considered likely (see **Pregnancy[‡]: Category C**).
483 Mothers should be instructed to discontinue nursing if they are receiving CYTOVENE-IV.

484 The minimum interval before nursing can safely be resumed after the last dose of
485 CYTOVENE-IV is unknown.

486 **Pediatric Use**

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

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

498 Sixteen pediatric patients (8 months to 15 years of age) with life- or sight-threatening CMV
499 infections were evaluated in an open-label, CYTOVENE-IV solution, pharmacokinetics
500 study. Adverse events reported for more than one pediatric patient were as follows:
501 hypokalemia (4/16, 25%), abnormal kidney function (3/16, 19%), sepsis (3/16, 19%),
502 thrombocytopenia (3/16, 19%), leukopenia (2/16, 13%), coagulation disorder (2/16, 13%),
503 hypertension (2/16, 13%), pneumonia (2/16, 13%) and immune system disorder (2/16,
504 13%).

505 There has been very limited clinical experience using CYTOVENE-IV for the treatment of
506 CMV retinitis in patients under the age of 12 years. Two pediatric patients (ages 9 and 5
507 years) showed improvement or stabilization of retinitis for 23 and 9 months, respectively.
508 These pediatric patients received induction treatment with 2.5 mg/kg tid followed by
509 maintenance therapy with 6 to 6.5 mg/kg once per day, 5 to 7 days per week. When retinitis
510 progressed during once-daily maintenance therapy, both pediatric patients were treated with
511 the 5 mg/kg bid regimen. Two other pediatric patients (ages 2.5 and 4 years) who received
512 similar induction regimens showed only partial or no response to treatment. Another
513 pediatric patient, a 6-year-old with T-cell dysfunction, showed stabilization of retinitis for 3
514 months while receiving continuous infusions of CYTOVENE-IV at doses of 2 to
515 5 mg/kg/24 hours. Continuous infusion treatment was discontinued due to
516 granulocytopenia.

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

526 **Geriatric Use**

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

531 Clinical studies of CYTOVENE-IV did not include sufficient numbers of subjects aged 65
532 and over to determine whether they respond differently from younger subjects. In general,
533 dose selection for an elderly patient should be cautious, reflecting the greater frequency of
534 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug
535 therapy. CYTOVENE-IV is known to be substantially excreted by the kidney, and the risk
536 of toxic reactions to this drug may be greater in patients with impaired renal function.
537 Because elderly patients are more likely to have decreased renal function, care should be
538 taken in dose selection. In addition, renal function should be monitored and dosage
539 adjustments should be made accordingly (see **Use in Patients With Renal Impairment**
540 and **DOSAGE AND ADMINISTRATION**).

541 **Use in Patients With Renal Impairment**

542 CYTOVENE-IV should be used with caution in patients with impaired renal function
543 because the half-life and plasma/serum concentrations of ganciclovir will be increased due
544 to reduced renal clearance (see **DOSAGE AND ADMINISTRATION** and **ADVERSE**
545 **EVENTS**).

546 Hemodialysis has been shown to reduce plasma levels of ganciclovir by approximately
547 50%.

548 **ADVERSE EVENTS**

549 Adverse events that occurred during clinical trials of CYTOVENE-IV solution are
550 summarized below, according to the participating study subject population.

551 **Subjects With AIDS**

552 Three controlled, randomized, phase 3 trials comparing CYTOVENE-IV and ganciclovir
553 capsules for maintenance treatment of CMV retinitis have been completed. During these
554 trials, CYTOVENE-IV or ganciclovir capsules were prematurely discontinued in 9% of
555 subjects because of adverse events. Laboratory data and adverse events reported during the
556 conduct of these controlled trials are summarized below.

557 Laboratory Data

558 **Table 4 Selected Laboratory Abnormalities in Trials for Treatment of**
 559 **CMV Retinitis**

Treatment	CMV Retinitis Treatment*	
	Ganciclovir Capsules† 3000 mg/day	CYTOVENE-IV‡ 5 mg/kg/day
Subjects, number	320	175
Neutropenia:		
<500 ANC/μL	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%

560 * Pooled data from Treatment Studies, ICM 1653, Study ICM 1774 and Study AVI 034

561 † Mean time on therapy = 91 days, including allowed reinduction treatment periods

562 ‡ Mean time on therapy = 103 days, including allowed reinduction treatment periods

563

564 (See [CLINICAL TRIALS.](#))

565 Adverse Events

566 The following table shows selected adverse events reported in 5% or more of the subjects
 567 in three controlled clinical trials during treatment with either CYTOVENE-IV solution (5
 568 mg/kg/day) or ganciclovir capsules (3000 mg/day), and in one controlled clinical trial
 569 with CYTOVENE capsules (3000 mg/day).

570 **Table 5 Selected Adverse Events Reported in \geq 5% of Subjects in**
 571 **Three Randomized Phase 3 Studies Comparing Ganciclovir**
 572 **Capsules to CYTOVENE-IV Solution for Maintenance**
 573 **Treatment of CMV Retinitis**

Body System	Adverse Event	Maintenance Treatment Studies	
		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	6%	22%
	Catheter Infection	4%	9%
	Catheter Sepsis	1%	8%

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

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

578 Retinal Detachment

579 Retinal detachment has been observed in subjects with CMV retinitis both before and after
 580 initiation of therapy with ganciclovir. Its relationship to therapy with ganciclovir is
 581 unknown. Retinal detachment occurred in 11% of patients treated with CYTOVENE-IV
 582 solution and in 8% of patients treated with ganciclovir capsules. Patients with CMV
 583 retinitis should have frequent ophthalmologic evaluations to monitor the status of their
 584 retinitis and to detect any other retinal pathology.

585 Transplant Recipients

586 There have been three controlled clinical trials of CYTOVENE-IV solution for the
 587 prevention of CMV disease in transplant recipients. Laboratory data and adverse events
 588 reported during these trials are summarized below.

589 Laboratory Data

590 The following table shows the frequency of granulocytopenia (neutropenia) and
 591 thrombocytopenia observed:

592 **Table 6 Controlled Trials – Transplant Recipients**

	CYTOVENE-IV			
	Heart Allograft*		Bone Marrow Allograft†	
	CYTOVENE-IV (n=76)	Placebo (n=73)	CYTOVENE-IV (n=57)	Control (n=55)
Neutropenia				
Minimum ANC <500/ μ L	4%	3%	12%	6%
Minimum ANC 500-1000/ μ L	3%	8%	29%	17%
TOTAL ANC \leq 1000/ μ L	7%	11%	41%	23%
Thrombocytopenia				
Platelet count <25,000/ μ L	3%	1%	32%	28%
Platelet count 25,000-50,000/ μ L	5%	3%	25%	37%
TOTAL Platelet \leq 50,000/ μ L	8%	4%	57%	65%

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

594 † Study ICM 1570 and ICM 1689. Mean duration of treatment = 45 days

595 (See [CLINICAL TRIALS.](#))

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

598 **Table 7 Controlled Trials - Transplant Recipients**

	CYTOVENE-IV					
	Heart Allograft ICM 1496		Bone Marrow Allograft ICM 1570		Bone Marrow Allograft ICM 1689	
	CYTOVENE-IV (n=76)	Placebo (n=73)	CYTOVENE-IV (n=20)	Control (n=20)	CYTOVENE-IV (n=37)	Placebo (n=35)
Maximum Serum Creatinine Levels						
Serum Creatinine \geq 2.5 mg/dL	18%	4%	20%	0%	0%	0%
Serum Creatinine \geq 1.5 - <2.5 mg/dL	58%	69%	50%	35%	43%	44%

599 In these three trials, patients receiving CYTOVENE-IV solution had elevated serum
 600 creatinine levels when compared to those receiving placebo. Most patients in these
 601 studies also received cyclosporine. The mechanism of impairment of renal function is not
 602 known. However, careful monitoring of renal function during therapy with CYTOVENE-
 603 IV solution is essential, especially for those patients receiving concomitant agents that
 604 may cause nephrotoxicity.

605 **General**

606 Other adverse events that were thought to be “probably” or “possibly” related to
607 CYTOVENE-IV solution or ganciclovir capsules in controlled clinical studies in either
608 subjects with AIDS or transplant recipients are listed below. These events all occurred in
609 at least 3 subjects.

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

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

614 *Hemic and Lymphatic System:* pancytopenia

615 *Respiratory System:* cough increased, dyspnea

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

618 *Skin and Appendages:* alopecia, dry skin

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

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

622 *Cardiovascular System:* hypertension, phlebitis, vasodilatation

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

625 *Musculoskeletal System:* arthralgia, leg cramps, myalgia, myasthenia

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

629 **Adverse Events Reported During Postmarketing Experience With**
630 **CYTOVENE-IV and Ganciclovir Capsules**

631 The following events have been identified during postapproval use of the drug. Because
632 they are reported voluntarily from a population of unknown size, estimates of frequency
633 cannot be made. These events have been chosen for inclusion due to either the
634 seriousness, frequency of reporting, the apparent causal connection or a combination of
635 these factors:

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

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

646 **OVERDOSAGE**

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

653 Irreversible pancytopenia developed in 1 adult with AIDS and CMV colitis after receiving
654 3000 mg of CYTOVENE-IV solution on each of 2 consecutive days. He experienced
655 worsening GI symptoms and acute renal failure that required short-term dialysis.
656 Pancytopenia developed and persisted until his death from a malignancy several months
657 later. Other adverse events reported following overdosage included: persistent bone marrow
658 suppression (1 adult with neutropenia and thrombocytopenia after a single dose of 6000
659 mg), reversible neutropenia or granulocytopenia (4 adults, overdoses ranging from 8 mg/kg
660 daily for 4 days to a single dose of 25 mg/kg), hepatitis (1 adult receiving 10 mg/kg daily,
661 and one 2 kg infant after a single 40 mg dose), renal toxicity (1 adult with transient
662 worsening of hematuria after a single 500 mg dose, and 1 adult with elevated creatinine
663 (5.2 mg/dL) after a single 5000 to 7000 mg dose), and seizure (1 adult with known seizure
664 disorder after 3 days of 9 mg/kg). In addition, 1 adult received 0.4 mL (instead of 0.1 mL)
665 CYTOVENE-IV solution by intravitreal injection, and experienced temporary loss of
666 vision and central retinal artery occlusion secondary to increased intraocular pressure
667 related to the injected fluid volume.

668 Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations.
669 Adequate hydration should be maintained. The use of hematopoietic growth factors should
670 be considered (see **DOSAGE AND ADMINISTRATION: Renal Impairment**).

671 **DOSAGE AND ADMINISTRATION**

672 CAUTION - DO NOT ADMINISTER CYTOVENE-IV SOLUTION BY RAPID OR
673 BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF CYTOVENE-IV MAY BE
674 INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS.

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

678 **Dosage**

679 THE RECOMMENDED DOSE FOR CYTOVENE-IV SOLUTION SHOULD NOT BE
680 EXCEEDED. THE RECOMMENDED INFUSION RATE FOR CYTOVENE-IV
681 SOLUTION SHOULD NOT BE EXCEEDED.

682 **For Treatment of CMV Retinitis in Patients With Normal Renal Function**

683 Induction Treatment

684 The recommended initial dosage for patients with normal renal function is 5 mg/kg (given
685 intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days.

686 Maintenance Treatment

687 Following induction treatment, the recommended maintenance dosage of CYTOVENE-IV
688 solution is 5 mg/kg given as a constant-rate intravenous infusion over 1 hour once daily, 7
689 days per week, or 6 mg/kg once daily, 5 days per week.

690 For patients who experience progression of CMV retinitis while receiving maintenance
691 treatment with CYTOVENE-IV, reinduction treatment is recommended.

692 **For the Prevention of CMV Disease in Transplant Recipients With Normal**
693 **Renal Function**

694 The recommended initial dosage of CYTOVENE-IV solution for patients with normal
695 renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12
696 hours for 7 to 14 days, followed by 5 mg/kg once daily, 7 days per week or 6 mg/kg once
697 daily, 5 days per week.

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

707 **Renal Impairment**

708 For patients with impairment of renal function, refer to **Table 8** for recommended doses of
709 CYTOVENE-IV solution and adjust the dosing interval as indicated:

710 **Table 8 Dosing for Patients with Renal Impairment**

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

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

712
$$(140 - \text{age [yrs]}) (\text{body wt [kg]})$$

713 Creatinine clearance for males =
$$\frac{\quad}{\quad}$$

714
$$(72) (\text{serum creatinine [mg/dL]})$$

715 Creatinine clearance for females = 0.85 x male value

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

720 **Patient Monitoring**

721 Due to the frequency of granulocytopenia, anemia and thrombocytopenia in patients
722 receiving ganciclovir (see **ADVERSE EVENTS**), it is recommended that complete blood
723 counts and platelet counts be performed frequently, especially in patients in whom
724 ganciclovir or other nucleoside analogues have previously resulted in cytopenia, or in
725 whom neutrophil counts are less than 1000 cells/ μ L at the beginning of treatment. Patients
726 should have serum creatinine or creatinine clearance values followed carefully to allow for
727 dosage adjustments in renally impaired patients (see **DOSAGE AND**
728 **ADMINISTRATION**).

729 **Reduction of Dose**

730 Dosage reductions in renally impaired patients are required for CYTOVENE-IV (see
731 **Renal Impairment**). Dosage reductions should also be considered for those with
732 neutropenia, anemia and/or thrombocytopenia (see **ADVERSE EVENTS**). Ganciclovir
733 should not be administered in patients with severe neutropenia (ANC less than 500/ μ L) or
734 severe thrombocytopenia (platelets less than 25,000/ μ L).

735 **Method of Preparation of CYTOVENE-IV Solution**

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

739 1. Reconstituted Solution:

740 a. Reconstitute lyophilized CYTOVENE-IV by injecting 10 mL of Sterile Water for
741 Injection, USP, into the vial.

742 DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING
743 PARABENS. IT IS INCOMPATIBLE WITH CYTOVENE-IV AND MAY CAUSE
744 PRECIPITATION.

745 b. Shake the vial to dissolve the drug.

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

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

751 2. Infusion Solution:

752 Based on patient weight, the appropriate volume of the reconstituted solution
753 (ganciclovir concentration 50 mg/mL) should be removed from the vial and added to an
754 acceptable infusion fluid (typically 100 mL) for delivery over the course of 1 hour.
755 Infusion concentrations greater than 10 mg/mL are not recommended. The following
756 infusion fluids have been determined to be chemically and physically compatible with
757 CYTOVENE-IV solution: 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection and
758 Lactated Ringer's Injection, USP.

759 CYTOVENE-IV, when reconstituted with sterile water for injection, further diluted with
760 0.9% sodium chloride injection, and stored refrigerated at 5°C in polyvinyl chloride
761 (PVC) bags, remains physically and chemically stable for 14 days.

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

766 **Handling and Disposal**

767 Caution should be exercised in the handling and preparation of solutions of CYTOVENE-
768 IV. Solutions of CYTOVENE-IV are alkaline (pH 11). Avoid direct contact of the skin or
769 mucous membranes with CYTOVENE-IV solutions. If such contact occurs, wash
770 thoroughly with soap and water; rinse eyes thoroughly with plain water.

771 Because ganciclovir shares some of the properties of antitumor agents (ie, carcinogenicity
772 and mutagenicity), consideration should be given to handling and disposal according to
773 guidelines issued for antineoplastic drugs. Several guidelines on this subject have been
774 published.⁷⁻⁹

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

777 **HOW SUPPLIED**

778 CYTOVENE[®]-IV (ganciclovir sodium for injection) is supplied in 10 mL sterile vials, each
779 containing ganciclovir sodium equivalent to 500 mg of ganciclovir, in cartons of 25 (NDC
780 0004-6940-03).

781 **Storage**

782 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP
783 Controlled Room Temperature].

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