



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

**Rx only**

**WARNING**

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

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

**DESCRIPTION**

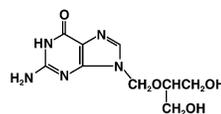
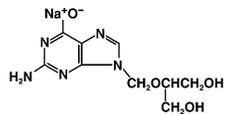
Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV). CYTOVENE-IV is the brand name for ganciclovir sodium for injection.

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](#)).

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 the molecular formula of  $C_9H_{12}N_5NaO_4$ , and a molecular weight of 277.22. The chemical name for ganciclovir sodium is 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine, monosodium salt. The lyophilized powder has an aqueous solubility of greater than 50 mg/mL at 25°C. At physiological pH, ganciclovir sodium exists as the un-ionized form with a solubility of approximately 6 mg/mL at 37°C.

The chemical structures of ganciclovir sodium and ganciclovir are:



37

38

ganciclovir sodium

ganciclovir

39

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

40

## VIROLOGY

41

### Mechanism of Action

42

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.

43

44

45

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.

46

47

48

49

50

51

52

53

### Antiviral Activity

54

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

55

56

57

58

59

60

### Clinical Antiviral Effect of CYTOVENE-IV and Ganciclovir Capsules

61

#### CYTOVENE-IV

62

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

63

64

65

66

67

68

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

69

70 **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%)

71 \* CMV seropositive or receiving graft from seropositive donor

72 † 5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for 14 days

73 ‡ 5 mg/kg bid for 7 days followed by 5 mg/kg qd until day 100 posttransplant

#### 74 Ganciclovir Capsules

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

#### 80 Viral Resistance

81 The current working definition of CMV resistance to ganciclovir in in vitro assays is IC<sub>50</sub>  
82 >3.0 µg/mL (12.0 µM). CMV resistance to ganciclovir has been observed in individuals  
83 with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance  
84 has also been observed in patients receiving prolonged treatment for CMV retinitis with  
85 CYTOVENE-IV. In a controlled study of oral ganciclovir for prevention of AIDS-  
86 associated CMV disease, 364 individuals had one or more cultures performed after at least  
87 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last  
88 available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were  
89 found to be resistant to ganciclovir. These resistant isolates were associated with  
90 subsequent treatment failure for retinitis.

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

### 97 **CLINICAL PHARMACOLOGY**

#### 98 **Pharmacokinetics**

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

104 **Absorption**

105 At the end of a 1-hour intravenous infusion of 5 mg/kg ganciclovir, total AUC ranged  
106 between  $22.1 \pm 3.2$  (n=16) and  $26.8 \pm 6.1$   $\mu\text{g}\cdot\text{hr}/\text{mL}$  (n=16) and  $C_{\text{max}}$  ranged between  
107  $8.27 \pm 1.02$  (n=16) and  $9.0 \pm 1.4$   $\mu\text{g}/\text{mL}$  (n=16).

108 **Distribution**

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

115 **Elimination**

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

126 **Special Populations**

127 **Renal Impairment**

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

131 **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	$128 \pm 63$	$4.6 \pm 1.4$
25-49	3	3-5 mg/kg	$57 \pm 8$	$4.4 \pm 0.4$
<25	3	1.25-5 mg/kg	$30 \pm 13$	$10.7 \pm 5.7$

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

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

136 **Race/Ethnicity and Gender**

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

143 **Pediatrics**

144 Ganciclovir pharmacokinetics were studied in 27 neonates, aged 2 to 49 days. At an  
145 intravenous dose of 4 mg/kg (n=14) or 6 mg/kg (n=13), the pharmacokinetic parameters  
146 were, respectively,  $C_{max}$  of  $5.5 \pm 1.6$  and  $7.0 \pm 1.6$   $\mu\text{g/mL}$ , systemic clearance of  
147  $3.14 \pm 1.75$  and  $3.56 \pm 1.27$  mL/min/kg, and  $t_{1/2}$  of 2.4 hours (harmonic mean) for both.

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

154 **Elderly**

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

156 **INDICATIONS AND USAGE**

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

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

165 **CLINICAL TRIALS**

166 **1. Treatment of CMV Retinitis**

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

174 **Studies With CYTOVENE-IV**

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

183 In a controlled, randomized study conducted between February 1989 and December 1990,<sup>1</sup>  
184 immediate treatment with CYTOVENE-IV was compared to delayed treatment in 42  
185 patients with AIDS and peripheral CMV retinitis; 35 of 42 patients (13 in the immediate-  
186 treatment group and 22 in the delayed-treatment group) were included in the analysis of  
187 time to retinitis progression. Based on masked assessment of fundus photographs, the mean  
188 [95% CI] and median [95% CI] times to progression of retinitis were 66 days [39, 94] and  
189 50 days [40, 84], respectively, in the immediate-treatment group compared to 19 days [11,  
190 27] and 13.5 days [8, 18], respectively, in the delayed-treatment group.

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

192 **Table 3 Population Characteristics in Studies ICM 1653, ICM 1774**  
193 **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 <sub>4</sub> 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)

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

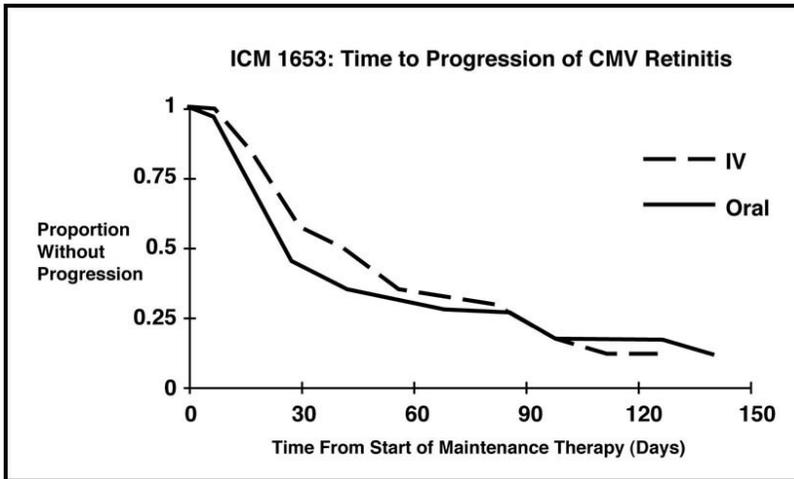
203 by masked reading of fundus photographs, were 57 days [44, 70] and 29 days [28, 43],  
204 respectively, for patients on oral therapy compared to 62 days [50, 73] and 49 days [29,  
205 61], respectively, for patients on intravenous therapy. The difference [95% CI] in the  
206 mean time to progression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

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

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

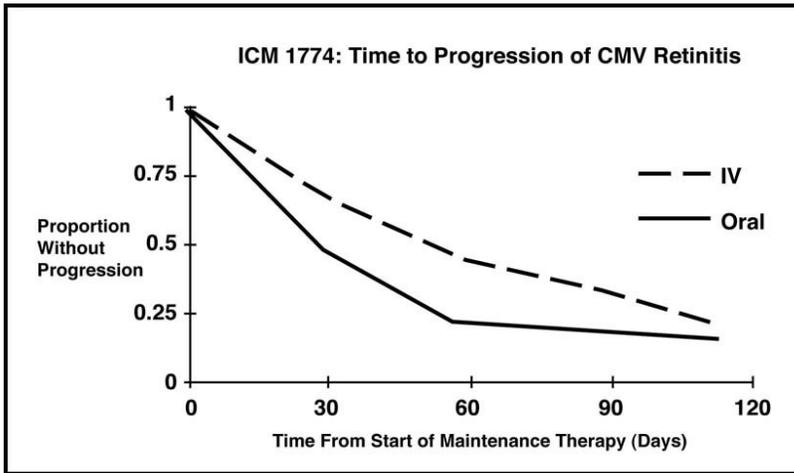
233 Comparison of other CMV retinitis outcomes between oral and IV formulations  
234 (development of bilateral retinitis, progression into Zone 1, and deterioration of visual  
235 acuity), while not definitive, showed no marked differences between treatment groups in  
236 these studies. Because of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

238 **Figure 1 ICM 1653**



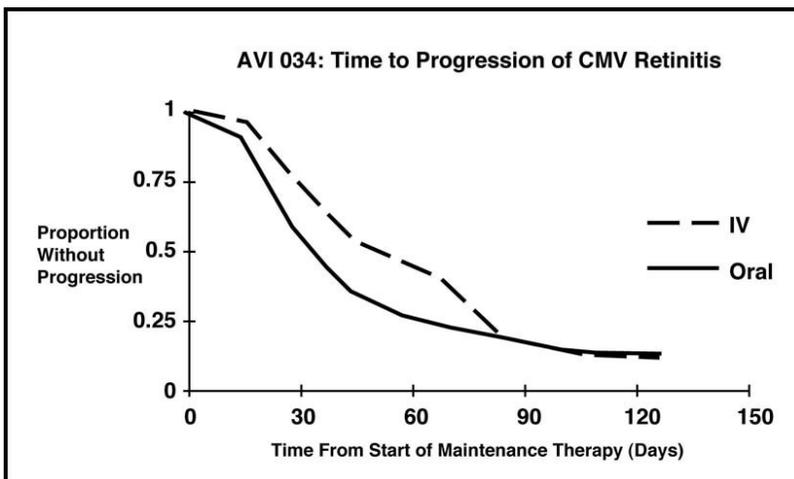
239

240 **Figure 2 ICM 1774**



241

242 **Figure 3 AVI 034**



243

244

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

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

248 *ICM 1496:* In a randomized, double-blind, placebo-controlled study of 149 heart transplant  
249 recipients<sup>4</sup> at risk for CMV infection (CMV seropositive or a seronegative recipient of an  
250 organ from a CMV seropositive donor), there was a statistically significant reduction in the  
251 overall incidence of CMV disease in patients treated with CYTOVENE-IV. Immediately  
252 posttransplant, patients received CYTOVENE-IV solution 5 mg/kg bid for 14 days  
253 followed by 6 mg/kg qd for 5 days/week for an additional 14 days. Twelve of the 76 (16%)  
254 patients treated with CYTOVENE-IV vs 31 of the 73 (43%) placebo-treated patients  
255 developed CMV disease during the 120-day posttransplant observation period. No  
256 significant differences in hematologic toxicities were seen between the two treatment  
257 groups (refer to **Table 6** in **ADVERSE EVENTS**).

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

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

283 **CONTRAINDICATIONS**

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

286 **WARNINGS**

287 **Hematologic**

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

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

300 **Impairment of Fertility**

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

308 **Teratogenesis**

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

313 **PRECAUTIONS**

314 **General**

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

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

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

### 329 **Information for Patients**

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

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

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

### 344 **All HIV+ Patients**

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

### 351 **HIV+ Patients With CMV Retinitis**

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

### 357 **Transplant Recipients**

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

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

### 366 **Laboratory Testing**

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

### 376 **Drug Interactions**

#### 377 **Didanosine**

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

#### 389 **Zidovudine**

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

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

#### 397 **Probenecid**

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

403 **Imipenem-cilastatin**

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

407 **Other Medications**

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

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

422 **Carcinogenesis, Mutagenesis<sup>†</sup>**

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

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

#### 444 **Impairment of Fertility<sup>‡</sup>**

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

#### 453 **Pregnancy<sup>‡</sup>**

##### 454 **Category C**

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

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

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

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

#### 479 **Nursing Mothers**

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

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

#### 487 **Pediatric Use**

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

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

499 Sixteen pediatric patients (8 months to 15 years of age) with life- or sight-threatening CMV  
500 infections were evaluated in an open-label, CYTOVENE-IV solution, pharmacokinetics  
501 study. Adverse events reported for more than one pediatric patient were as follows:  
502 hypokalemia (4/16, 25%), abnormal kidney function (3/16, 19%), sepsis (3/16, 19%),  
503 thrombocytopenia (3/16, 19%), leukopenia (2/16, 13%), coagulation disorder (2/16, 13%),  
504 hypertension (2/16, 13%), pneumonia (2/16, 13%) and immune system disorder (2/16,  
505 13%).

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

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

527 **Geriatric Use**

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

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

542 **Use in Patients With Renal Impairment**

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

547 Hemodialysis has been shown to reduce plasma levels of ganciclovir by approximately  
548 50%.

549 **ADVERSE EVENTS**

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

552 **Subjects With AIDS**

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

558 Laboratory Data

559 **Table 4 Selected Laboratory Abnormalities in Trials for Treatment of**  
560 **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%

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

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

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

564

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

566 Adverse Events

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

571 **Table 5 Selected Adverse Events Reported in  $\geq 5\%$  of Subjects in**  
572 **Three Randomized Phase 3 Studies Comparing Ganciclovir**  
573 **Capsules to CYTOVENE-IV Solution for Maintenance**  
574 **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%

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

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

### 579 Retinal Detachment

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

### 586 Transplant Recipients

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

590 Laboratory Data

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

593 **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/μL	4%	3%	12%	6%
Minimum ANC 500-1000/μL	3%	8%	29%	17%
TOTAL ANC ≤1000/μL	7%	11%	41%	23%
Thrombocytopenia				
Platelet count <25,000/μL	3%	1%	32%	28%
Platelet count 25,000-50,000/μL	5%	3%	25%	37%
TOTAL Platelet ≤50,000/μL	8%	4%	57%	65%

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

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

596 (See **CLINICAL TRIALS.**)

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

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

	CYTOVENE-IV					
	Heart Allograft ICM1496		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 ≥2.5 mg/dL	18%	4%	20%	0%	0%	0%
Serum Creatinine ≥1.5 - <2.5 mg/dL	58%	69%	50%	35%	43%	44%

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

606 **General**

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

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

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

615 *Hemic and Lymphatic System:* pancytopenia

616 *Respiratory System:* cough increased, dyspnea

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

619 *Skin and Appendages:* alopecia, dry skin

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

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

623 *Cardiovascular System:* hypertension, phlebitis, vasodilatation

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

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

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

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

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

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

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

## 647 **OVERDOSAGE**

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

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

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

## 672 **DOSAGE AND ADMINISTRATION**

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

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

### 679 **Dosage**

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

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

684 **Induction Treatment**

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

687 **Maintenance Treatment**

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

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

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

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

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

708 **Renal Impairment**

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

711 **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

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

$$\begin{array}{l} 713 \\ 714 \\ 715 \end{array} \quad \text{Creatinine clearance for males} = \frac{(140 - \text{age}[\text{yrs}]) (\text{body wt} [\text{kg}])}{(72) (\text{serum creatinine} [\text{mg/dL}])}$$

716 Creatinine clearance for females = 0.85 x male value

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

### 721 **Patient Monitoring**

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

### 730 **Reduction of Dose**

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

### 736 **Method of Preparation of CYTOVENE-IV Solution**

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

#### 740 1. Reconstituted Solution:

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

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

746 b. Shake the vial to dissolve the drug.

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

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

752 2. Infusion Solution:

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

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

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

767 **Handling and Disposal**

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

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

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

778 **HOW SUPPLIED**

779 CYTOVENE<sup>®</sup>-IV (ganciclovir sodium for injection) is supplied in 10 mL sterile vials, each  
780 containing ganciclovir sodium equivalent to 500 mg of ganciclovir, in cartons of 25 (NDC  
781 0004-6940-03).

782 **Storage**

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

784 **REFERENCES**

785 1. Spector SA, Weingeis T, Pollard R, et al. A randomized, controlled study of  
786 intravenous ganciclovir therapy for cytomegalovirus peripheral retinitis in patients with  
787 AIDS. *J Inf Dis.* 1993; 168:557-563. 2. Drew WL, Ives D, Lalezari JP, et al. Oral

788 ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS.  
789 *New Engl J Med.* 1995; 333:615-620. **3.** The Oral Ganciclovir European and Australian  
790 Cooperative Study Group. Intravenous vs oral ganciclovir: European/Australian  
791 comparative study of efficacy and safety in the prevention of cytomegalovirus retinitis  
792 recurrence in patients with AIDS. *AIDS.* 1995; 9:471-477. **4.** Merigan TC, Renlund DG,  
793 Keay S, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after  
794 heart transplantation. *New Engl J Med.* 1992; 326:1182-1186. **5.** Goodrich JM, Mori M,  
795 Gleaves CA, et al. Early treatment with ganciclovir to prevent cytomegalovirus disease  
796 after allogeneic bone marrow transplantation. *New Engl J Med.* 1991; 325:1601-1607.  
797 **6.** Schmidt GM, Horak DA, Niland JC, et al. The City of Hope-Stanford-Syntex CMV  
798 Study Group. A randomized, controlled trial of prophylactic ganciclovir for  
799 cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow  
800 transplants. *New Engl J Med.* 1991; 15:1005-1011. **7.** Recommendations for the Safe  
801 Handling of Cytotoxic Drugs. US Department of Health and Human Services, National  
802 Institutes of Health, Bethesda, MD, September 1992. NIH Publication No. 92-2621.  
803 **8.** American Society of Hospital Pharmacists technical assistance bulletin on handling  
804 cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990; 47:1033-1049. **9.** Controlling  
805 Occupational Exposures to Hazardous Drugs. US Department of Labor. Occupational  
806 Health and Safety Administration. OSHA Technical Manual. Section V - Chapter 3.  
807 September 22, 1995.

808

809 Distributed by:



**Pharmaceuticals**

Roche Laboratories Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

810

811 xxxxxxxx

812 xxxxxxxx

813 Revised: Month Year

814 Copyright ©1999-xxxx by Roche Laboratories Inc. All rights reserved.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Jeffrey Murray  
1/31/2006 03:04:29 PM