PRODUCT MONOGRAPH

CYTOVENE ®

ganciclovir capsules

ganciclovir sodium for injection (sterile powder)

Antiviral Agent

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CYTOVENE®

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ganciclovir sodium for injection (sterile powder)

THERAPEUTIC CLASSIFICATION

Antiviral Agent

ACTIONS

CYTOVENE (ganciclovir and ganciclovir sodium) is a synthetic nucleoside analogue of guanine which inhibits the replication of herpes viruses both *in vitro* and *in vivo*.

Intracellular ganciclovir is phosphorylated to ganciclovir monophosphate by a cellular deoxyguanosine kinase. Further phosphorylation occurs by several cellular kinases to produce ganciclovir triphosphate. It has been shown *in vitro* that the levels of ganciclovir triphosphate are as much as 100-fold greater in CMV-infected cells than non-infected cells. Thus, there is a preferential phosphorylation of ganciclovir in virus-infected cells. In virus-infected cells, ganciclovir triphosphate is metabolized slowly, with 60 to 70% remaining intracellularly 18 hours after removal of ganciclovir from the extracellular fluid. The antiviral activity of ganciclovir is the result of inhibition of viral DNA synthesis by two modes: (1) ganciclovir triphosphate competitively inhibits dGTP incorporation into DNA by DNA polymerase and (2) incorporation of ganciclovir triphosphate into viral DNA causes subsequent termination or very limited viral DNA elongation.

Ganciclovir inhibits mammalian cell proliferation *in vitro* at concentrations from 10 to 60 μg/mL, with bone marrow colony forming cells being most sensitive (IC_{50} of 10 μg/mL).

The pharmacokinetics of CYTOVENE (ganciclovir sodium for injection) have been evaluated in immunocompromised patients with serious CMV disease. In patients with normal renal

function, the plasma half-life was 2.9 $\pm$ 1.3 hours. Dose independent kinetics were demonstrated over the range of 1.6 to 5.0 mg/kg. Renal excretion through both glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir (see PRECAUTIONS for use in patients with renal impairment). At the end of a one-hour intravenous infusion of 5 mg/kg CYTOVENE (ganciclovir sodium for injection), total ganciclovir area under the serum concentration vs. time curve (AUC) ranged between 22.1±3.2 (n=16) and 26.8±6.1 μg·hr/mL (n=16) and maximum serum concentration (C_{max}) ranged between 8.27±1.02 (n=16) and 9.0±1.4 μg/mL (n=16).

The absolute bioavailability of ganciclovir following oral administration of CYTOVENE (ganciclovir capsules) under fasting conditions was approximately 5% (n=6) and following food was 6-9% (n=32). When CYTOVENE (ganciclovir capsules) were administered orally with food at a total daily dose of 3 g/day (500 mg q3h, 6 times daily and 1000 mg TID), the steady-state absorption of ganciclovir as measured by AUC over 24 hours and C_{max} were similar following both regimens with an AUC_{0-24} of 15.9±4.2 (mean±SD) and 15.4±4.3 μg·hr/mL and C_{max} of 1.02±0.24 and 1.18±0.36 μg/mL, respectively (n=16).

Food Effects

When CYTOVENE (ganciclovir capsules) were given with a meal containing 602 calories and 46.5% fat at a dose of 1000 mg every 8 hours to 20 HIV-positive subjects, the steady-state AUC increased by 22±22% (range: -6% to 68%) and there was a significant prolongation of time to peak serum concentrations (T_{max}) from 1.8±0.8 to 3.0±0.6 hours and a higher C_{max} (0.85±0.25 vs. 0.96±0.27 μg/mL) (n=20).

INDICATIONS AND CLINICAL USE

Intravenous

CYTOVENE (ganciclovir sodium for injection) is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS), iatrogenic suppression secondary to organ transplantation or those administered chemotherapy for neoplasia. CYTOVENE (ganciclovir sodium for injection) is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease.

Oral

CYTOVENE (ganciclovir capsules) are indicated for the prevention of CMV disease in solid organ transplant recipients at risk of developing CMV disease.

CYTOVENE (ganciclovir capsules) are also indicated for the maintenance treatment of CMV retinitis in immunocompromised patients, including patients with AIDS, where the retinitis is stable following at least 3 weeks of therapy with CYTOVENE (ganciclovir sodium for injection). Oral CYTOVENE (ganciclovir capsules) provides an alternative to continued therapy with CYTOVENE (ganciclovir sodium for injection) following satisfactory induction treatment in patients who have been diagnosed with CMV retinitis, and for whom the risk of more rapid progression is balanced by the benefit associated with avoiding daily intravenous infusions.

Diagnosis of CMV Retinitis

The diagnosis of CMV retinitis is primarily an ophthalmologic one and should be made by indirect ophthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis include candidiasis, toxoplasmosis, histoplasmosis, retinal scars, and cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason it is essential that the diagnosis of CMV be established by an ophthalmologist familiar with the retinal presentation of these conditions. The diagnosis of CMV retinitis may be aided by culture of CMV from

urine, blood, throat, or other sites, but a negative CMV culture does not rule out CMV retinitis.

CONTRAINDICATIONS

CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection) is contraindicated in patients who are hypersensitive to ganciclovir , valganciclovir or to any component of the product.

Due to the similarity of the chemical structure of CYTOVENE and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these drugs is possible.

WARNINGS

THE CLINICAL TOXICITY OF CYTOVENE (GANCICLOVIR CAPSULES AND GANCICLOVIR SODIUM FOR INJECTION) INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL AND *IN VITRO* STUDIES GANCICLOVIR WAS MUTAGENIC, TERATOGENIC, CARCINOGENIC AND CAUSED ASPERMATOGENISIS; THEREFORE IT SHOULD BE CONSIDERED A POTENTIAL TERATOGEN AND CARCINOGEN IN HUMANS. CYTOVENE (BOTH FORMULATIONS) IS INDICATED FOR USE ONLY IN IMMUNOCOMPROMISED PATIENTS, WHERE THE POTENTIAL BENEFIT OUTWEIGHS THE RISKS STATED HEREIN. THE SAFETY AND EFFICACY OF CYTOVENE (BOTH FORMULATIONS) HAVE NOT BEEN EVALUATED FOR CONGENITAL OR NEONATAL CMV DISEASE, NOR FOR TREATMENT OF CMV INFECTION IN NON-IMMUNOCOMPROMISED INDIVIDUALS.

Hematologic

CYTOVENE (both formulations) should not be administered if the absolute neutrophil count is less than 500 cells/μL or the platelet count is less than 25,000 cells/μL or the hemoglobin is less than 80 g/L. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with CYTOVENE (both formulations). The frequency and severity of these events vary widely in different patient populations (see PRECAUTIONS, Laboratory Testing; DOSAGE AND ADMINISTRATION, Patients with severe leukopenia, neutropenia, anemia, thrombocytopenia and/or pancytopenia; ADVERSE REACTIONS). CYTOVENE (both formulations) should therefore, be used with caution in patients with pre-existing cytopenias, or with a history of cytopenic reactions to other drugs, chemicals, or irradiation.

Neutropenia: Neutropenia typically occurs during the first or second week of induction therapy and prior to administration of a total cumulative dose of 200 mg/kg of CYTOVENE (ganciclovir sodium for injection) but may occur at any time during treatment with either formulation. Evidence of recovery of cell counts usually occurs within 3 to 7 days after discontinuing the drug. Colony stimulating factors have been shown to increase neutrophil and white blood cell counts in patients receiving CYTOVENE (ganciclovir sodium for injection) for treatment of CMV retinitis [12, 17].

Thrombocytopenia: Thrombocytopenia (platelet count of less than 50, 000 cells/μL) was observed in patients treated with CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection). Immunodeficient patients without AIDS were more likely to develop lowered platelet counts than those with AIDS. Patients with initial platelet counts less than 100, 000 cells/μL were also at increased risk of this toxicity of CYTOVENE (both formulations).

Pregnancy and Reproduction

Animal data indicate that administration of ganciclovir caused inhibition of spermatogenesis and subsequent infertility, which were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS, Mutagenesis/Carcinogenesis). Although clinical data have not yet been

obtained regarding this effect, it is considered probable that CYTOVENE (both formulations) at the recommended doses may cause temporary or permanent inhibition of spermatogenesis in humans. Animal data also indicate that suppression of fertility in females may occur.

Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment with CYTOVENE (both formulations). Similarly men should be advised to practice barrier contraception during and for at least 90 days following treatment with CYTOVENE (see PRECAUTIONS, Mutagenesis/Carcinogenesis).

CYTOVENE (both formulations) is considered to be a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see HANDLING AND DISPOSAL).
Female mice exhibited decreased fertility, decreased mating behaviour, and increased embryolethality after daily intravenous doses of 90 mg/kg (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons).

In male mice, fertility was decreased after daily intravenous doses of ≥ 2 mg/kg and daily oral doses of ≥ 10 mg/kg. These effects were reversible after daily intravenous doses of 2 mg/kg and daily oral doses of 10 mg/kg, but were irreversible or incompletely reversible after daily intravenous doses of 10 mg/kg and daily oral doses of 100 or 1000 mg/kg. Ganciclovir has also caused hypospermatogenesis in rats after daily oral doses of ≥ 100 mg/kg and in dogs after daily intravenous and oral doses of ≥ 0.4 mg/kg and 0.2 mg/kg, respectively.

Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate,

anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

Daily intravenous doses of 90 mg/kg ganciclovir administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach. The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Data obtained using an *ex vivo* human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion.

The safety of CYTOVENE for use in human pregnancy has not been established. The use of CYTOVENE should be avoided in pregnant woman unless the benefit to the mother outweighs the potential risk to the fetus.

Breastfeeding Mothers

It is not known if ganciclovir is excreted in human milk. Since many drugs are, and, because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely. CYTOVENE (both formulations) should not be given to breastfeeding mothers. Mothers should be instructed to discontinue the drug or discontinue nursing if they are receiving CYTOVENE (both formulations).

PRECAUTIONS

General

In clinical studies with CYTOVENE (ganciclovir sodium for injection), the maximum single dose studied has been 6 mg/kg infused intravenously over one hour. It is likely that larger doses, or more rapid infusions, could result in increased toxicity.

Administration of CYTOVENE (ganciclovir sodium for injection) should be accompanied by adequate hydration. Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED. Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION, Renal Impairment).

For patients on hemodialysis (CrCl < 10 mL/min) it is recommended that intravenous ganciclovir be used rather than oral ganciclovir (see DOSAGE AND ADMINISTRATION, Renal Impairment).

Hemodialysis reduces plasma concentrations of ganciclovir by approximately 50% after both i.v. and oral administration (See DOSAGE AND ADMINISTRATION, Hemodialysis).

Solutions of ganciclovir have a high pH (approximately 11) and may cause phlebitis and/or pain at the site of intravenous infusion. Therefore, care must be taken to infuse ganciclovir solutions only into veins with adequate blood flow to afford rapid dilution and distribution.

Information for Patients

All patients should be informed that the major toxicities of ganciclovir include granulocytopenia (neutropenia), anemia, and thrombocytopenia and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized.

Patients should be instructed to take CYTOVENE (ganciclovir capsules) with food to maximize bioavailability.

Convulsions, sedation, dizziness, ataxia, confusion and/or coma may occur in patients taking CYTOVENE. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

Patients should be informed that convulsions have been reported in patients taking imipenem-cilastatin and ganciclovir. CYTOVENE should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see PRECAUTIONS, Drug Interactions).

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause infertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Because of the potential for serious adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection). Women of childbearing potential should be advised to use effective contraception during treatment with CYTOVENE (both formulations). Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with CYTOVENE (both formulations).

Patients should be advised that ganciclovir causes tumors in animals. Although there is no information from human studies, CYTOVENE (both formulations) should be considered a potential carcinogen.

Patients With AIDS and CMV Retinitis: CYTOVENE (both formulations) is not a cure for CMV retinitis, and immunocompromised patients may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic

followup examinations at a minimum of every 4 to 6 weeks while being treated with CYTOVENE (both formulations). Some patients will require more frequent followup. Patients with AIDS may be receiving zidovudine (ZDV; AZT); patients should be counselled that as Zidovudine and CYTOVENE each have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy at full dosage (see PRECAUTIONS, Drug Interactions). Patients with AIDS may be receiving didanosine (ddI); patients should be counselled that concomitant treatment with both ganciclovir and didanosine can cause didanosine levels to be significantly increased.

Transplant Recipients: Transplant recipients should be counseled regarding the high frequency of impaired renal function in transplant recipients who received CYTOVENE (ganciclovir sodium for injection) in controlled clinical trials, particularly in patients receiving concomitant administration of nephrotoxic agents such as cyclosporine and amphotericin B. Although the specific mechanism of this toxicity, which in most cases was reversible, has not been determined, the higher rate of renal impairment in patients receiving CYTOVENE (ganciclovir sodium for injection) compared with those who received placebo in the same trials may indicate that CYTOVENE (ganciclovir sodium for injection) played a significant role.

Concomitant use of other drugs that are known to be myelosuppressive or associated with renal impairment with CYTOVENE may result in added toxicity.

Drug Interactions

Drug interactions with ganciclovir

Binding of ganciclovir to plasma proteins is only about 1% - 2%, and drug interactions involving binding site displacement are not anticipated.

Probenecid

At a dose of 1000 mg of CYTOVENE (ganciclovir capsules) every 8 hours, ganciclovir serum concentrations increased 45% in the presence of probenecid, 500 mg every 6 hours. Renal clearance of ganciclovir decreased 22%,which is consistent with an interaction involving competition for renal tubular secretion. Patients taking probenecid and CYTOVENE should be closely monitored for ganciclovir toxicity.

Zidovudine

At a dose of 1000 mg of CYTOVENE (ganciclovir capsules) every 8 hours, there was a trend for decreased ganciclovir AUC in the presence of zidovudine, 100 mg every 4 hours (18%), but the decrease was not statistically significant. There was a statistically significant increase in AUC for zidovudine (15%) in the presence of ganciclovir.

Since both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, many patients will not tolerate combination therapy with these two drugs at full dosage strength. However, studies with CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection) for the treatment of CMV retinitis in AIDS showed no difference in the rate of severe neutropenia (ANC $< 0.5 \times 10^9$ cells/L) or of severe anemia (hemoglobin < 8.0 g/dL), with or without concomitant zidovudine.

Didanosine

At an oral dose of 1000 mg of CYTOVENE (ganciclovir capsules) every 8 hours, the steady state AUC_{0-12} for didanosine, 200 mg every 12 hours, increased approximately 80% when didanosine was administered 2 hours prior to or concurrently with administration of CYTOVENE (ganciclovir capsules). Decreased steady state AUC (23%) was observed for ganciclovir in the presence of didanosine when the drug was administered 2 hours prior to administration of CYTOVENE (ganciclovir capsules), but AUC was not affected by the presence of didanosine when the two drugs were administered simultaneously. There were no significant changes in renal clearance for either drug.

When the standard CYTOVENE (ganciclovir sodium for injection) induction dose (5 mg/kg infused over 1 hour every 12 hours) was co-administered with didanosine at a dose of 200 mg orally every 12 hours, the steady state didanosine AUC_{0-12} increased 70±40% (range, 3 to 121%, n=11) and C_{max} increased 49±48% (range, -28 to 125%). In a separate study, when the standard CYTOVENE (ganciclovir sodium for injection) maintenance dose (5 mg/kg infused over 1 hour every 24 hours) was co-administered with didanosine at a dose of 200 mg orally every 12 hours, didanosine AUC_{0-12} increased 50±26% (range, 22 to 110%, n=11) and C_{max} increased 36±36% (range, -27 to 94%) over the first didanosine dosing interval. Didanosine plasma concentrations (AUC_{12-24}) were unchanged during the dosing intervals when CYTOVENE (ganciclovir sodium for injection) was not co-administered. Ganciclovir pharmacokinetics were not affected by didanosine. In neither study were there significant changes in the renal clearance of either drug.

This increase in didanosine plasma concentration cannot be explained by competition for renal tubular secretion, as there was an increase in the percentage of didanosine dose excreted. This increase could arise from either increased bioavailability or decreased metabolism. However, given the increase in didanosine plasma concentrations in the presence of ganciclovir, patients should be closely monitored for didanosine toxicity (see PRECAUTIONS, Information for Patients, Patients with AIDS and CMV Retinitis).

Didanosine has been associated with pancreatitis. In three controlled trials, pancreatitis was reported in 2% of patients taking didanosine and CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection). The rates of pancreatitis were similar in the intravenous solution and capsule groups.

Other than laboratory abnormalities, concomitant treatment with zidovudine, didanosine, or zalcitabine did not appear to affect the type or frequency of reported adverse events, with the exception of moderately increased rates of diarrhea. Among patients taking CYTOVENE, as ganciclovir sodium for injection or ganciclovir capsules, the diarrhea rates were 51% and 49% respectively with didanosine versus 39% and 35%respectively, without didanosine.

Zalcitabine

Zalcitabine increased the AUC_{0-8} of oral ganciclovir by 13%. There were no statistically significant changes in any of the other pharmacokinetic parameters assessed. Additionally, there were no clinically relevant changes in zalcitabine pharmacokinetics in the presence of oral ganciclovir although a small increase in the elimination rate constant was observed.

Stavudine

No statistically significant pharmacokinetic interaction was observed when stavudine and oral ganciclovir were given in combination.

Trimethoprim

Trimethoprim statistically significantly decreased the renal clearance of oral ganciclovir by 16.3% and this was associated with a statistically significant decrease in the terminal elimination rate and corresponding increase in half-life by 15%. However, these changes are unlikely to be clinically significant, as AUC_{0-8} and C_{max} were unaffected. The only statistically significant change in trimethoprim pharmacokinetic parameters when co-administered with ganciclovir was an increase in C_{min}. However, this is unlikely to be of clinical significance and no dose adjustment is recommended.

Cyclosporin

There was no evidence that introduction of ganciclovir affects the pharmacokinetics of cyclosporin based on the comparison of cyclosporin trough concentrations. However, there was some evidence of increases in the maximum serum creatinine value observed following initiation of ganciclovir therapy.

Imipenem-cilastatin

Generalized convulsions have been reported in patients who received CYTOVENE (ganciclovir sodium for injection) and imipenem-cilastatin. These drugs should not be used

concomitantly unless the potential benefits outweigh the risks (see PRECAUTIONS, Information for Patients).

Mycophenolate Mofetil

Following single-dose administration to twelve stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and CYTOVENE (ganciclovir sodium for injection; 5 mg/kg). Mean (±SD) ganciclovir AUC and C_{max} were 54.3 (±19.0) μg●h/mL and 11.5 (±1.8) μg/mL, respectively after coadministration of the two drugs, compared to 51.0 (±17.0) μg●h/mL and 10.6 (±2.0) μg/mL, respectively after administration of CYTOVENE alone. The mean (±SD) AUC and C_{max} of MPA (active metabolite of mycophenolate) after coadministration were 80.9 (±21.6) μg●h/mL and 27.8 (±13.9) μg/mL, respectively compared to values of 80.3 (±16.4) μg●h/mL and 30.9 (±11.2) μg/mL, respectively after administration of mycophenolate mofetil alone. However, based on the known effects of renal impairment on the pharmacokinetics of ganciclovir and mycophenlate, it is anticipated that coadministration of these agents (which have the potential to compete for mechanisms of renal tubular secretion) will result in increases in ganciclovir concentration and MPAG (inactive metabolite of mycophenolate). In patients with renal impairment in which ganciclovir and mycophenolate are co-administered, the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Other Medications

It is possible that drugs that inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia, and germinal layers of skin and gastrointestinal mucosa, may have additive toxicity when administered concomitantly with CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection). In addition, toxicity may be enhanced when ganciclovir is coadministered with other drugs known to be associated with renal impairment. Therefore, drugs known to be myelosuppressive or associated with renal impairment such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulfamethoxazole combinations or other nucleoside analogues, or hydroxyurea,

should be considered for concomitant use with CYTOVENE (both formulations) only if the potential benefits are judged to outweigh the risks.

Allograft recipients treated with CYTOVENE (ganciclovir sodium for injection) in three controlled clinical studies also received a variety of concomitant medications, including amphotericin B, azathioprine, cyclosporine, muromonab-CD3 (OKT3), and/or prednisone. Increases in serum creatinine were observed in patients treated with CYTOVENE (ganciclovir sodium for injection) plus either cyclosporine or amphotericin B, drugs with known potential for nephrotoxicity (see ADVERSE REACTIONS). In a retrospective analysis of 93 liver allograft recipients receiving ganciclovir (5 mg/kg infused over 1 hour every 12 hours) and oral cyclosporine (at therapeutic doses), there was no evidence of an effect on cyclosporine whole blood concentrations.

Laboratory Testing

Due to the frequency of neutropenia, anemia or thrombocytopenia observed in patients receiving CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection; see ADVERSE REACTIONS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom CYTOVENE (both formulations) or other nucleoside analogs have previously resulted in leukopenia, or in whom pretreatment neutrophil counts are less than 1000 cells/μL at the beginning of treatment. In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia, it is recommended that treatment with hematopoietic growth factors and/or dose interruption be considered (see DOSAGE AND ADMINISTRATION, Patient Monitoring, Reduction of Dose).

Because dosing modifications based on creatinine clearance are required in patients with renal impairment and because of the incidence of increased serum creatinine levels observed in transplant recipients treated with CYTOVENE (both formulations), patients should have serum creatinine or creatinine clearance monitored carefully (See also sections under ADVERSE

REACTIONS, Renal adverse events and DOSAGE AND ADMINISTRATION, Patient monitoring).

Mutagenesis/Carcinogenesis

Ganciclovir caused point mutations and chromosomal damage in mammalian cells *in vitro* and *in vivo,* but did not cause point mutations in bacterial or yeast cells, dominant lethality in mice, or morphologically transformed cells *in vitro.*

In a study conducted over 18 months, ganciclovir was carcinogenic in the mouse after oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 1.4x, respectively, based on area under the plasma concentration curve [AUC] comparisons). The principally affected tissues at the dose of 1000 mg/kg/day were the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues and liver in females. At dose of 20 mg/kg/day, slightly increased tumor incidences occurred in the preputial and harderian glands in males, forestomach in males and females, and liver in females. All ganciclovir-induced tumours were of epithelial or vascular origin except for histiocytic sarcoma of the liver. No carcinogenic effect occurred at 1 mg/kg/day (estimated as 0.01x the human dose based on AUC comparison). The preputial and clitoral glands, forestomach and harderian glands of mice have no human counterpart. CYTOVENE (both formulations) should be considered a potential carcinogen in humans.

Pediatric Use

SAFETY AND EFFICACY OF CYTOVENE (BOTH FORMULATIONS) IN CHILDREN HAVE NOT BEEN ESTABLISHED. THE USE OF CYTOVENE (BOTH FORMULATIONS) IN CHILDREN WARRANTS EXTREME CAUTION DUE TO THE PROBABILITY OF LONG-TERM CARCINOGENICITY AND REPRODUCTIVE TOXICITY. ADMINISTRATION TO CHILDREN SHOULD BE UNDERTAKEN ONLY AFTER CAREFUL EVALUATION AND ONLY IF THE POTENTIAL BENEFITS OF TREATMENT OUTWEIGH THESE CONSIDERABLE RISKS.

There has been very limited clinical experience using CYTOVENE (both formulations) for the treatment of CMV retinitis in patients under the age of 12 years.

Use In The Elderly: No studies on the efficacy or safety of CYTOVENE (both formulations) specifically in elderly patients have been conducted. Since elderly individuals may have reduced renal function, CYTOVENE (both formulations) should be administered to the elderly patients with care and with special consideration of their renal status (See DOSAGE AND ADMINISTRATION, Renal Impairment).

Renal Considerations

It is possible that probenecid, as well as other drugs which inhibit renal tubular secretion or resorption, may reduce renal clearance of ganciclovir and could increase its plasma half-life.

Use In Patients With Renal Impairment: CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection) should be used with caution in patients with impaired renal function. Both the plasma half-life of ganciclovir as well as peak plasma levels are increased in patients with elevated serum creatinine levels.

Patients undergoing Hemodialysis: Hemodialysis reduces plasma concentrations of ganciclovir by approximately 50% after both i.v. and oral administration (See DOSAGE AND ADMINISTRATION, Hemodialysis).

ADVERSE REACTIONS

Adverse events that occurred during clinical trials of CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection) are summarized below, according to the participating study subject population.

Adverse events seen in studies using CYTOVENE capsules might also occur in studies using CYTOVENE sterile powder for injection, and vice versa.

SUBJECTS WITH AIDS

The safety of oral and intravenous ganciclovir in AIDS patients was studied in several clinical trials. The pooled safety information of the use of oral and intravenous ganciclovir for the treatment of CMV disease in HIV infected patients in six clinical trials is displayed below. The data is shown in comparison to the control arm (oral placebo plus intravitreal ganciclovir implant) of one of these studies. Clinical adverse events, which occurred in ≥2% of patients taking oral or intravenous ganciclovir, regardless of causal relationship or seriousness, however at a greater frequency than in the control arm, are summarized in Table 1.

Injection site reactions occurred more frequently in patients taking i.v. ganciclovir compared to oral ganciclovir.

Table 1: Percentage of Patients with Adverse Events Occurring in ≥ 2% of All Patients Receiving Oral or Intravenous Ganciclovir

Body systems Adverse events	**Intravenous Ganciclovir** N=412	**Oral Ganciclovir** N=536	**Control** N=119
Hemic and lymphatic system			
Neutropenia	25.7%	22.6%	11.8%
Anemia	19.7%	17.2%	16.8%
Thrombocytopenia	6.6%	6.9%	5.0%
Leukopenia	3.2%	3.4%	0.8%
Lymphadenopathy	2.9%	-	1.7%
Gastrointestinal system			
Diarrhea	26.5%	31.2%	24.4%
Nausea	-	24.6%	21.8%
Vomiting	-	12.9%	12.6%
Abdominal pain	9.0%	9.5%	7.6%
Flatulence	-	3.5%	1.7%
Loose stools	-	2.4%	1.7%
Dysphagia	2.7%	2.2%	1.7%
Esophageal candidiasis	2.2%	2.6%	1.7%
Body as a whole			
Pyrexia	35.9%	-	35.3%
Headache	18.7%	-	16.0%
Candida	10.4%	6.2%	4.2%
Injection site infection	8.0%	-	0.8%
Sepsis	6.1%	-	3.4%
Sepsis secondary	5.8%	-	-
Anorexia	4.9%	5.8%	-
Mycobacterium avium complex	4.9%	5.0%	4.2%
Pain	4.6%	-	2.5%
Chest pain	4.4%	-	3.4%
Malaise	-	2.6%	0.8%
Asthenia	-	2.4%	0.8%
Toxoplasmosis	-	3.5%	-
Blood culture positive	3.2%	-	1.7%
Injection site inflammation	2.2%	-	-

Body systems Adverse events	**Intravenous Ganciclovir** N=412	**Oral Ganciclovir** N=536	**Control** N=119
Central and peripheral nervous system			
Confusion	-	4.7%	2.5%
Hypoesthesia	3.2%	2.1%	1.7%
Anxiety	2.4%	-	1.7%
Skin and appendages			
Pruritus	3.2%	4.7%	2.5%
Respiratory system			
Cough	16.0%	-	15.1%
Pneumocystis carinii pneumonia	7.3%	6.3%	2.5%
Productive cough	3.6%	3.5%	2.5%
Upper respiratory tract infection	-	2.4%	0.8%
Lower respiratory tract infection	-	2.2%	1.7%
Sinus congestion	3.4%	3.7%	2.5%
Special senses			
Taste disturbance	-	2.1%	-
Metabolic and nutritional disorders			
Blood alkaline phosphatase increased	4.4%	4.5%	4.2%
Blood creatinine increased	3.2%	2.1%	1.7%
Urogenital system			
Creatinine renal clearance decreased	-	2.4%	-
Musculoskeletal system			
Arthralgia	2.4%	-	1.7%

The safety of oral ganciclovir capsules (3 grams per day) was studied in a randomized, double-blind study for the prevention of CMV disease in over 700 HIV infected patients. Adverse events, which occurred in ≥5% of patients taking oral ganciclovir in this study, regardless of causal relationship or seriousness, however at a greater frequency than in the placebo arm, are listed in Table 2.

Table 2: Percentage of patients with adverse events occurring at ≥5% of patients receiving oral ganciclovir

Body system	**Oral ganciclovir**	**Placebo**
Adverse events	N= 478	N= 234
Hemic and lymphatic system		
Leukopenia	16.5%	8.5%
Anemia	8.8%	6.8%
Lymphadenopathy	5.9%	5.1%
Gastrointestinal system		
Diarrhea	47.7%	41.9%
Vomiting	14.2%	10.7%
Dyspepsia	6.9%	6.4%
Body as a whole		
Pyrexia	34.5%	32.5%
Anorexia	18.8%	16.2%
Pain	12.8%	9.4%
Infection	7.7%	4.3%
Rigors	6.5%	4.3%
Central and peripheral nervous system		
Peripheral neuropathy	20.9%	15.4%
Insomnia	10.7%	9.4%
Anxiety	5.9%	3.8%
Skin and appendages		
Sweating increased	14.4%	11.5%
Pruritus	9.6%	8.5%
Skin infection	6.1%	3.8%
Respiratory system		
Sinusitis	17.6%	17.1%
Dyspnea	15.7%	14.1%
Rhinitis	8.6%	7.7%
Pharyngitis	5.2%	3.0%

Special senses		
Conjunctivitis	5.0%	4.3%
Metabolic and nutritional disorders		
Weight decreased	16.1%	13.7%

Retinal Detachment

Retinal detachment has been observed in subjects with CMV retinitis both before and after initiation of therapy with CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection). The relationship of retinal detachment to therapy with CYTOVENE (both formulations) is unknown. Retinal detachment occurred in 11% of patients treated with CYTOVENE (ganciclovir sodium for injection) and in 8% of patients treated with CYTOVENE (ganciclovir capsules). Patients with CMV retinitis should have frequent ophthalmologic evaluations to monitor the status of their retinitis and to detect any other retinal pathology.

Laboratory abnormalities reported from three clinical trials in HIV infected patients taking oral or intravenous ganciclovir as maintenance treatment for CMV retinitis are listed below. Three hundred twenty-six patients receiving CYTOVENE (ganciclovir capsules) and 179 patients receiving CYTOVENE (ganciclovir sodium for injection) were eligible for the laboratory abnormality analysis.

Table 3: Laboratory Data

Minimum ANC, Hemoglobin, and Platelets and Maximum Serum Creatinine Values During Treatment With CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection) In Three Controlled Clinical Trials*

	% of subjects Capsules† (3000 mg/day) (n= 326)	**% of subjects Intravenous Solution‡ 5mg/kg/day (n= 179)**
Neutropenia [n(%)] ANC/µL <500 500 to <750 750 to <1000	 18 17 19	 251426
Anemia [n(%)] Hemoglobin g/dL < 6.5 6.5 to <8.0 8.0 to <9.5	21025	51626
Thrombocytopenia Platelets/µL <25,000 25,000 to <50,000 50000-<100000	1820	3523
Serum Creatinine (SeCr) SeCr mg/dL ≥2.5 ≥1.5 to <2.5	112	214

* Data from Study ICM 1653, Study ICM 1774, and Study AVI034 pooled.
† Mean time on therapy = 103 days, including allowed reinduction treatment periods
‡ Mean time on therapy = 91 days, including allowed reinduction treatment periods

Overall, patients treated with CYTOVENE (ganciclovir sodium for injection) experienced lower minimum ANCs and hemoglobin levels, consistent with more neutropenia and anemia, compared with those who received CYTOVENE (ganciclovir capsules) ; P=0.024 for neutropenia; P=0.027 for anemia.

For the majority of subjects, maximum serum creatinine levels were less than 1.5 mg/dL and no difference was noted between the two CYTOVENE formulations for the occurrence of renal impairment. Serum creatinine elevations ≥2.5 mg/dL occurred in <2% of all subjects and no significant differences were noted in the time from the start of maintenance to the occurrence of elevations in serum creatinine values.

TRANSPLANT RECIPIENTS

Several clinical trials have investigated oral and intravenous ganciclovir for the treatment or prevention of CMV disease in transplant patients.

The safety data of a randomized, placebo controlled study of oral ganciclovir (3 gram per day) for the prevention of CMV disease in liver transplant recipients is given below. Clinical adverse events which occurred in > 5% of patients in this study, regardless of causal relationship or seriousness, but which occurred in a higher frequency in the oral ganciclovir arm compared to placebo, are summarized in Table 4.

Also summarized below are clinical adverse events, which occurred in ≥5% of patients taking i.v. ganciclovir in three pooled bone marrow studies, regardless of causal relationship or seriousness. Adverse events which occurred in a higher frequency in the placebo / observational control arm compared to the i.v. ganciclovir arm, have not been included in the Table 4 below.

Table 4: Adverse Events Occurring in ≥ 5% of Patients Taking iv and oral Ganciclovir

Body system Adverse event	**Bone marrow transplant patients** (ICM 1308, 1570 and 1689)		**Liver transplant patients** (AV 040)	
	i.v. ganciclovir (N=122)	**Placebo/ observational control** (N=120)	**Oral ganciclovir** (N=150)	**Oral placebo** (N=154)
Hemic and lymphatic system				
Anemia	-	-	21%	18%
Pancytopenia	31%	25%	-	-
Leukopenia	20%	7%	16%	12%
Leukocytosis	-	-	15%	9%
Body as a whole				
Pain	-	-	32%	31%
Headache	15%	13%	35%	27%
Back pain	-	-	30%	25%
Ascites	-	-	23%	16%
Asthenia	-	-	12%	9%
Mucous membrane disorder	14%	13%	-	-
Pyrexia	11%	8%	-	-
Rigors	7%	4%	-	-
Sepsis	7%	2%	-	-
Anorexia	7%	5%	-	-
Abdominal distension	-	-	6%	3%
Hemorrhage	-	-	7%	2%
Peritonitis	-	-	5%	2%
Face edema	5%	2%	-	-
Gastrointestinal system				
Diarrhea	24%	23%	30%	29%
Nausea	20%	19%	22%	18%
Constipation	-	-	22%	16%
Vomiting	-	-	14%	12%
Dyspepsia	8%	6%	10%	8%
Abdominal distension	8%	6%	-	-
Cholangitis	-	-	7%	5%
Metabolic and nutritional disorders				
Edema peripheral	-	-	23%	21%
Blood creatinine increased	16%	13%	-	-
Hepatic function abnormal	11%	10%	28%	26%
Blood magnesium	11%	10%	9%	7%

	i.v. ganciclovir (N=122)	**Placebo/ observational control** (N=120)	**Oral ganciclovir** (N=150)	**Oral placebo** (N=154)
decreased				
Hyponatremia	-	-	9%	7%
Hypocalcemia	9%	8%	-	-
Hypokalemia	9%	8%	-	-
Hypoproteinemia	-	-	5%	3%
Diabetes mellitus	-	-	8%	3%
Central and peripheral nervous system				
Tremor	8%	7%	23%	14%
Confusion	5%	3%	9%	4%
Paresthesia	-	-	11%	10%
Depression	-	-	10%	7%
Anxiety	-	-	8%	8%
Dizziness	-	-	6%	4%
Skin and appendages				
Dermatitis exfoliative	10%	9%	-	-
Respiratory system				
Pleural effusion	-	-	18%	16%
Upper respiratory tract infection	-	-	10%	5%
Rhinitis	9%	5%	-	-
Dyspnea	6%	4%	13%	10%
Cardiovascular system				
Tachycardia	16%	15%	5%	3%
Hypotension	11%	7%	-	-
Vasodilation	-	-	6%	3%
Urogenital system				
Renal impairment	-	-	17%	12%
Hematuria present	16%	13%	-	-
Renal failure acute	-	-	10%	5%
Renal failure	-	-	8%	3%
Special senses				
Amblyopia	-	-	7%	3%
Eye hemorrhage	5%	3%	-	-
Hepatic system				
Cholestatic jaundice	-	-	12%	10%
Musculoskeletal system				

	i.v. ganciclovir (N=122)	**Placebo/ observational control** (N=120)	**Oral ganciclovir** (N=150)	**Oral placebo** (N=154)
Myalgia	5%	3%	-	-

Clinical adverse events, which occurred in ≥5% of patients taking i.v. ganciclovir in a placebo controlled heart transplant study (ICM 1496), regardless of causal relationship or seriousness, but which occurred in a higher frequency in the i.v. ganciclovir arm (N=76) compared to the placebo arm (N=73), are listed below.

Body as a whole: headache (18%), infection (18%)
Metabolic and nutritional disorders: edema (9%)
Central and peripheral nervous system: confusion (5%), peripheral neuropathy (7%)
Respiratory system: pleural effusion (5%)
Cardiovascular system: hypertension (20%)
Urogenital system: renal impairment (14%), renal failure (12%)

Laboratory data from three controlled clinical trials of CYTOVENE (ganciclovir sodium for injection) and one controlled clinical trial of CYTOVENE (ganciclovir capsules) for the prevention of CMV disease in transplant recipients are summarized below.

Table 5: Laboratory Data

Neutropenia and Thrombocytopenia in Trials for the Prevention of CMV Disease in Transplant Recipients

	CYTOVENE intravenous*				CYTOVENE oral**	
	Heart Allograft§		Bone Marrow Allograft†		Liver Allograft‡	
	CYTOVENE	Placebo	CYTOVENE	Placebo	CYTOVENE	Placebo
Subjects (number)	n=76	n=73	n=57	n=55	n=150	n=154
Neutropenia (ANC/μL)						
<500	4%	3%	12%	6%	3%	1%
500 - 1000	3%	8%	29%	17%	3%	2%
Thrombocytopenia (platelets/μL)						
<25,000	3%	1%	32%	28%	0%	3%
25,000 - 50,000	5%	3%	25%	37%	5%	3%

§ Study ICM 1496: Mean duration of treatment = 28 days
† Studies ICM 1570 and ICM 1689: Mean duration of treatment = 45 days
‡ Study GAN040: Mean duration of ganciclovir treatment = 82 days
* ganciclovir sodium for injection
** ganciclovir capsules

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

Table 6: Laboratory Data
Elevated Serum Creatinine Values in Trials for the Prevention of CMV Disease in Transplant Recipients

	CYTOVENE intravenous*						CYTOVENE oral**	
	Heart Allograft ICM 1496		Bone Marrow Allograft ICM 1570		ICM 1689		Liver Allograft GAN 040	
Maximum Serum Creatinine Levels	CYTOVENE (N=76)	Placebo (n=73)	CYTOVENE (n=20)	Control (n=20)	CYTOVENE (n=37)	Placebo (n=35)	CYTOVENE (n=150)	Placebo (n=154)
Serum Creatinine (≥ 2.5 mg/dL)	18%	4%	20%	0%	0%	0%	16%	10%
Serum Creatinine (≥1.5-<2.5 mg/dL)	58%	69%	50%	35%	43%	44%	39%	42%

* ganciclovir sodium for injection
** ganciclovir capsules

In 3 out of 4 trials, patients receiving CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection) had elevated serum creatinine levels when compared to those receiving placebo. Most patients in these studies also received cyclosporine. The mechanism of impairment of renal function is not known. However, careful monitoring of renal function during therapy with CYTOVENE (both formulations) is essential, especially for those patients receiving concomitant agents that may cause nephrotoxicity.

ADDITIONAL ADVERSE REACTIONS

Relevant adverse events, which are not listed above, as they did not fulfil the criteria for inclusion into any of the tables of previous sections are given below.

Body as a Whole: cachexia, dehydration, fatigue, injection site abscess, injection site edema, injection site hemorrhage, injection site pain, injection site thrombosis, malaise, photosensitivity reaction.

Gastrointestinal system: pancreatitis, gastrointestinal disorder, gastrointestinal hemorrhage, eructation, esophagitis, fecal incontinence, gastritis, mouth ulceration, tongue disorder.

Hemic and Lymphatic System: aplastic anemia, bone marrow depression, eosinophilia, splenomegaly.

Central and Peripheral Nervous System: hallucinations, psychotic disorder, euphoric mood, emotional disturbance, hyperkinetic syndrome, myoclonic jerks, abnormal dreams, agitation, amnesia, ataxia, coma, convulsion, dry mouth, hypertonia, libido decreased, nervousness, somnolence, thinking abnormal.

Skin and Appendages: dermatitis, acne, alopecia, dry skin, herpes simplex, urticaria.

Special Senses: retinal detachment, vision abnormal, earache, blindness, deafness, eye pain, glaucoma, tinnitis, vitreous disorder.

Metabolic and Nutritional Disorders: blood creatine phosphokinase increased, blood glucose decreased, blood lactic dehydrogenase increased.

Cardiovascular System: arrhythmia (including ventricular arrhythmia), thrombophlebitis deep, phlebitis, migraine.

Urogenital System: impotence, urinary frequency.

Musculoskeletal System: myasthenic syndrome

Infections: events related to bone marrow depression and immune system compromise such as local and systemic infections and sepsis.

Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia.

Hepatic System: hepatitis, jaundice

ADVERSE EVENTS REPORTED IN POST-MARKET SURVEILLANCE OF CYTOVENE (both formulations)

The following adverse events have been reported since the marketing introduction of CYTOVENE (both formulations), and are not listed under adverse reactions above. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either the seriousness frequency of reporting, the apparent causal connection, or a combination of these factors:

Acidosis, allergic reaction, anaphylactic reaction, arthritis, bronchospasm, cardiac arrest, cardiac conduction abnormality, cataracts, cholelithiasis, cholestasis, congenital anomaly, dry eyes, dysesthesia, dysphasia, elevated triglyceride levels, exfoliative dermatitis, extrapyramidal reaction, facial palsy, hallucinations, hemolytic anemia, hemolytic-uremic syndrome, hepatic failure, hepatitis, hypercalcemia, hyponatremia inappropriate serum ADH, infertility, intestinal ulceration, intracranial hypertension, irritability, ischemia, loss of memory, loss of sense of smell, myelopathy, peripheral oculomotor nerve paralysis, pulmonary fibrosi, renal tubular disorder, rhabdomyolysis, Stevens-Johnson syndrome, stroke, testicular hypotrophy, Toursades de Pointes, vasculitis, ventricular tachycardia.

Adverse events from post-marketing spontaneous reports with intravenous and oral ganciclovir that were reported in HIV infected or other immunocompromised patients such as transplant recipients, which are not mentioned in any section above, and for which a causal relationship can not be excluded, are: anaphylaxis, decreased fertility in males.

Adverse events that have been reported during the post-marketing period are consistent with those seen in clinical trials with ganciclovir.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms:

CYTOVENE (ganciclovir sodium for injection): Overdosage with CYTOVENE (ganciclovir sodium for injection) has been reported in both adults and children below 2 years of age. In two cases of overdosage in adults, no adverse events were reported after patients received either one dose of 3500 mg or 7 doses of 11 mg/kg over a 3 day period. Similarly, the following overdoses in pediatric patients did not result in adverse events: a single dose of 500 mg (72.5 mg/kg) followed by 48 hours of peritoneal dialysis (4 month-old), single dose of approximately 60 mg/kg followed by exchange transfusion (18 month-old), two doses of 500 mg instead of 31 mg (21 month-old).

Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during post-marketing experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:

Hematological toxicity: pancytopenia, bone marrow depression, medullary aplasia, leukopenia, neutropenia, granulocytopenia
Hepatotoxicity: hepatitis, liver function disorder
Renal Toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine
Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting
Neurotoxicity: generalized tremor, convulsion

In addition, one adult received 0.4 mL (instead of 0.1 mL) CYTOVENE (ganciclovir sodium for injection) by intravitreal injection, and experienced temporary loss of vision and central retinal artery occlusion secondary to increased intraocular pressure related to the injected fluid volume.

CYTOVENE (ganciclovir capsules): There have been no reports of overdosage with orally administered CYTOVENE (ganciclovir capsules). Doses as high as 6000 mg/day, given either as 1000 mg 6 times daily or as 2000 mg TID, did not result in overt toxicity other than transient neutropenia. Daily doses of more than 6000 mg have not been studied.

Overdose Experience with Valganciclovir

One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patients degree of renal impairment (decreased creatinine clearance).

Treatment:

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered.

DOSAGE AND ADMINISTRATION

CAUTION - DO NOT ADMINISTER CYTOVENE (GANCICLOVIR SODIUM FOR INJECTION) BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF GANCICLOVIR MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS.

CAUTION - INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MAY RESULT IN SEVERE TISSUE IRRITATION DUE TO THE HIGH PH (APPROXIMATELY 11) OF CYTOVENE (GANCICLOVIR SODIUM FOR INJECTION) SOLUTIONS.

DOSAGE

THE RECOMMENDED DOSE FOR CYTOVENE (GANCICLOVIR CAPSULES AND GANCICLOVIR SODIUM FOR INJECTION) SHOULD NOT BE EXCEEDED. THE RECOMMENDED INFUSION RATE FOR CYTOVENE (GANCICLOVIR SODIUM FOR INJECTION) SOLUTION SHOULD NOT BE EXCEEDED.

Because of individual patient variations in the clinical response of CMV disease and the sensitivity to the myelosuppressive effects of CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection), the treatment of each patient with CYTOVENE (both formulations) should be individualized on a case by case basis. Changes in dose should be based on regular clinical evaluations as well as on regular hematologic monitoring.

For Treatment of CMV Retinitis:

Induction Treatment

The recommended dose of CYTOVENE (ganciclovir sodium for injection) for patients with normal renal function is 5 mg/kg every 12 hours for 14 to 21 days, given as a constant intravenous infusion over one hour. CYTOVENE (ganciclovir capsules) should not be used for induction treatment.

Maintenance Treatment

Intravenous: Following the induction treatment, the recommended dose of CYTOVENE (ganciclovir sodium for injection) is 5 mg/kg given as an intravenous infusion over one hour once per day for seven days each week, or 6 mg/kg once per day for five days each week.

Oral: For patients with stable CMV retinitis following at least 3 weeks of treatment with CYTOVENE (ganciclovir sodium for injection), the recommended maintenance dose of CYTOVENE (ganciclovir capsules) is 1000 mg TID with food. Alternatively, the dosing regimen of 500 mg 6 times daily with food, during waking hours, may be used.

For patients who experience progression of CMV retinitis while receiving maintenance treatment with either formulation of CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection), reinduction treatment using the twice daily regimen of CYTOVENE (ganciclovir sodium for injection) is recommended.

The safety and efficacy of CYTOVENE (ganciclovir capsules) have not been established for treating any manifestation of CMV disease other than maintenance treatment of CMV retinitis.

For the Prevention of CMV Disease in Transplant Recipients:

Intravenous: The recommended initial dose for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7 to 14 days, followed by either 5 mg/kg once per day if on a seven-day weekly regimen, or 6 mg/kg once per day if on a five-day weekly regimen.

Oral: The recommended prophylactic dose of CYTOVENE (ganciclovir capsules) in patients with normal renal function is 1000 mg TID (3000 mg/day) with food.

The duration of treatment with CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection) in transplant recipients is dependent upon the duration and degree of immunosuppression. In controlled clinical trials in bone marrow allograft recipients, treatment with CYTOVENE (ganciclovir sodium for injection) was continued until day 100 to 120 post-transplantation. CMV disease occurred in several patients who discontinued treatment with CYTOVENE (ganciclovir sodium for injection) prematurely. In heart allograft recipients, the onset of newly diagnosed CMV disease occurred after treatment with CYTOVENE (ganciclovir sodium for injection) was stopped at day 28 post-transplant, suggesting that continued dosing may be necessary to prevent late occurrence of CMV disease in this patient population. In a controlled clinical trial of liver allograft recipients, treatment with CYTOVENE (ganciclovir capsules) was continued through Week 14 post-transplantation.

Patients with severe leukopenia, neutropenia, anemia, thrombocytopenia and/or pancytopenia

Severe leukopenia, neutropenia, anemia, thrombocytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with ganciclovir. Therapy should not be initiated if the absolute neutrophil count is less than 500 cells /mL or the platelet count is less than 25000/ mL or the hemoglobin is less than 80 g/L (see WARNINGS, Hematologic; PRECAUTIONS, Laboratory Testing and ADVERSE REACTIONS).

Patient Monitoring

Due to the frequency of leukopenia, granulocytopenia (neutropenia), anemia, thrombocytopenia, pancytopenia, bone marrow depression, and aplastic anemia in patients receiving ganciclovir (see ADVERSE REACTIONS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in cytopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment. Patients should have serum creatinine or creatinine clearance values followed carefully to allow for dosage adjustments in renally impaired patients (see Renal Impairment).

Reduction of Dose

Dosage reductions in renally impaired patients are required for CYTOVENE (ganciclovir sodium for injection) and for CYTOVENE (ganciclovir capsules; see Renal Impairment section). Dosage reductions should also be considered for patients with neutropenia, anemia and/or thrombocytopenia. CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection) should not be administered in patients with severe neutropenia (ANC less than 500/μL) or severe thrombocytopenia (platelets less than 25,000/μL) or severe anemia (hemoglobin less than 80 g/L).

Renal Impairment

CYTOVENE (ganciclovir sodium for injection):

For patients with impairment of renal function (see PRECAUTIONS), refer to the table below for recommended doses of CYTOVENE (ganciclovir sodium for injection), and adjust the dosing interval as indicated.

Induction and Maintenance Doses of CYTOVENE (ganciclovir sodium for injection) in Renal Impairment

Creatinine Clearance* (mL/min)	Induction Dose (mg/kg)	Dosing Interval (hours)	Maintenance Dose (mg/kg)	Dosing Interval (hours)
≥70	5.0	12	5.0	24
50 to 69	2.5	12	2.5	24
25 to 49	2.5	24	1.25	24
10 to 24	1.25	24	0.625	24
<10	1.25	3 times per week, following hemodialysis	0.625	3 times per week, following hemodialysis

Hemodialysis

Dosing for patients undergoing hemodialysis should not exceed 1.25 mg/kg three times per week, following each hemodialysis session. CYTOVENE (ganciclovir sodium for injection) should be given shortly after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50%.

CYTOVENE (ganciclovir capsules):

In patients with renal impairment, modify the dose of CYTOVENE (ganciclovir capsules) as shown below.

Maintenance Doses of CYTOVENE (ganciclovir capsules) in Renal Impairment

Creatinine Clearance* mL/min	CYTOVENE (ganciclovir capsules) Oral dose
≥ 70	1000 mg TID or 500 mg q3h (6x/day)
50 to 69	1500 mg QD or 500 mg TID
25 to 49	1000 mg QD or 500 mg BID
10 to 24	500 mg QD
<10	500 mg three times per week, following hemodialysis

* Creatinine clearance can be related to serum creatinine by the formulae below:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [years]}) \times (\text{body wt [kg]})}{(72) \times (0.011 \times \text{serum creatinine [}\mu\text{mol/L]})}$$

Creatinine clearance for females = 0.85 x male value
Creatinine Clearance in SI units (mL/S) = 0.01667 x value obtained from the above formula in traditional units (mL/min).

INTRAVENOUS ADMINISTRATION

Infusion concentrations greater than 10 mg/mL are not recommended. Do not administer CYTOVENE (ganciclovir sodium for injection) by rapid or bolus intravenous injection. It should be given by constant intravenous infusion over 1 hour.

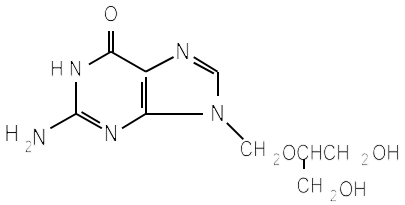
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

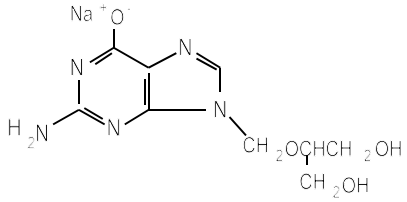
Trade Name: CYTOVENE

Proper Name: Ganciclovir and ganciclovir sodium

Chemical Name: 9-(1,3-Dihydroxy-2-propoxymethyl) guanine and mono sodium salt



Ganciclovir



Ganciclovir Sodium

Molecular Formula: $C_9H_{13}N_5O_4$ $C_9H_{13}N_5O_4 \cdot Na$

Molecular Weight: 255.23 277.21

Description: Ganciclovir is a white to off-white crystalline powder which decomposes between 225°C and 252°C with a 5°C range. It has a solubility in water of 2.6 mg/mL. Ganciclovir sodium is a white to off-white amorphous powder with a solubility in water of more than 100 mg/mL.

COMPOSITION

CYTOVENE Sterile Powder: Each 10 mL vial contains ganciclovir sodium equivalent to 500 mg of ganciclovir. The sodium content is 46 mg (2 mEq).

CYTOVENE Capsules: Each capsule contains 250 mg or 500 mg ganciclovir. The non-medicinal ingredients are: croscarmellose sodium, gelatin, indigotine, iron oxide, magnesium stearate, povidone, and titanium dioxide.

Reconstitution of Sterile Lyophilized Powder: Reconstitute by injecting sterile water for injection into the vial.

Vial Size	**Diluent to be added**	**Approx. available Volume**	**Approximate Concentration**
500 mg	10 mL	10.29 mL	50 mg/mL

Shake well, until dissolved.

DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING PARABENS, SINCE THESE ARE INCOMPATIBLE WITH GANCICLOVIR SODIUM STERILE POWDER AND MAY CAUSE PRECIPITATION.

The reconstituted solution should be inspected for particulate matter or discolouration prior to proceeding with admixture preparation.

Admixture Preparation: The reconstituted solution is further diluted in one of the solutions listed below for intravenous infusion.

Solutions for intravenous infusion: normal saline, dextrose 5% in water, Ringer's injection, lactated Ringer's injection.

STABILITY AND STORAGE RECOMMENDATIONS

CYTOVENE Sterile Powder: Store at room temperature (15-30°C), avoid excessive heat above 40°C (104°F). The reconstituted solution in the vial may be stored at room temperature up to 12 hours and should not be refrigerated.

CYTOVENE, when reconstituted with sterile water for injection, further diluted with 0.9% sodium chloride injection, and stored refrigerated at 5°C in polyvinyl chloride (PVC) bags, remain physically and chemically stable for 14 days. **However, because CYTOVENE is reconstituted with nonbacteriostatic sterile water, it is recommended that the infusion solution be used within 24 hours of dilution to reduce the risk of bacterial contamination.** The reconstituted and further diluted solutions should be stored under refrigeration. Freezing is not recommended.

CYTOVENE Capsules: Store between 15 - 25°C. Keep tightly closed.

HANDLING AND DISPOSAL

Caution should be exercised in the handling and preparation of CYTOVENE. Avoid ingestion, inhalation or direct contact with the skin and mucous membranes. CYTOVENE should be considered a potential teratogen and carcinogen in humans. CYTOVENE solutions are alkaline (pH approximately 11). The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution contacts the skin or mucous membranes, wash thoroughly with soap and water; rinse eyes for at least 15 minutes with plain water. CYTOVENE capsules should not be opened or crushed.

Several guidelines for the handling and disposal of hazardous pharmaceuticals (including

cytotoxic drugs) are available (e.g. CSHP, 1991). Disposal of CYTOVENE should follow provincial, municipal, and local hospital guidelines or requirements.

AVAILABILITY

CYTOVENE (ganciclovir sodium for injection) sterile powder is supplied in 10 mL clear glass vials, containing ganciclovir sodium equivalent to 500 mg of ganciclovir.

CYTOVENE (ganciclovir) 250 mg capsules are available in bottles of 84, as opaque green hard gelatin capsules printed in blue with CY250 on cap and two blue lines partially encircling the capsule body.

CYTOVENE (ganciclovir) 500 mg capsules are available in bottles of 90, as opaque yellow/opaque green hard gelatin capsules printed in blue with CY500 on cap and two blue lines partially encircling the capsule body.

VIROLOGY

Clinical Antiviral Effect of CYTOVENE (ganciclovir capsules and ganciclovir sodium for injection).

CYTOVENE (ganciclovir sodium for injection)

Of 314 immunocompromised patients enrolled in an open-label study of the treatment of life- or sight-threatening CMV disease with CYTOVENE (ganciclovir sodium for injection), 121 patients were identified who had a positive culture for CMV within 7 days prior to treatment and had sequential viral cultures after treatment with CYTOVENE (ganciclovir sodium for injection). Post-treatment virologic response was defined as conversion to culture negativity, or a greater than 100-fold decrease in CMV infectious units, as shown in the following table:

Table 7: Virologic Response

Culture Source	No. Patients Cultured	No. (%) Patients Responding	Median Days to Response
Urine	107	93 (87%)	8
Blood	41	34 (83%)	8
Throat	21	19 (90%)	7
Semen	6	6 (100%)	15

The antiviral activity of CYTOVENE (ganciclovir sodium for injection) was demonstrated in two separate placebo-controlled studies for the prevention of CMV disease in transplant recipients. One hundred forty-nine heart allograft recipients who were either CMV seropositive or had received seropositive heart allografts were randomized to treatment with CYTOVENE (ganciclovir sodium for injection; 5 mg/kg BID for 14 days followed by 6 mg/kg QD for 5 days/week for an additional 14 days) or placebo. Seventy-two CMV culture-positive allogeneic bone marrow transplant recipients were randomized to treatment with CYTOVENE (ganciclovir sodium for injection; 5 mg/kg BID for 7 days followed by 5 mg/kg QD) or placebo until day

100 post-transplant. CYTOVENE (ganciclovir sodium for injection) suppressed CMV shedding in heart allograft and bone marrow allograft recipients. The antiviral effect of CYTOVENE (ganciclovir sodium for injection) in these patients is summarized in the following table:

Table 8: Patients with Positive CMV Cultures

Time	Heart Allograft		Bone Marrow Allograft	
	CYTOVENE	Placebo	CYTOVENE	Placebo
Pre-Treatment	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%)

CYTOVENE (ganciclovir capsules)

The antiviral activity of CYTOVENE (ganciclovir capsules) was confirmed in two randomized, controlled trials comparing CYTOVENE (ganciclovir sodium for injection) with CYTOVENE (ganciclovir capsules) for the maintenance treatment of CMV retinitis in patients with AIDS. Serial cultures of urine were obtained, and cultures of semen, biopsy specimens, blood, and other sources also were obtained when available. Only a small proportion of patients remained culture-positive during maintenance therapy with either formulation of ganciclovir. There were no statistically significant differences in the rates of positive cultures between the treatment groups. The antiviral effect of CYTOVENE (ganciclovir capsules) in the patients in the two studies is summarized in the following table:

Table 9: Patients with Positive CMV Cultures in Two Controlled Clinical Trials

	Patients with Newly Diagnosed CMV Retinitis*		Patients with Stable, Previously Treated CMV Retinitis**	
	intravenous	**Capsules**	**intravenous**	**Capsules**
Start of Maintenance	5/37 (13.5%)	9/37 (24.3%)	2/66 (3.0%)	5/137 (3.6%)
Anytime During Maintenance	3/48 (6.3%)	4/44 (9.1%)	1/45 (2.2%)	7/99 (7.1%)

* Study ICM1653: 3 weeks of treatment with intravenous ganciclovir before start of maintenance
** Study ICM1774: 4 weeks to 4 months treatment with intravenous ganciclovir before start of maintenance

Viral Resistance

The current working definition of CMV resistance to ganciclovir in *in vitro* assays is IC_{50}>1.5 μg/mL (6.0 μM). CMV resistance to ganciclovir in individuals with AIDS and CMV retinitis who have not previously been treated with ganciclovir does occur. Viral resistance has been observed in patients receiving prolonged treatment with CYTOVENE (ganciclovir sodium for injection) for CMV retinitis. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate moiety; resistant viruses have been described which contain mutations in the UL97 gene of CMV which controls the phosphorylation of ganciclovir. Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir, and may show cross-resistance to other antivirals with a similar mechanism of action.

In two randomized controlled trials, the incidence of reduced sensitivity appeared to be no more common during treatment with CYTOVENE (ganciclovir capsules) than during treatment with CYTOVENE (ganciclovir sodium for injection).

In Vitro Studies

Ganciclovir is an inhibitor of viral replication *in vitro* (see Table 10). The relationship between *in vitro* sensitivity of CMV to antiviral drugs and clinical response has not been established.

TABLE 10

IN VITRO ACTIVITY OF GANCICLOVIR

Virus	IC_{50}(μM)*
Herpes simplex virus (HSV)	2.4[ab]
Human cytomegalovirus (HCMV)	0.4 - 11.0
Varicella Zoster virus (VZV)	32.0
Epstein-Barr virus (EBV)	1.0
Murine cytomegalovirus (MCMV)	15.0
Guinea pig cytomegalovirus (GPCMV)	70.0

[*] $\mu M = 10^{-6} M$
[a] Plaque Reduction Assay

The antiviral activity of ganciclovir against a number of strains of human CMV, in cell culture, is shown in Table 11.

TABLE 11

IN VITRO ANTIVIRAL ACTIVITY OF GANCICLOVIR

AGAINST HUMAN CMV STRAINS

Human CMV Strain	**Cell Culture**	**IC_{50}(μM)[a] ganciclovir**
AD 169	MRC-5	7
AD 169	MRC-5	1.5-6.2
Towne	MRC-5	0.4-6.2
Towne	WI-38	1.0
Major	WI-38	4.8
BT 1943	WI-38	1.1
AD 169	HET	7
Davis	MRC-5	7
Davis	HET	5
Towne	MRC-5	2.0
Davis	MRC-5	3.1
AD 16	MRC-5	3.1
Eisenhardt-CID9	HEL	2.0
AIDS-O.L.	HEL	0.8
AIDS-O.C.	HEL	5.5
CHMC-CID	HEL	5.9
CMV mononucleosis patients	HEL	1.0-11.0
Renal transplant patients	HEL	0.5-9.5
Male homosexual subjects	HEL	1.0-5.0

[a]IC_{50}: Median inhibitory dose (μM)

The IC_{50} of ganciclovir for a variety of cultured mammalian cells is shown in Table 12.

TABLE 12

EFFECTS OF GANCICLOVIR ON HOST CELL PROLIFERATION

Cell Type	**Ganciclovir IC_{50} (µM S.D.)**
Human Bone Marrow Colony-forming Cells	39±73
Human Embryonic Lung (MRC-5)	110±50
Human Embryonic Tonsil (HET)	250±80
Squirrel Monkey Lung (SML)	1500±95
Guinea Pig Embryo (GPE)	2900±844
Mouse Embryo Fibroblast (MEF)	210±80

[a]Results eliminate one marrow resistant to ganciclovir.

***In Vivo* Studies**

In three animal models of CMV infection ganciclovir has shown *in vivo* activity. These models are acute MCMV infection, MCMV lung infection and interstitial pneumonia, and acute GPCMV.

As shown in Table 13, various doses of ganciclovir were tested for efficacy against mice infected with CMV. A statistically significant increase in numbers of survivors were observed at doses of 10 mg/kg or more. A dose of 25 mg/kg of acyclovir was required to induce a statistically significant effect in the number of surviving mice.

TABLE 13

EFFECTS OF GANCICLOVIR ON MCMV (SMITH STRAIN) INDUCED MORTALITY WHEN TREATMENT WAS STARTED 6 HOURS AFTER INFECTION

Drug (mg/kg)[a]	Survivors/ Total	Mean Survival time (days)[b]
Saline	2/20 (10)[c]	4.4 ± 0.78[d]
Ganciclovir		
1	2/20 (10)	6.2 ± 1.8[f]
5	2/20 (10)	6.3 ± 1.4[f]
10	8/20 (40)[e]	7.7 ± 1.8[f]
25	15/20 (75)[e]	6.4 ± 0.55[f]
50	19/20 (95)[e]	7.0 ± 0.0[f]

[a]Half-daily doses were administered s.c. at 9am and 3pm for 5 days
[b]Of the mice that died
[c]Percent survival
[d]Standard deviation
[e]Statistically significant ($p<.05$) by Fisher exact test
[f]Statistically significant ($p<.05$) by Mann-Whitney U-test

In another experiment, treatment began either 6, 24, 48, 72 or 96 hours after the infection. A statistically significant increase in the number of survivors was observed when ganciclovir therapy was started 48 hours or less after inoculation (Table 14).

TABLE 14

EFFECTS OF 50 mg/kg GANCICLOVIR ON MCMV (SMITH STRAIN) INDUCED MORTALITY WHEN TREATMENT WAS STARTED 6, 24, 48, 72, or 96 HOURS AFTER INFECTION

Drug (hours after infection)[a]	Survivors/Total	Mean Survival time (days)[b]
Saline	2/19 (11)[c]	5.2 ± 1.2[d]
Ganciclovir		
6	18/20 (90)[e]	6.5 ± 0.71
24	15/19 (79)[e]	10.7 ± 3.8
48	9/19 (47)[e]	8.0 ± 2.5
72	6/20 (30)	6.1 ± 1.6
96	1/20 (5)	4.8 ± 0.71

[a]Half-daily doses were administered s.c. at 9 am and 3 pm for 5 days
[b]Of the mice that died
[c]Percent survival
[d]Standard deviation
[e]Statistically significant ($p<.05$) by Fisher exact test
[f]Statistically significant ($p<.05$) by Mann-Whitney U-test

Doses of ganciclovir ranging from approximately 40-300 mg/kg (ad libitum in drinking water starting 24 hours post-infection) reduced salivary titers of MCMV by 84-99 percent and lung titers by 97-99 percent. Ganciclovir treatment of diffuse interstitial pneumonitis also reduced the replication of MCMV in both lung and salivary glands but did not block pneumonitis development.

Guinea pig CMV is very insensitive to ganciclovir (Table 10), nevertheless, ganciclovir (25 mg/kg intraperitoneally, BID for 7 days) reduces GPCMV titers in the salivary glands. Histopathology showed that the lesions in the kidney and salivary gland from ganciclovir treated animals were significantly less severe than controls.

PHARMACOLOGY

Animal Pharmacodynamic Studies

Ganciclovir exhibited minimal pharmacological activity in a battery of tests for effects on the central nervous, cardiovascular, and immune systems. No consistent effect was observed when ganciclovir was co-administered with different autonomic drugs.

Human Pharmacology

Absorption: The absolute bioavailability of oral ganciclovir under fasting conditions was approximately 5% (n=6) and following food was 6-9% (n=32). When ganciclovir was administered orally with food at a total daily dose of 3 g/day (500 mg q3h, 6 times daily and 1000 mg TID), the steady-state absorption as measured by area under the serum concentration vs. time curve (AUC) over 24 hours and maximum serum concentrations (C_{max}) were similar following both regimens with an AUC_{0-24} of 15.9±4.2 (mean±SD) and 15.4±4.3 μg·hr/mL and C_{max} of 1.02±0.24 and 1.18±0.36 μg/mL, respectively (n=16).

At the end of a one-hour intravenous infusion of 5 mg/kg ganciclovir, total AUC ranged between 22.1±3.2 (n=16) and 26.8±6.1 μg·hr/mL (n=16) and C_{max} ranged between 8.27±1.02 (n=16) and 9.0±1.4 μg/mL (n=16).

Distribution: The steady-state volume of distribution of ganciclovir after intravenous administration was 0.74±0.15 L/kg (n=98). For CYTOVENE (ganciclovir capsules), no correlation was observed between AUC and reciprocal weight (range of 55-128 kg); oral dosing according to weight is not required. Cerebrospinal fluid concentrations obtained 0.25 and 5.67 hours post-dose in 3 patients who received 2.5 mg/kg ganciclovir intravenously q8h or q12h ranged from 0.31 to 0.68 μg/mL representing 24 to 70% of the respective plasma concentrations. Binding to plasma proteins was only 1-2% over ganciclovir concentrations of 0.5 and 51 μg/mL; as such, drug interactions involving binding site displacement are not anticipated.

Metabolism: When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6 to 5.0 mg/kg and when administered orally, it exhibits linear kinetics up to a total daily dose of 4 g/day. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. In patients with normal renal function, 91.3±5.0% (n=4) of intravenously administered ganciclovir was recovered unmetabolized in the urine. Systemic clearance of intravenously administered ganciclovir was 3.52±0.80 mL/min/kg (n=98) while renal clearance was 3.20±0.80 mL/min/kg (n=47), accounting for 91±11% of the systemic clearance (n=47). After oral administration of ganciclovir, steady-state is achieved within 24 hours. Renal clearance following oral administration was 3.1±1.2 mL/min/kg (n=22). Half-life was 3.5±0.9 hours (n=98) following intravenous administration and 4.8±0.9 (n=39) following oral administration.

Special Populations

Renal Impairment: The pharmacokinetics following intravenous administration of CYTOVENE (ganciclovir sodium for injection) were evaluated in 10 immunocompromised patients with renal impairment who received doses ranging from 1.25 to 5 mg/kg (see Table 15).

Table 15

CrCl (mL/min)	n	Dose	Clearance (mL/min) Mean±SD	Half-life (hours) Mean±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

The pharmacokinetics following oral administration of CYTOVENE (ganciclovir capsules) were evaluated in 44 patients who were either solid organ transplant recipients or HIV-positive. Apparent oral clearance of ganciclovir decreased and AUC_{0-24} increased with diminishing renal

function (as expressed by creatinine clearance). Based on these observations, it is necessary to modify the dosage of CYTOVENE (ganciclovir capsules) in patients with renal impairment (see DOSAGE AND ADMINISTRATION, Renal Impairment).

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both i.v. and oral administration (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Race and Gender: The effects of race and gender were examined in pharmacokinetic studies, among 50 patients receiving an oral dose of 1000 mg every 8 hours. Although the numbers of blacks (n=8; 16%) and hispanics (n=10; 20%) were small, there appeared to be a trend towards a lower steady-state C_{max} and AUC_{0-8} in these subpopulations as compared to caucasians. No definitive conclusions regarding gender differences could be made because of the small number of females (n=6; 12%); however, no differences between males and females were observed.

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

Ganciclovir pharmacokinetics were also studied in 10 children, aged 9 months to 12 years. The pharmacokinetic characteristics of ganciclovir were the same after single and multiple (q12h) intravenous doses (5 mg/kg). The steady state volume of distribution was 0.64±2.2 L/kg, C_{max} was 7.9±3.9 μg/mL, systemic clearance was 4.7±2.2 mL/min/kg, and $t_{½}$ was 2.4±0.7 hours. The pharmacokinetics of intravenous ganciclovir in neonates and children are similar to those observed in adults.

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

TOXICOLOGY

Tables 16 to 20 summarize the toxicological studies conducted with ganciclovir.

The most sensitive target organ for the primary toxic effects of ganciclovir was the testis. Other systems affected by ganciclovir treatment, but less sensitive than the male reproductive system, were the hematopoietic, integumentary, female reproductive, gastrointestinal, and urinary systems and the developing embryo/fetus. Except for the effects on the male reproductive system, and for some effects on the hematopoietic system and the skin, the changes induced by the administration of the drug occurred at dosages greater than the proposed clinical dose. The adverse effects due to ganciclovir treatment were generally reversible on withdrawal of drug treatment unless the doses used were exceptionally high and except for certain effects on the developing embryo/fetus.

TABLE 16

ACUTE TOXICOLOGY

SPECIES STRAIN SEX (N) AGE	ROUTE PROCEDURE VOLUME	PRETEST CONDITIONING	DOSE (MG/KG)	MORTALITY STUDY DAY	MORTALITY ANIMALS (N)	LD_{50}	SIGNS OF TOXICITY
Mouse Swiss-Webster Male (12) Female (12) 8-12 weeks	Oral Stomach tube 0.2 mL/10 g body weight	1 mo. acclim. period; 3 hr. fast prior to dosing	900 2000	- -	0 0	LD_{50}>2000 mg/kg	Clinical condition normal except for occasional inactivity and/or rough coat. No treatment related effects for body weight intakes.
Mouse Swiss-Webster Male (18) Female (18) 8-12 weeks	Intravenous tail-vein inject. 0.2mL/10 g body weight	1 mo. accilm. period	0 900 2000 	- 1** 6 7 8 1** 4 8	0 1M,1F 1F 1M,1F 1M,1F 3M 1M,5F 1F	Estimated LD_{50} 900 mg/kg	Rough coat recorded for vehicle-treated mice. Drug related effects: pallor, unthriftiness, hypothermia, inactivity, labored/increased respiration, necrosis and ulceration at injection site. Decreased body weight and food intakes observed during week 1 postdosing.
Dog Beagle Male (1) Female (1) 9-16 months	Oral Stomach tube 10 mL/kg body weight	5-10 mo. acclim. period; overnite fast prior to dosing	1000	-	0	LD_{50}>1000mg/kg	No treatment-related changes observed in body weight, gross pathology, hematology or clinical chemistry.
Dog Beagle Male (1) Female (1) 18-29 months	Intravenous cephalic vein injection 5 mL/kg	13-22 mo acclim. period	500	5 7	1M 1F	Estimated LD_{50} <500 mg/kg	Anorexia, diarrhea, hypothermia, vomiting, collapse, salivation, unthriftiness. Body weight loss of 15-20% Sanguinous changes in stomach and intestines. Male: leukopenia; increased BUN, GOT, GPT
Dog Beagle Male (1) Female (1) 10 Months	Intravenous Cephalic vein injection 1.5 mL/kg	6 mo. acclim. period	150	-	0	Estimated >150 mg/kg	No treatment-related effects on clinical condition or body weight. Male (day after dosing): slight increase in RBC count, hemoglobin hematocrit, total protein and albumin.

* M = MALE; F = FEMALE

** Deaths for all animals occurred during or within 1 minute of dosing and were therefore not considered drug-related.

TABLE 17

MULTIDOSE TOXICITY STUDIES

SPECIES STRAIN DURATION OF DOSING	ROUTE DOSE (MG/KG/DAY)	MORTALITY	HEMATOLOGY	CLINICAL CHEMISTRY	ORGAN WEIGHTS	PATHOLOGY	COMMENTS
Mouse Swiss-Webster 3 months	Gavage (Only male dosed)						
	0	1/45	-	-	-	-	-
	10	1/45	NDE	NDE	Testes decreased	Testicular atrophy & hypospermatogenesis, with complete recovery by 130 days postdosing.	Decreased fertility & increased abnormal sperm morphology, with recovery between 30-130 days post-dosing. No dominant lethal effect.
	100	0/45	NDE	NDE	Testes decreased	Testicular atrophy & aspermatogenesis	Infertility & increased abnormal sperm morphology.
	1000	4/45	NDE	NDE. No treatment-related changes in plasma FSH, LH, or testosterone	Testes decreased	Testicular atrophy & aspermatogenesis	Infertility & increased abnormal sperm morphology. Decreased food intake & body weight.
Mouse Swiss-Webster 3 months	Gavage (only females dosed)						
	0	1/85	-	-	-	-	-
	100	0/85	NDE	NDE	NDE	NDE	NDE
	300	1/85	NDE	NDE	NDE	NDE	NDE
	1000	2/85	NDE	NDE. No treatment - related changes in plasma FSH and LH.	NDE	NDE	NDE

NDE = no drug-related effect
ND = not done

TABLE 17 (Cont'd)

SPECIES STRAIN DURATION OF DOSING	ROUTE DOSE (MG/KG/DAY)	MORTALITY	SIGNS OF TOXICITY	HEMATOLOGY	CLINICAL CHEMISTRY	ORGAN WEIGHTS	PATHOLOGY
Mouse Swiss-Webster 1 month	Intravenous (males & females dosed)						
	0	0/25 (M) 0/25 (F)	-	-	-	-	-
	15	0/25 (M) 0/25 (F)	NDE	NDE	NDE	Testes decreased Spleen increased (females)	Aspermatogenesis and reproductive organ atrophy (males). Partial recovery at 1 month postdosing.
	45	5/25 (M) 3/25 (F)	Hypothermia, inactivity, pallor, rough coat, wasting, unthriftiness. Recovery 1 week post-dosing.	NDE	NDE	Testes decreased. Spleen increased.	Aspermatogenesis and reproductive organ atrophy (males). Renal cortical damage. Atrophy of skin adnexal tissue. Little evidence of recovery at 1 month postdosing.
	135	8/25 (M) 7/25 (F)	Decreased body weight during first &/or second week of treatment. Hypothermia inactivity, pallor, rough coat, wasting, unthriftiness. Recovery 1 week postdosing.	Decreased erythrocyte count, hemoglobin & haematocrit. Abnormal erythrocyte morphology in some mice. Complete recovery at 1 month postdosing.	Increased GOT, GPT, & BUN in females. Complete recovery at 1 month postdosing.	Males: testes, prostate gland & seminal vesicles decreased; spleen increased. Females: uterus decreased; spleen liver and kidney increased.	Aspermatogenesis. Reproductive organ atrophy (males & females). Inhibition of ovarian cycling. Renal cortical damage. Atrophy of skin adnexal tissue. Little evidence of recovery at 1 month postdosing.

NDE = no drug-related effect; Observations apply to both male and females, unless specified otherwise.

TABLE 17 (Cont'd)

SPECIES STRAIN DURATION OF DOSING	ROUTE DOSE (MG/KG/DAY)	MORTALITY	SIGNS OF TOXICITY	HEMATOLOGY	CLINICAL CHEMISTRY	ORGAN WEIGHTS	PATHOLOGY
Rat Sprague-Dawley 3 months	Oral (in feed) (males and females dosed)						
	0	0/6 (M) 0/6 (F)	-	-	-	-	-
	100	0/6 (M) 0/6 (F)	NDE	NDE	NDE	Testes decreased	Testicular atrophy and aspermatogenic tubules.
	500	0/6 (M) 0/6 (F)	NDE	NDE	NDE	Testes decreased	Testicular atrophy and aspermatogenic tubules.
	1400	0/6 (M) 0/6 (F)	NDE	NDE	NDE	Testes decreased	Testicular atrophy and aspermatogenic tubules.
	5000	1/6 (M) 0/6 (F)	8-12% decrease in body weight gain	NDE	NDE	Testes decreased	Testicular atrophy and aspermatogenic tubules.
Dog Beagle 1 month	Intravenous						
	0	0/3(M) 0/2(F)	-	-	-		-
	0.4	0/3(M)	NDE	NDE	NDE		Testicular atrophy and hypospermatogenesis after a one month recovery.
	1.2	0/3(M) 0/2(F)	NDE	NDE	NDE		Testicular atrophy and hypospermatogenesis after a one month recovery.
	3.6	0/3(M) 0/2(F)	NDE	NDE	NDE		Testicular atrophy and hypospermatogenesis. Recovery expected based on presence of spermatogonia and primary spermatocytes one month postdosing.

NDE = no drug-related effect; Observations apply to both male and females, unless specified otherwise.

TABLE 17 (Cont'd)

SPECIES STRAIN DURATION OF DOSING	ROUTE DOSE (MG/KG/DAY)	MORTALITY	SIGNS OF TOXICITY	HEMATOLOGY	CLINICAL CHEMISTRY	ORGAN WEIGHTS	PATHOLOGY
Dog Beagle 3 months	Oral tube (stomach)						

Males						
0	0/6	-	-	-	-	-
0.2	0/6	NDE	NDE	NDE	NDE	Minimal-to-slight testicular atrophy and hypospermatogenesis. Sebaceous gland atrophy. Complete recovery from all lesions by 65 days postdosing
2.0	0/6	Decr. body weight & testes vol.	NDE	NDE	Testes dec.	Testicular atrophy & aspermatogenesis. Decr. epididymal sperm. Sebaceous gland atrophy. Complete recovery from all lesions by 4 mths postdosing.
20.0	0/6	Decr. body wgt. and testes vol. lacrimation	Decr. hemoglobin & hematocrit. Decr. erythrocyte, leukocyte & platelet counts.	No treatment related changes in FSH, LH or testosterone	Testes dec.	Testicular atrophy & aspermatogenesis. Decr. epididymal sperm. Bone marrow hypocellularity. Sebaceous gland & hair follicle atrophy. Complete recovery from all lesions by 4 months postdosing.
Females						
0	0/6	-	-	-	-	-
2.0	0/6	NDE	NDE	NDE	NDE	NDE
6.0	0/6	Decr. body weight Lacrimination	Decr. leukocyte and platelet counts.	NDE	NDE	Bone marrow hypocellularity. Sebaceous gland atrophy. Complete recovery from all lesions by 65 days postdosing.
20.0	1/6	Decr. body weight Lacrimination	Decr. hemoglobin & hematocrit. Decr. erythrocyte, leukocyte & platelet counts.	No treatment related changes in FSH, LH or testosterone.	NDE	Bone marrow hypocellularity. Sebaceous gland and hair follicle atrophy. Complete recovery from all lesions by 4 months postdosing.

NDE = no drug-related effect

TABLE 17 (Cont'd)

SPECIES STRAIN DURATION OF DOSING	ROUTE DOSE (MG/KG/DAY)	MORTALITY	SIGNS OF TOXICITY	HEMATOLOGY	CLINICAL CHEMISTRY	ORGAN WEIGHTS	PATHOLOGY
Dog Beagle 1 month	I.V. 0	0/3 (M) 0/3 (F)	-	-	-	-	-
	10	0/3 (M) 0/3 (F)	Clear ocular discharge	Leukocyte count slightly decreased	NDE	Testes decr.	Decr. bone marrow cellularity. Atrophic testes. Sebaceous gland atrophy.
	30	0/3 (M) 1/3 (F)	Clear ocular discharge in all dogs. Decr. body wgt, anorexia emesis hypothermia & bloody diarrhea in female that died.	Decr. leukocytes, platelets, and/or reticulocytes in all dogs partial recovery at 2 wks postdosing. Decr. erythrocytes, hemoglobin & hematocrit in female that died.	Effects similar to high-dose dogs were seen in female that died.	Testes decr.	Decr. bone marrow cellularity. Partial recovery at 2 wks. postdosing. Atrophic testes. Epidermal, sebaceous and hair follicle atrophy.
	90	3/3 (M) 3/3 (F)	Decr. body weight anorexia emesis, hypothermia bloody diarrhea dehydration and clear ocular discharge in all dogs.	Decr. leukocytes, reticulocytes & platelets. Incr. erythrocytes hemoglobin and hematocrit.	Decr. Na & Cl. Incr. BUN creatinine alkaline Phosphatase, phosphorous, cholesterol & triglycerides.	Testes normal dogs died too early to show effects.	Decr. bone marrow cellularity. Severe gastrointestinal degeneration & atrophy. Renal tubular dilation. Epidermal sebaceous and hair follicle atrophy. Thymic involution. Ovarian suppression and lymphoid atrophy, possibly secondary to stress of systemic illness.

NDE = no drug-related effect

TABLE 18

REPRODUCTION STUDIES

SPECIES STRAIN & SEX/GROUP	DOSE ROUTE BREEDING/ SACRIFICE SCHEDULE	RESULTS/CONCLUSIONS
FERTILITY AND REPRODUCTION		
Mouse Swiss-Webster Males: 20/group, dosed for 60 days before mating plus 9 days during mating. Females: 38-40/group, undosed	0, 0.4, 2.0, and 10.0 mg/kg/day intravenous breeding postdosing. 2 months and 6 months. Necropsy (males): 2 months and 7 months.	Decreased fertility in mid- and high-dose males at the end of treatment, associated with atrophy and decreased sperm in testes and epididymis. Mid-dose fertility completely recovered after 2 months, high-dose fertility minimally recovered after 6 months. No treatment-related effects on mating behavior, litter size and survival indices. No dominant lethal effects.
Mouse Swiss-Webster Males: Undosed Females: 40/group, dosed from 14 days before mating through weaning.	0, 5, 20 and 90 mg/kg/day intravenous breeding after 14 days dosing (females allowed to litter) and at 2 months postdosing. Necropsy (females): at both mating periods.	Decreased receptivity to mating, decreased pregnancy rate and increased resorption rate in high-dose females at first mating period; offspring showed hypoplastic testes and seminal vesicles, and increased incidence of epithelial hyperplasia and hyperkeratosis of the non-glandular stomach. Complete recovery at 2 months from treatment related changes in mating, fertility and embryolethality. Offspring of low and mid-dose females showed no treatment-related changes, and had normal mating behavior, fertility, and offspring viability for second-generation mating cycle.
TERATOLOGY		
Mouse Swiss-Webster Females: 25/group dosed days 7-16 gestation	0, 12, 36 and 108 mg/kg/day Necropsy day 18 gestation	Decreased body weight gain in high-dose dams, associated with increased resorptions, decreased live-litter size and decreased live-fetus weights. Growth retardation in high-dose fetuses, but no treatment-related teratologic changes noted after external, skeletal and visceral examination.
Rabbit Dutch-Belted Females: 21/group dosed days 7-19 gestation	0, 6, 20 and 60 mg/kg/day Necropsy day 29 gestation	High-dose dams showed clinical signs of toxicosis, decreased body weights and resorption of 12/14 litters. Decreased fetal weight and fetal growth retardation in both mid- and high-dose groups. Fetal malformations observed in two mid-dose and two high-dose dams, including cleft palate, hydrocephaly and microphthalmia; teratogenic effects did not appear to be secondary to maternal toxicity.

TABLE 19

MUTAGENICITY STUDIES

STUDY TYPE	DOSE	EFFECTS	CONCLUSION
Ames plate test with Salmonella and mitotic gene conversion assay with Saccharomyces (both assays with and without activation)	1, 10, 100, 500, 1000, 2500, 5000 and 10000 mcg/plate	Not toxic to bacterial strain TA-100 or yeast strain D__ at 10,000 mcg/plate; cytotoxicity not evaluated in four other bacterial strains used. Results of both tests conducted in the presence or absence of activation were negative.	DHPG did not demonstrate mutagenic activity in any assays conducted in this evaluation and was considered not mutagenic under these test conditions.
Ames suspension test with Salmonella (with and without activation)	500, 1000, 1250, 2500, and 5000 mcg/mL	Not toxic to bacterial strain TA-100 - cytoxicity not evaluated in four other bacterial strains used. Results of both tests conducted in the presence or absence of activation were negative.	DHPG did not demonstrate mutagenic activity in any assays conducted in this evaluation and was considered not mutagenic under these test conditions.
Sister chromatid exchange assay with human lymphocytes (with activation only)	0.250, 0.500, 0.750, 1.0, 1.5 & 2.0 mg/mL	Delayed cell growth at concentrations of 1.0 mg/mL and greater. Results of tests conducted in the presence of activation were positive, at all doses tested.	DHPG was positive at all dose levels in human lymphoblasts under the conditions of this test.
Mouse lymphoma forward mutation assay in L5178Y cells, with and without activation	50, 100, 400, 500, 600, & 800 mcg/mL without activation; 100, 400, 800, & 1000 mcg/mL with activation	Moderate to very high toxicity induced by range of doses used. Results of all tests conducted under conditions of moderate toxicity were positive, with or without activation.	DHPG was positive over a wide range of dose levels under the conditions of this test.
Cell transformation assay in BALB/c-3T3 cells, without activation	1.88, 7.5, 15, 25 and 40 mcg/mL	Complete lethality at concentrations of 62.5 mcg/mL and greater. Cell survival 12.8% at 31.3 mcg/mL, near control levels at concentrations of 3.91 mcg/mL and less. Transformation responses to doses tested not significantly elevated relative to spontaneous transformant frequencies; no evidence of dose-related increase in transforming activity.	DHPG was considered inactive in this assay at the concentrations tested.
Mouse micronucleus assay in CD-1(1CR) male and female mice	50, 150, and 500 mg/kg body weight, intravenous	Bone marrow cytotoxicity observed at high dose. Positive dose response trends seen in both sexes at mid and high doses, with max.	DHPG was considered negative in this assay at 50 mg/kg and positive at 150 and 500 mg/kg.

TABLE 20

OTHER TOXICITY STUDIES

PROTOCOL	SPECIES STRAIN	ROUTE DOSE	NO./SEX PER GROUP	STUDY DURATION	RESULTS
Single-Dose Gonadotoxicity	Mouse Swiss-Webster	Intravenous 0, 2, 10, 30, 100 & 300 mg/kg	Males: 15/dose group Females: 15/dose group (30,100 & 300 mg/kg only)	Single dose with necropsy at 2 wks., 1 mo. and 3 mos. postdosing	Testicular atrophy & hypospermatogenesis in males at 2 wks. and 1 mo. postdosing after 30, 100 or 300 mg/kg; complete or partial recovery at 3 mos. No treatment-related changes seen in females.
Single-Dose Gonadotoxicity	Dog Beagle	Intravenous 0, 1, 6, 30 & 150 mg/kg	Males: 2/dose group	Single dose with hemicastration at 1 mo. followed by necropsy at 2 mos, or hemicastration at 2 mos. Followed by necropsy at 4 mos. (1 dog each per dose group)	Hypospermatogenesis at 1 & 2 mos. post-treatment after 30 or 150 mg/kg; complete recovery at 4 mos. No treatment-related changes in clinical condition, body weight, FSH, LH or testosterone.
Vein Irritation	Rabbit New Zealand	Intravenous 45 mg/ml solution	Females: 2/dose group	Single dose with necropsy at 10, 30 & 240 minutes postdosing.	No gross or microscopic pathological changes were observed in the treated ear veins.

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