HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GANZYK-RTU safely and effectively. See full prescribing information for GANZYK-RTU.

GANZYK-RTU (ganciclovir injection), for intravenous use
Initial U.S. Approval: 1989

WARNING: HEMATALOGIC TOXICITY, IMPAIRMENT OF FERTILITY, TERATOGENICITY, and CARCINOGENICITY

See full prescribing information for complete boxed warning.

- **Hematologic Toxicity: Granulocytopenia, anemia, thrombocytopenia, and pancytopenia have been reported in patients treated with ganciclovir. (5.1)**
- **Impairment of Fertility: Based on animal data, GANZYK-RTU may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females. (5.3)**
- **Fetal Toxicity: Based on animal data, GANZYK-RTU has the potential to cause birth defects in humans. (5.4)**
- **Mutagenesis and Carcinogenesis: Based on animal data, GANZYK-RTU has the potential to cause cancer in humans. (5.5)**

----------INDICATIONS AND USAGE----------

GANZYK-RTU is a deoxynucleoside analogue CMV DNA polymerase inhibitor indicated for the:

- treatment of CMV retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome (AIDS). (1.1)
- prevention of CMV disease in adult transplant recipients at risk for CMV disease. (1.2)

----------DOSAGE AND ADMINISTRATION----------

Dosage in Adult Patients with Normal Renal Function	
Treatment of CMV retinitis (2.3)	Induction: 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days. Maintenance: 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week.
Prevention of CMV disease in transplant recipients (2.4)	Induction: 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7 to 14 days. Maintenance: 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week until 100 to 120 days post-transplantation.

- Adult patients with renal impairment: Adjust dosage based on creatinine clearance. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 500 mg ganciclovir in 250 mL (2 mg per mL) solution in a single-dose bag for intravenous use. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to ganciclovir or valganciclovir. (4)

----------WARNINGS AND PRECAUTIONS----------

- Impairment of renal function: Increased serum creatinine levels have been observed with the use of ganciclovir, particularly in elderly patients and transplant patients receiving concomitant nephrotoxic drugs. Monitor renal function during therapy with GANZYK-RTU, particularly in elderly patients and in patients taking other nephrotoxic drugs, and reduce dosage in patients with renal impairment. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions and laboratory abnormalities reported in at least 20% of patients were pyrexia, diarrhea, leukopenia, nausea, anemia, asthenia, headache, cough, decreased appetite, dyspnea, abdominal pain, sepsis, hyperhidrosis, and blood creatinine increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, Contact Exela Pharma Sciences, LLC at 1-888-451-4321 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Imipenem-cilastatin: Seizures were reported in patients receiving ganciclovir and imipenem-cilastatin. Concomitant use is not recommended unless the potential benefits outweigh the risks. (7)
- Cyclosporine or amphotericin B: When coadministered with ganciclovir, the risk of nephrotoxicity may be increased. Monitor renal function. (5.2, 7)
- Mycophenolate mofetil (MMF): When coadministered with ganciclovir, the risk of hematological and renal toxicity may be increased. Monitor for ganciclovir and MMF toxicity. (7)
- Other drugs associated with myelosuppression or nephrotoxicity: Due to potential for increased toxicity, such drugs should be considered for concomitant use with ganciclovir only if the potential benefits are judged to outweigh the risks. (7)
- Didanosine: Ganciclovir coadministered with didanosine may increase didanosine levels. Monitor for didanosine toxicity (e.g., pancreatitis). (7)
- Probenecid: May increase ganciclovir levels. Monitor for evidence of ganciclovir toxicity. (7)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Breastfeeding is not recommended with use of **GANZYK-RTU**. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: HEMATALOGIC TOXICITY, IMPAIRMENT OF FERTILITY, TERATOGENICITY, and CARCINOGENICITY

- **Hematologic Toxicity: Granulocytopenia, anemia, thrombocytopenia, and pancytopenia have been reported in patients treated with ganciclovir *[see Warnings and Precautions (5.1)]*.**
- **Impairment of Fertility: Based on animal data, GANZYK-RTU may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females *[see Warnings and Precautions (5.3)]*.**
- **Fetal Toxicity: Based on animal data, GANZYK-RTU has the potential to cause birth defects in humans *[see Warnings and Precautions (5.4)]*.**
- **Mutagenesis and Carcinogenesis: Based on animal data, GANZYK-RTU has the potential to cause cancer in humans *[see Warnings and Precautions (5.5)]*.**

1 INDICATIONS AND USAGE

1.1 Treatment of CMV Retinitis

GANZYK-RTU is indicated for the treatment of cytomegalovirus (CMV) retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome (AIDS) *[see Clinical Studies (14.1)]*.

1.2 Prevention of CMV Disease in Transplant Recipients

GANZYK-RTU is indicated for the prevention of CMV disease in adult transplant recipients at risk for CMV disease *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing and Administration Information

- Do not administer GANZYK-RTU by rapid or bolus intravenous injection which may increase toxicity as a result of excessive plasma levels.
- Do not add supplemental medication to the intravenous bag.
- The recommended dosage and infusion rate for GANZYK-RTU should not be exceeded.
- Administration of GANZYK-RTU should be accompanied by adequate hydration.
- GANZYK-RTU should only be infused into veins with adequate blood flow to permit rapid dilution and distribution.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.2 Testing Before and During Treatment

- Females of reproductive potential should undergo pregnancy testing before initiation of GANZYK-

RTU *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

- Complete blood counts with differential and platelet counts should be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in cytopenias, or in whom absolute neutrophil counts are less than 1000 cells/μL at the beginning of treatment *[see Warnings and Precautions (5.1)]*.
- All patients should be monitored for renal function before and during treatment with GANZYK-RTU and dosage should be adjusted as needed *[see Dosage and Administration (2.5), Warnings and Precautions (5.2)]*.
- Patients with CMV retinitis should have frequent ophthalmological examinations during treatment with GANZYK-RTU to monitor disease status and for other retinal abnormalities *[see Adverse Reactions (6.1)]*.

2.3 Recommended Dosage for Treatment of CMV Retinitis in Adult Patients with Normal Renal Function

Induction Dosage: The recommended initial dosage of GANZYK-RTU for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days.

Maintenance Dosage: Following induction treatment, the recommended maintenance dosage of GANZYK-RTU is 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week.

2.4 Recommended Dosage for Prevention of CMV Disease in Adult Transplant Recipients with Normal Renal Function

Induction Dosage: The recommended initial dosage of GANZYK-RTU 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.

Maintenance Dosage: Following induction, the recommended maintenance dosage of GANZYK-RTU is 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week until 100 to 120 days post-transplantation.

2.5 Recommended Dosage in Adult Patients with Renal Impairment

For patients with renal impairment, refer to Table 1 for recommended doses of GANZYK-RTU for induction and maintenance dosage for treatment of CMV retinitis and prevention of CMV disease in transplant patients. Monitor serum creatinine or creatinine clearance during treatment to allow for dosage adjustments in patients with impaired renal function.

Table 1. Recommended Induction and Maintenance Dosage for Adult Patients with Renal Impairment

Creatinine Clearance* (mL/min)	GANZYK-RTU Induction Dose (mg/kg)	Dosing Interval (hours) for Induction	GANZYK-RTU Maintenance Dose (mg/kg)	Dosing Interval (hours) for Maintenance
Greater than or equal to 70	5	12	5	24
50-69	2.5	12	2.5	24
25-49	2.5	24	1.25	24

10-24	1.25	24	0.625	24
Less than 10	1.25	3 times per week, following hemodialysis	0.625	3 times per week, following hemodialysis

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

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

Patients Undergoing Hemodialysis

Induction dosing for GANZYK-RTU in patients undergoing hemodialysis should not exceed 1.25 mg per kg 3 times per week, and maintenance dosing should not exceed 0.625 mg/kg 3 times per week following each hemodialysis session. GANZYK-RTU should be given shortly after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50% *[see Clinical Pharmacology (12.3)]*.

2.6 Handling and Disposal

Because ganciclovir shares some of the properties of antitumor agents (i.e., carcinogenicity and mutagenicity), procedures for proper handling and disposal for cytotoxic drugs should be considered[1] *[see How Supplied/Storage and Handling (16)]*. The premix flexible plastic container bag contains no preservative; therefore, any unused portion should be discarded after each use.

3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mg of ganciclovir in 250 mL (2 mg per mL) sterile, unpreserved, colorless solution in a single-dose bag for intravenous use.

4 CONTRAINDICATIONS

GANZYK-RTU is contraindicated in patients who have experienced a clinically significant hypersensitivity reaction (e.g., anaphylaxis) to ganciclovir, valganciclovir, or any component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity

Granulocytopenia (neutropenia), anemia, thrombocytopenia, and pancytopenia have been observed in patients treated with ganciclovir. The frequency and severity of these events vary widely in different patient populations *[see Adverse Reactions (6.1)]*. GANZYK-RTU is not recommended if the absolute neutrophil count is less than 500 cells/µL, hemoglobin is less than 8 g/dL, or the platelet count is less than 25,000 cells/µL. GANZYK-RTU should also be used with caution in patients with pre-existing cytopenias and in patients receiving myelosuppressive drugs or irradiation. Neutropenia usually occurs during the first or second week of treatment but may occur at any time during treatment. Cell counts usually begin to recover within 3 to 7 days after discontinuing drug. Colony-stimulating factors have been

shown to increase neutrophil and white blood cell counts in patients receiving ganciclovir for treatment of CMV retinitis.

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving GANZYK-RTU, complete blood counts with differential and platelet counts should be performed frequently in all patients, especially in patients with renal impairment and in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/µL at the beginning of treatment *[see Dosage and Administration (2.2)]*.

5.2 Impairment of Renal Function

Increased serum creatinine levels have been reported in elderly patients and in transplant patients receiving concomitant nephrotoxic medications (i.e., cyclosporine and amphotericin B). Monitoring renal function during therapy with GANZYK-RTU is essential, especially for elderly patients and those patients receiving concomitant agents that may cause nephrotoxicity *[see Dosage and Administration (2.5), Drug Interactions (7), Use in Specific Populations (8.5)]*.

5.3 Impairment of Fertility

Based on animal data, GANZYK-RTU at the recommended human dose (RHD) may cause temporary or permanent inhibition of spermatogenesis in males, and may cause suppression of fertility in females. Advise patients that fertility may be impaired with use of GANZYK-RTU *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

5.4 Fetal Toxicity

GANZYK-RTU may cause fetal toxicity when administered to pregnant women based on findings in animal studies. Systemic exposure of ganciclovir in animals at approximately 2 times the RHD caused fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes in animals included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with GANZYK-RTU. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with GANZYK-RTU *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

5.5 Mutagenesis and Carcinogenesis

Animal data indicate that ganciclovir is mutagenic and carcinogenic. GANZYK-RTU should therefore be considered a potential carcinogen in humans *[see Dosage and Administration (2.6), Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Hematologic Toxicity *[see Warnings and Precautions (5.1)]*
- Impairment of Renal Function *[see Warnings and Precautions (5.2)]*
- Impairment of Fertility *[see Warnings and Precautions (5.3)]*
- Fetal Toxicity *[see Warnings and Precautions (5.4)]*
- Mutagenesis and Carcinogenesis *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience in Adult Patients

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse reactions and laboratory abnormalities reported in at least 20% of patients were pyrexia, diarrhea, leukopenia, nausea, anemia, asthenia, headache, cough, decreased appetite, dyspnea, abdominal pain, sepsis, hyperhidrosis, and blood creatinine increased.

Selected adverse reactions that occurred during clinical trials of intravenous ganciclovir are summarized below, according to the participating study patient population.

Adverse Reactions in Patients with CMV Retinitis: Three controlled, randomized, phase 3 trials comparing intravenous ganciclovir and ganciclovir capsules for maintenance treatment of CMV retinitis have been completed. During these trials, 9% of subjects were prematurely discontinued because of adverse reactions. Selected adverse reactions and laboratory abnormalities reported during the conduct of these controlled trials are summarized in Table 2 and Table 3, respectively *[see Clinical Studies (14)]*.

Table 2. Pooled Selected Adverse Events Reported in ≥ 5% of Subjects Comparing Intravenous Ganciclovir to Ganciclovir Capsules for Maintenance Treatment of CMV Retinitis

Adverse Event	Maintenance Treatment Studies	
	Intravenous Ganciclovir (n=179)	Ganciclovir Capsules (n=326)
Pyrexia	48%	38%
Diarrhea	44%	41%
Leukopenia	41%	29%
Anemia	25%	19%
Total catheter events:	22%	6%
Catheter infection	9%	4%
Catheter sepsis	8%	1%
Other catheter related events	5%	1%
Sepsis	15%	4%
Decreased appetite	14%	15%
Vomiting	13%	13%
Infection	13%	9%
Hyperhidrosis	12%	11%
Chills	10%	7%
Neuropathy peripheral	9%	8%
Thrombocytopenia	6%	6%
Pruritus	5%	6%

Retinal Detachment: Retinal detachment has been observed in subjects with CMV retinitis both before and after initiation of therapy with ganciclovir. Its relationship to therapy with ganciclovir is unknown. Retinal detachment occurred in 11% of patients treated with intravenous ganciclovir and in 8% of patients treated with ganciclovir capsules.

Table 3. Selected Laboratory Abnormalities in Trials for Treatment of CMV Retinitis

Laboratory Abnormalities	CMV Retinitis Treatment*	
	Intravenous Ganciclovir† 5 mg/kg/day (N=175) %	Ganciclovir Capsules‡ 3000 mg/day (N=320) %
Neutropenia with Absolute Neutrophil Count (ANC) per µL:		
<500	25%	18%
500 - <749	14%	17%
750 - <1000	26%	19%
Anemia with Hemoglobin (g/dL):		
<6.5	5%	2%
6.5 - <8.0	16%	10%
8.0 - <9.5	26%	25%
Serum Creatinine (mg/dL):		
≥2.5	2%	1%
≥1.5 - <2.5	14%	12%

* Pooled data from treatment studies ICM 1653, ICM 1774, and AVI 034
† Mean time on therapy = 103 days, including allowed re-induction treatment periods
‡ Mean time on therapy = 91 days, including allowed re-induction treatment periods

Adverse Reactions in Transplant Recipients: There have been three controlled clinical trials of intravenous ganciclovir for the prevention of CMV disease in transplant recipients. Selected laboratory abnormalities are summarized in Tables 4 and 5 below. Table 4 shows the frequency of neutropenia and thrombocytopenia and Table 5 shows the frequency of elevated serum creatinine values observed in these trials *[see Clinical Studies (14)]*.

Table 4. Laboratory Abnormalities in Controlled Trials – Transplant Recipients who Received Intravenous Ganciclovir or Placebo

Laboratory Abnormality	Heart Allograft*		Bone Marrow Allograft†	
	Intravenous Ganciclovir (n=76)	Placebo (n=73)	Intravenous Ganciclovir (n=57)	Control (n=55)
Neutropenia				
Absolute Neutrophil Count (ANC) per µL:				
<500	4%	3%	12%	6%
<500-1000	3%	8%	29%	17%
TOTAL ANC ≤1000/µL	7%	11%	41%	23%
Thrombocytopenia				
Platelet count per µL:				
<25,000	3%	1%	32%	28%
25,000-50,000	5%	3%	25%	37%
TOTAL Platelet Count ≤50,000/µL	8%	4%	57%	65%

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

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

Table 5. Serum Creatinine Levels in Controlled Trials – Transplant Recipients who Received Intravenous Ganciclovir or Placebo

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

Other Adverse Reactions in Clinical Trials in Patients with CMV Retinitis and in Transplant Recipients

Other adverse reactions with intravenous ganciclovir or ganciclovir capsules in controlled clinical trials in either subjects with AIDS or transplant recipients are listed below *[see Clinical Studies (14)]*. All these events occurred in at least 3 subjects.

Blood and lymphatic disorders: pancytopenia, bone marrow failure

Cardiac disorders: arrhythmias

Ear and labyrinth disorders: tinnitus, ear pain, deafness

Eye disorders: visual impairment, vitreous disorders, eye pain, conjunctivitis, macular edema

Gastrointestinal disorders: nausea, abdominal pain, dyspepsia, flatulence, constipation, mouth ulceration, dysphagia, abdominal distention, pancreatitis, gastrointestinal perforation, eructation, dry mouth

General disorders and administration site conditions: fatigue, injection site inflammation, edema, pain, malaise, asthenia, chest pain, multiple organ failure

Immune system disorders: hypersensitivity

Infections and infestations: candida infections including oral candidiasis, upper respiratory infection, influenza, urinary tract infections, cellulitis

Investigations: blood alkaline phosphatase increased, hepatic function abnormal, aspartate aminotransferase increased, alanine aminotransferase increased, creatinine clearance decreased

Metabolism and nutrition disorders: weight decreased

Musculoskeletal and connective tissue disorders: back pain, myalgia, arthralgia, muscle spasms, leg cramps, myasthenia

Nervous system disorders: headache, insomnia, dizziness, paresthesia, hypoaesthesia, seizures, somnolence, dysgeusia (taste disturbance), tremor

Psychiatric disorders: depression, confusional state, anxiety, agitation, psychotic disorder, thinking abnormal, abnormal dreams

Renal and urinary disorders: kidney failure, renal function abnormal, urinary frequency, hematuria

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Skin and subcutaneous tissues disorders: dermatitis, alopecia, dry skin, urticaria, rash

Vascular disorders: hypotension, hypertension, phlebitis, vasodilation

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of intravenous ganciclovir or ganciclovir capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic disorders: hemolytic anemia, agranulocytosis, granulocytopenia

Cardiac disorders: cardiac arrest, conduction disorder, torsade de pointes, ventricular tachycardia

Congenital, familial and genetic disorders: congenital anomaly

Endocrine disorders: inappropriate antidiuretic hormone secretion

Eye disorders: cataracts, dry eyes

Gastrointestinal disorders: intestinal ulcer

Hepatobiliary disorders: cholelithiasis, cholestasis, hepatic failure, hepatitis

Immune system disorders: anaphylactic reaction, allergic reaction, vasculitis

Investigations: blood triglycerides increased

Metabolism and nutrition disorders: acidosis, hypercalcemia, hyponatremia

Musculoskeletal and connective tissue disorders: arthritis, rhabdomyolysis

Nervous system disorders: dysesthesia, dysphasia, extrapyramidal disorder, facial paralysis, amnesia, anosmia, myelopathy, cerebrovascular accident, third cranial nerve paralysis, aphasia, encephalopathy, intracranial hypertension

Psychiatric disorders: irritability, hallucinations

Renal and urinary disorders: renal tubular disorder, hemolytic uremic syndrome

Reproductive system and breast disorders: infertility, testicular hypotrophy

Respiratory, thoracic and mediastinal disorders: bronchospasm, pulmonary fibrosis

Skin and subcutaneous tissues disorders: exfoliative dermatitis, Stevens-Johnson syndrome

Vascular disorders: peripheral ischemia

7 DRUG INTERACTIONS

Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of GANZYK-RTU and drugs excreted by the same pathway as

ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

Established and other potentially significant drug interactions conducted with ganciclovir are listed in Table 6 *[see Clinical Pharmacology (12.3)]*.

Table 6. Established and Other Potentially Significant Drug Interactions with Ganciclovir

Name of the Concomitant Drug	**Change in the Concentration of Ganciclovir or Concomitant Drug**	**Clinical Comment**
Imipenem-cilastatin	Unknown	Coadministration with imipenem-cilastatin is not recommended because generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin.
Cyclosporine or amphotericin B	Unknown	Monitor renal function when GANZYK-RTU is co-administered with cyclosporine or amphotericin B because of potential increase in serum creatinine *[see Warnings and Precautions (5.2)]*.
Mycophenolate mofetil (MMF)	↔ Ganciclovir (in patients with normal renal function) ↔ MMF (in patients with normal renal function)	Based on increased risk, patients should be monitored for hematological and renal toxicity.
Other drugs associated with myelosuppresion or nephrotoxicity (e.g., dapsone, doxorubicin, flucytosine, hydroxyurea, pentamidine, tacrolimus, trimethoprim/ sulfamethoxazole, vinblastine, vincristine and zidovudine)	Unknown	Because of potential for higher toxicity, coadministration with GANZYK-RTU should be considered only if the potential benefits are judged to outweigh the risks.
Didanosine	↔ Ganciclovir ↑ Didanosine	Patients should be closely monitored for didanosine toxicity (e.g., pancreatitis).
Probenecid	↑ Ganciclovir	GANZYK-RTU dose may need to be reduced. Monitor for evidence of ganciclovir toxicity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In animal studies, ganciclovir caused maternal and fetal toxicity and embryo-fetal mortality in pregnant mice and rabbits as well as teratogenicity in rabbits at exposures two times the exposure at the

recommended human dose (RHD) *[see Data]*. Although placental transfer of ganciclovir has been shown to occur based on ex vivo experiments with human placenta and on at least one case report in a pregnant woman, no adequate human data are available to establish whether GANZYK-RTU poses a risk to pregnancy outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2-4% and 15−20%, respectively.

Clinical considerations

Disease-associated maternal and/or fetal risk

Most maternal CMV infections are subclinical or they may be associated with a mononucleosis-like syndrome. However, in immunocompromised patients, CMV infections are often symptomatic and are associated with significant morbidity and mortality. The transmission of CMV to the fetus is a result of maternal viremia and transplacental infection. CMV infection can also occur perinatally from mother to infant by exposure to CMV in cervicovaginal secretions. Approximately 10% of children with congenital CMV infection are symptomatic at birth. Mortality in symptomatic infants is about 10%, and approximately 50 to 90% of symptomatic surviving newborns experience significant problems, including sensorineural hearing loss, mental retardation, and other neurologic deficits. The risk and severity of congenital CMV infection appear to be higher in infants born to mothers with primary CMV infection than in those born to mothers with reactivation of CMV infection.

Data

Animal Data

Daily intravenous doses of ganciclovir were administered to pregnant mice (108 mg/kg/day) and rabbits (60 mg/kg/day), and also to female mice (90 mg/kg) prior to mating, during gestation, and during lactation. Fetal resorptions were present in at least 85% of rabbits and mice. Additional 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 pre/postnatal development studies in mice, there were maternal/fetal toxicity and embryolethality which included fetal effects of hypoplasia of the testes and seminal vesicles in the male offspring, as well as pathologic changes in the nonglandular region of the stomach. The systemic exposure (AUC) of ganciclovir during these studies was approximately 2-times (pregnant mice and rabbits) and 1.7-times (pre/postnatal mice) the exposure in humans at the RHD *[see Nonclinical Toxicology (13.1)]*.

8.2 Lactation

Risk Summary

No data are available regarding the presence of ganciclovir in human milk, the effects on the breastfed infant, or the effects on milk production. When ganciclovir was administered to lactating rats, ganciclovir was present in milk *[see Data]*. Advise nursing mothers that breastfeeding is not recommended during treatment with GANZYK-RTU because of the potential for serious adverse reactions in nursing infants. Furthermore, the Centers for Disease Control and Prevention recommends that HIV-infected mothers not breastfeed their infants to avoid potential postnatal transmission of HIV *[see Warnings and Precautions (5.1, 5.3, 5.5), Nonclinical Toxicology (13.1)]*.

Data

Animal Data

Ganciclovir administered intravenously (at 0.13 mg/h) to lactating rats (on lactation day 15) resulted in passive transfer into milk. The milk-to-serum ratio for ganciclovir at steady state was 1.6 ± 0.33.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Females of reproductive potential should undergo pregnancy testing before initiation of treatment with GANZYK-RTU *[see Dosage and Administration (2.2), Use in Specific Populations (8.1)]*.

Contraception

Females

Because of the mutagenic and teratogenic potential of ganciclovir, females of reproductive potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with GANZYK-RTU *[see Warnings and Precautions (5.4), Nonclinical Toxicology (13.1)]*.

Males

Because of its mutagenic potential, males should be advised to practice barrier contraception during and for at least 90 days following, treatment with GANZYK-RTU *[see Warnings and Precautions (5.4), Nonclinical Toxicology (13.1)]*.

Infertility

GANZYK-RTU at the recommended doses may cause temporary or permanent female and male infertility *[see Warnings and Precautions (5.3), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and efficacy of GANZYK-RTU have not been established in pediatric patients.

A total of 120 pediatric patients with serious CMV infections participated in clinical trials. Granulocytopenia and thrombocytopenia were the most common adverse reactions.

The pharmacokinetic characteristics of ganciclovir after administration of intravenous ganciclovir were studied in 27 neonates (aged 2 to 49 days) and 10 pediatric patients, aged 9 months to 12 years. In neonates, the pharmacokinetic parameters after ganciclovir intravenous doses of 4 mg/kg (n=14) and 6 mg/kg (n=13) were C_{max} 5.5 ± 1.6 and 7.0 ± 1.6 mcg/mL, systemic clearance 3.14 ± 1.75 and 3.56 ± 1.27 mL/min/kg, and $t_{1/2}$ of 2.4 hours (harmonic mean) for both doses, respectively.

In pediatric patients 9 months to 12 years of age, the pharmacokinetic characteristics of ganciclovir were the same after single and multiple (every 12 hours) intravenous doses (5 mg/kg). The steady-state volume of distribution was 0.64 ± 0.22 L/kg, C_{max} was 7.9 ± 3.9 mcg/mL, systemic clearance was 4.7 ± 2.2 mL/min/kg, and $t_{1/2}$ was 2.4 ± 0.7 hours.

Although the pharmacokinetics of intravenous ganciclovir in pediatric patients were similar to those observed in adults, the safety and efficacy of ganciclovir at these exposures in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of intravenous ganciclovir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Ganciclovir is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly *[see Dosage and Administration (2.5), Warnings and Precautions (5.2), Use in Specific Populations (8.6)]*.

8.6 Renal Impairment

Dose reduction is recommended when administering GANZYK-RTU to patients with renal impairment *[see Dosage and Administration (2.5), Warnings and Precautions (5.2)]*.

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

8.7 Hepatic Impairment

The safety and efficacy of GANZYK-RTU have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

Reports of adverse reactions after overdoses with intravenous ganciclovir, some with fatal outcomes, have been received from clinical trials and during post-marketing experience. One or more of the following adverse reactions has been reported with overdoses:

Hematological toxicity: myelosuppression including pancytopenia, leukopenia, neutropenia, granulocytopenia, thrombocytopenia, bone marrow failure

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: seizures

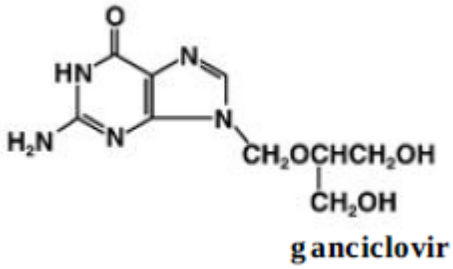
Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of GANZYK-RTU *[see Clinical Pharmacology (12.3)]*. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered in patients with cytopenias *[see Warnings and Precautions (5.1)]*.

11 DESCRIPTION

GANZYK-RTU, 500 mg is a sterile, unpreserved solution for intravenous administration. The appearance of the solution is clear and colorless. Each mL contains 2.0 mg of ganciclovir, and 8.0 mg of sodium chloride in water for injection, and may contain sodium hydroxide, and/or hydrochloric acid, as required to adjust the pH to 7.5.

Ganciclovir, an antiviral agent, is a synthetic guanine derivative, 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine. Ganciclovir is a white to off-white crystalline powder with a molecular formula of $C_9H_{13}N_5O_4$ and a molecular weight of 255.23. Ganciclovir is a polar hydrophilic compound with a solubility of 2.6 mg/mL in water at 25°C and an n-octanol/water partition coefficient of 0.022. The pK_a values for ganciclovir are 2.2 and 9.4.

The chemical structure of ganciclovir is:



ganciclovir

The plastic container is fabricated from a multilayer film designed for medical use. The solution is in contact with the inner polypropylene layer of the container. No components of the plastic container material were found to migrate into the solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ganciclovir is an antiviral drug with activity against cytomegalovirus (CMV) *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Absorption:

At the end of a 1-hour intravenous infusion of 5 mg/kg ganciclovir, total AUC ranged between 22.1 ±3.2 (n=16) and 26.8 ± 6.1 mcg·hr/mL (n=16) and C_{max} ranged between 8.27 ± 1.02 (n=16) and 9.0 ± 1.4 mcg/mL (n=16).

Distribution:

The steady-state volume of distribution of ganciclovir after intravenous administration was 0.74 ± 0.15 L/kg (n=98). Ganciclovir diffuses across the placenta. Cerebrospinal fluid concentrations obtained 0.25 to 5.67 hours post-dose in 3 patients who received 2.5 mg/kg ganciclovir intravenously every 8 hours or

every 12 hours ranged from 0.31 to 0.68 mcg/mL representing 24% to 70% of the respective plasma concentrations. Binding to plasma proteins was 1% to 2% over ganciclovir concentrations of 0.5 and 51 mcg/mL.

Elimination:

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 unchanged 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). Following intravenous administration, ganciclovir half-life was 3.5 ± 0.9 hours (n=98) with linear pharmacokinetics over the dose range of 1.6 to 5.0 mg/kg.

Specific Populations

Pharmacokinetics in Patients with Renal Impairment

The pharmacokinetics of ganciclovir following intravenous administration of ganciclovir were evaluated in 10 immunocompromised patients with renal impairment who received doses ranging from 1.25 to 5.0 mg/kg. Decreased renal function results in decreased clearance of ganciclovir (Table 7).

Table 7. Pharmacokinetics of Ganciclovir in Patients with Renal Impairment

Estimated Creatinine Clearance (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

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

Pharmacokinetics in Geriatric Patients
The pharmacokinetic profiles of intravenous ganciclovir in patients 65 years of age and older have not been established. As ganciclovir is mainly renally excreted and since renal clearance decreases with age, a decrease in ganciclovir total body clearance and a prolongation of ganciclovir half-life can be anticipated in patients 65 years of age and older *[see Dosage and Administration (2.5), Use in Specific Populations (8.5)]*.

Drug Interaction Studies
Tables 8 and 9 provide a listing of established drug interaction studies with ganciclovir. Table 8 provides the effects of coadministered drug on ganciclovir plasma pharmacokinetic parameters, whereas Table 9 provides the effects of ganciclovir on plasma pharmacokinetic parameters of coadministered drug.

Table 8. Results of Drug Interaction Studies with Ganciclovir: Effects of Coadministered Drug on Ganciclovir Pharmacokinetic Parameters

Coadministered Drug	Ganciclovir Dosage	N	Ganciclovir Pharmacokinetic (PK) Parameter
Mycophenolate mofetil (MMF) 1.5 g single dose	5 mg/kg IV single dose	12	No effect on ganciclovir PK parameters observed (patients with normal renal function)
Trimethoprim 200 mg once daily	1000 mg orally every 8 hours	12	No effect on ganciclovir PK parameters observed.
Didanosine 200 mg every 12 hours simultaneously administered with ganciclovir	5 mg/kg IV twice daily	11	No effect on ganciclovir PK parameters observed
	5 mg/kg IV once daily	11	No effect on ganciclovir PK parameters observed
Probenecid 500 mg every 6 hours	1000 mg orally every 8 hours	10	AUC ↑ 53 ± 91% (range: -14% to 299%) Ganciclovir renal clearance ↓ 22 ± 20% (range: -54% to -4%)

Table 9. Results of Drug Interaction Studies with Ganciclovir: Effects of Ganciclovir on Pharmacokinetic Parameters of Coadministered Drug

Coadministered Drug	Ganciclovir Dosage	N	Coadministered Drug Pharmacokinetic (PK) Parameter
Oral cyclosporine at therapeutic doses	5 mg/kg infused over 1 hour every 12 hours	93	In a retrospective analysis of liver allograft recipients, there was no evidence of an effect on cyclosporine whole blood concentrations.
Mycophenolate mofetil (MMF) 1.5 g single dose	5 mg/kg IV single dose	12	No PK interaction observed (patients with normal renal function)
Trimethoprim 200 mg once daily	1000 mg orally every 8 hours	12	No effect on trimethoprim PK parameters observed.
Didanosine 200 mg every 12 hours	5 mg/kg IV twice daily	11	AUC_{0-12} ↑70 ± 40% (range: 3% to 121%) C_{max} ↑49 ± 48% (range: -28% to 125%)

Didanosine 200 mg every 12 hours	5 mg/kg IV once daily	11	AUC_{0-12} ↑50 ± 26% (range: 22% to 110%) C_{max} ↑36 ± 36% (range: -27% to 94%)

12.4 Microbiology

Mechanism of Action

Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of human CMV in cell culture and *in vivo*. In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells. The virustatic activity of ganciclovir is due to inhibition of the viral DNA polymerase, pUL54, by ganciclovir triphosphate.

Antiviral Activity

The quantitative relationship between the cell culture susceptibility of human herpes viruses to antivirals and clinical response to antiviral therapy has not been established, and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit the growth of virus in cell culture by 50% (EC_{50}), vary greatly depending upon a number of factors including the assay used. Thus the median concentration of ganciclovir that inhibits CMV replication (EC_{50} value) in cell culture (laboratory strains or clinical isolates) has ranged from 0.08 to 13.6 µM (0.02 to 3.48 mcg/mL). Ganciclovir inhibits mammalian cell proliferation (CC_{50} value) in cell culture at higher concentrations ranging from 118 to 2840 µM (30 to 725 mcg/mL). Bone marrow-derived colony-forming cells are more sensitive [CC_{50} value = 0.1 to 2.7 µM (0.028 to 0.7 mcg/mL)]. The relationship between the antiviral activity in cell culture and clinical response has not been established.

Viral Resistance

Cell Culture: CMV isolates with reduced susceptibility to ganciclovir have been selected in cell culture. Growth of CMV strains in the presence of ganciclovir resulted in the selection of amino acid substitutions in the viral protein kinase pUL97 and the viral DNA polymerase pUL54.

In vivo: Viruses resistant to ganciclovir can arise after prolonged treatment or prophylaxis with ganciclovir by selection of substitutions in pUL97 and/or pUL54. Limited clinical data are available on the development of clinical resistance to ganciclovir and many pathways to resistance likely exist. In clinical isolates, seven canonical pUL97 substitutions, (M460V/I, H520Q, C592G, A594V, L595S, C603W) are the most frequently reported ganciclovir resistance-associated substitutions. These and other substitutions less frequently reported in the literature, or observed in clinical trials, are listed in Table 10.

Table 10. Summary of Resistance-associated Amino Acid Substitutions Observed in the CMV of Patients Failing Ganciclovir Treatment or Prophylaxis

pUL97	L405P, A440V, M460I/V/T/L, V466G/M, C518Y, H520Q, P521L, del 590-593, A591D/V, C592G, A594E/G/T/V/P, L595F/S/T/W, del 595, del 595-603,

	E596D/G/Y, K599E/M, del 600-601, del 597-600, del 601-603, C603W/R/S/Y, C607F/S/Y, I610T, A613V
pUL54	E315D, N408D/K/S, F412C/L/S, D413A/E/N, L501F/I, T503I, K513E/N/R, D515E, L516W, I521T, P522A/L/S, V526L, C539G, L545S/W, Q578H/L, D588E/N, G629S, S695T, I726T/V, E756K, L773V, V781I, V787L, L802M, A809V, T813S, T821I, A834P, G841A/S, D879G, A972V, del 981-982, A987G

Note: Many additional pathways to ganciclovir resistance likely exist.

CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with intravenous ganciclovir. In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced susceptibility, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.

The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

Cross-Resistance

Cross-resistance has been reported for amino acid substitutions selected in cell culture by ganciclovir, cidofovir or foscarnet. In general, amino acid substitutions in pUL54 conferring cross-resistance to ganciclovir and cidofovir are located within the exonuclease domains and region V of the viral DNA polymerase; whereas, amino acid substitutions conferring cross-resistance to foscarnet are diverse, but concentrate at and between regions II (codons 696-742) and III (codons 805-845). The amino acid substitutions that resulted in reduced susceptibility to ganciclovir and either cidofovir and/or foscarnet are summarized in Table 11.

Table 11. Summary of pUL54 Amino Acid Substitutions with Cross-Resistance between Ganciclovir, Cidofovir, and/or Foscarnet

Cross-resistant to cidofovir	D301N, N408D/K, N410K, F412C/L/S/V, D413E/N, P488R, L501I, T503I, K513E/N, L516R/W, I521T, P522S/A, V526L, C539G/R, L545S/W, Q578H, D588N, I726T/V, E756K, L773V, V812L, T813S, A834P, G841A, del 981-982, A987G
Cross-resistant to foscarnet	F412C, Q578H/L, D588N, V715A/M, E756K, L773V, V781I, V787L, L802M, A809V, V812L, T813S, T821I, A834P, G841A/S, del 981-982

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, Mutagenesis

Ganciclovir was carcinogenic in mice at the same mean drug exposure in humans as at the RHD (5 mg/kg). At the dose of 1000 mg/kg/day (1.4 times the exposure at the RHD) there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the dose of 20 mg/kg/day (0.1 times the exposure at the RHD), a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (exposure estimated as 0.01 times the RHD). Except for histiocytic sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestomach and harderian glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans.

Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations between 50 to 500 and 250 to 2000 mcg/mL, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (2.8 to 10 times the exposure at the RHD) but not at doses of 50 mg/kg (exposure approximately comparable to the RHD). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 mcg/mL.

Impairment of Fertility

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following doses of 90 mg/kg/day (exposures approximately 1.7 times the RHD). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1 times the exposure at the RHD.

14 CLINICAL STUDIES

14.1 Treatment of CMV Retinitis

In a retrospective, non-randomized, single-center analysis of 41 patients with AIDS and CMV retinitis diagnosed by ophthalmologic examination between August 1983 and April 1988, treatment with intravenous ganciclovir resulted in a delay in mean (median) time to first retinitis progression compared to untreated controls [105 (71) days from diagnosis vs. 35 (29) days from diagnosis]. Patients in this series received induction treatment of intravenous ganciclovir 5 mg/kg twice daily for 14 to 21 days followed by maintenance treatment with either 5 mg/kg once daily, 7 days per week or 6 mg/kg once daily, 5 days per week.

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

Data from trials ICM 1653, ICM 1774, and AVI034, which were performed comparing intravenous to oral ganciclovir for treatment of CMV retinitis in patients with AIDS, are shown in Table 12, and Figures 1, 2, and 3, and are discussed below.

Table 12. Population Characteristics in Studies ICM 1653, ICM 1774 and AVI 034

Demographics		ICM 1653 (n=121)	ICM 1774 (n=225)	AVI 034 (n=159)
Median age (years) Range		38 24-62	37 22-56	39 23-62
Sex	Males	116 (96%)	222 (99%)	148 (93%)
	Females	5 (4%)	3 (1%)	10 (6%)
Ethnicity	Asian	3 (3%)	5 (2%)	7 (4%)
	Black	11 (9%)	9 (4%)	3 (2%)
	Caucasian	98 (81%)	186 (83%)	140 (88%)
	Other	9 (7%)	25 (11%)	8 (5%)
Median CD_4+ cell count (cells/mm^3) Range		9.5 0-141	7.0 0-80	10.0 0-320
Mean (SD) Observation Time (days)		107.9 (43.0)	97.6 (42.5)	80.9 (47.0)

Trial ICM 1653

In this randomized, open-label, parallel group trial, conducted between March 1991 and November1992, patients with AIDS and newly diagnosed CMV retinitis received a 3-week induction course of intravenous ganciclovir, 5 mg/kg twice daily for 14 days followed by 5 mg/kg once daily for 1 additional week. Following the 21-day intravenous induction course, patients with stable CMV retinitis were randomized to receive 20 weeks of maintenance treatment with either intravenous ganciclovir, 5 mg/kg once daily, or ganciclovir capsules, 500 mg 6 times daily (3000 mg/day). The study showed that the mean [95% CI] and median [95% CI] times to progression of CMV retinitis, as assessed by masked reading of fundus photographs, were 57 days [44, 70] and 29 days [28, 43], respectively, for patients on oral therapy compared to 62 days [50, 73] and 49 days [29, 61], respectively, for patients on intravenous therapy. The difference [95% CI] in the mean time to progression between the oral and intravenous therapies (oral - IV) was -5 days [-22, 12]. See Figure 1 for comparison of the proportion of patients remaining free of progression over time.

Trial ICM 1774

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

Trial AVI 034

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

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

Figure 1. ICM 1653: Time to Progression of CMV Retinitis

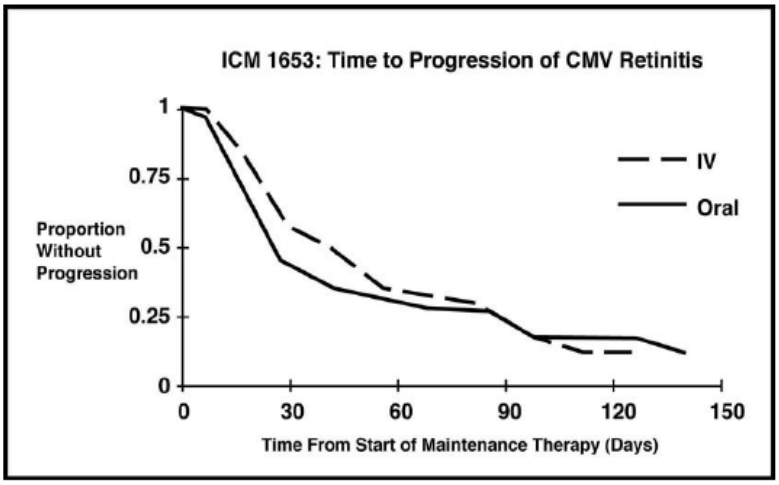


Figure 2. ICM 1774: Time to Progression of CMV Retinitis

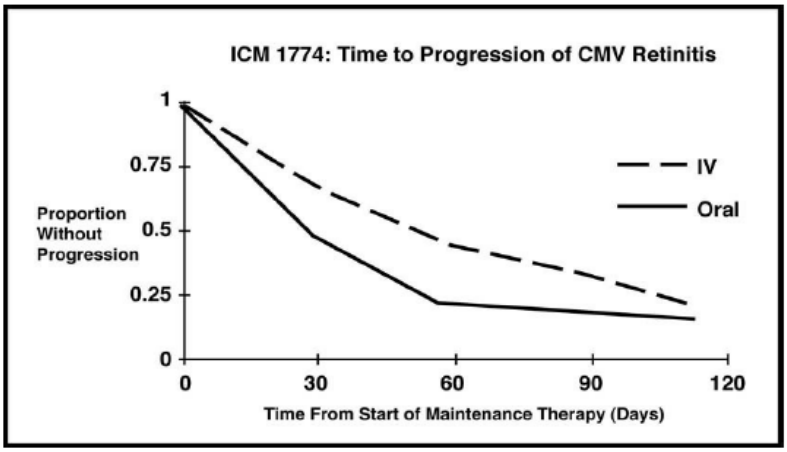
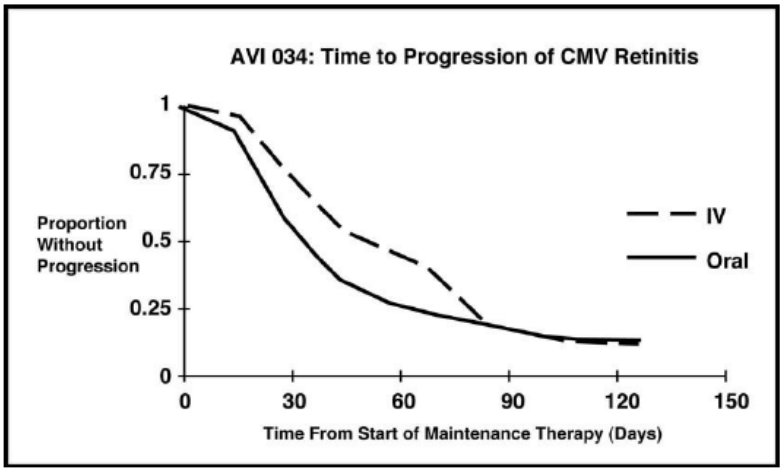


Figure 3. AVI 034: Time to Progression of CMV Retinitis



14.2 Prevention of CMV Disease in Transplant Recipients

Intravenous ganciclovir was evaluated in three randomized, controlled trials of prevention of CMV disease in organ transplant recipients.

Trial ICM 1496

In a randomized, double-blind, placebo-controlled study of 149 heart transplant recipients at risk for CMV infection (CMV seropositive or a seronegative recipient of an organ from a CMV seropositive donor), there was a reduction in the overall incidence of CMV disease in patients treated with intravenous ganciclovir. Immediately post-transplant, patients received intravenous ganciclovir 5 mg/kg twice daily for 14 days followed by 6 mg/kg once daily for 5 days/week for an additional 14 days. Twelve of the 76 (16%) patients treated with intravenous ganciclovir vs. 31 of the 73 (43%) placebo-treated patients developed CMV disease during the 120-day post-transplant observation period. No significant differences in hematologic toxicities were seen between the two treatment groups *[see Adverse Reactions (6.1)]*.

Trial ICM 1689

In a randomized, double-blind, placebo-controlled study of 72 bone marrow transplant recipients with asymptomatic CMV infection (CMV positive culture of urine, throat or blood) there was a reduction in the incidence of CMV disease in patients treated with intravenous ganciclovir following successful hematopoietic engraftment. Patients with virologic evidence of CMV infection received intravenous ganciclovir 5 mg/kg twice daily for 7 days followed by 5 mg/kg once daily through day 100 post-transplant. One of the 37 (3%) patients treated with intravenous ganciclovir vs. 15 of the 35 (43%) placebo-treated patients developed CMV disease during the study. At 6 months post-transplant, there continued to be a reduction in the incidence of CMV disease in patients treated with intravenous ganciclovir. Six of 37 (16%) patients treated with intravenous ganciclovir vs. 15 of the 35 (43%) placebo-treated patients developed disease through 6 months post-transplant. The overall rate of survival was higher in the group treated with intravenous ganciclovir, both at day 100 and day 180 post-transplant. Although the differences in hematologic toxicities were not statistically significant, the incidence of neutropenia was higher in the group treated with intravenous ganciclovir *[see Dosage and Administration (2.4), Adverse Reactions (6.1)*].

Trial ICM 1570

This was a randomized, unblinded trial which evaluated 40 allogeneic bone marrow transplant recipients at risk for CMV disease. Patients underwent bronchoscopy and bronchoalveolar lavage (BAL) on day 35 post-transplant. Patients with histologic, immunologic or virologic evidence of CMV infection in the lung were then randomized to observation or treatment with intravenous ganciclovir (5 mg/kg twice daily for 14 days followed by 5 mg/kg once daily 5 days/week until day 120). Four of 20 (20%) patients treated with intravenous ganciclovir and 14 of 20 (70%) control patients developed interstitial pneumonia. The incidence of CMV disease was lower in the group treated with intravenous ganciclovir *[see Dosage and Administration (2.4)]*.

15 REFERENCES

1. "OSHA Hazardous Drugs." *OSHA*. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*.

16 HOW SUPPLIED/STORAGE AND HANDLING

GANZYK-RTU is supplied as a sterile, unpreserved, colorless solution in a single-dose polymeric bag containing 500 mg ganciclovir in 250 mL of solution (2 mg/mL) sealed with a Twist Off port from Technoflex, and oversealed in an aluminum pouch (NDC 51754-2500-1). Follow guidelines for handling and disposal for cytotoxic drugs.[1]

The premix flexible plastic container bag contains no preservative; any unused portion should be discarded *[see Dosage and Administration (2.6)]*.

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Hematologic Toxicity
Inform patients of the potential for hematologic toxicity associated with the use of GANZYK-RTU including granulocytopenia (neutropenia), anemia and thrombocytopenia. Inform patients that their blood counts will be closely monitored while on therapy *[see Warnings and Precautions (5.1)]*.

Impairment of Renal Function
Inform patients that ganciclovir has been associated with decreased renal function and that serum creatinine or creatinine clearance will be monitored carefully to allow for dosage adjustment in patients with renal impairment *[see Dosage and Administration (2.5), Warnings and Precautions (5.2)]*.

Impairment of Fertility
Inform patients that ganciclovir has caused decreased fertility in animals and may cause temporary or permanent infertility in humans *[see Warnings and Precautions (5.3), Use in Specific Populations (8.3)]*.

Pregnancy and Contraception
Inform women of childbearing potential that ganciclovir causes birth defects in animals. Advise female patients to use effective contraception during treatment and for at least 30 days following treatment with GANZYK-RTU. Similarly, advise men to practice barrier contraception during and for at least 90 days

following treatment with GANZYK-RTU *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Carcinogenicity

Inform patients that ganciclovir causes tumors in animals. Although there is no information from human studies, ganciclovir should be considered a potential carcinogen *[see Warnings and Precautions (5.5)]*.

Drug Interactions

Inform patients that GANZYK-RTU may interact with other drugs. Advise patients to report to their healthcare provider the use of any other medication *[see Drug Interactions (7)]*.

Impairment of Cognitive Ability

Based on the adverse reaction profile, ganciclovir may affect cognitive abilities including on the ability to drive and operate machinery as seizures, dizziness, and/or confusion have been reported with the use of ganciclovir *[see Adverse Reaction (6.1)]*.

Ophthalmological Examination in Patients with CMV Retinitis

Inform patients that GANZYK-RTU is not a cure for CMV retinitis, and they may continue to experience progression of retinitis during or following treatment. Advise patients to have frequent ophthalmological examinations while being treated with GANZYK-RTU to monitor disease status and for other retinal abnormalities. More frequent ophthalmological follow-up may be needed in some cases *[see Dosage and Administration (2.2), Adverse Reactions (6.1)]*.

Lactation

Advise nursing mothers that breastfeeding is not recommended during treatment with GANZYK-RTU because of the potential for serious adverse reactions in nursing infants and because HIV can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)]*.

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EXELA
PHARMA SCIENCES

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