GANCICLOVIR- ganciclovir sodium injection, powder, lyophilized, for solution
Hikma Pharmaceuticals USA Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GANCICLOVIR FOR INJECTION safely and effectively. See full prescribing information for GANCICLOVIR FOR INJECTION.

GANCICLOVIR for injection, for intravenous use
Initial U.S. Approval: 1989

WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS

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 and limited human data, ganciclovir may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females. (5.3)**
- **Fetal Toxicity: Based on animal data, ganciclovir has the potential to cause birth defects in humans. (5.4)**
- **Mutagenesis and Carcinogenesis: Based on animal data, ganciclovir has the potential to cause cancer in humans. (5.5)**

INDICATIONS AND USAGE

Ganciclovir for Injection, USP is a deoxynucleoside analogue cytomegalovirus (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

- Ganciclovir for injection is administered only intravenously. (2.1)

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, 7 days per week, or 6 mg/kg once daily, 5 days per week until 100 to 120 days post-transplantation.

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

DOSAGE FORMS AND STRENGTHS

- For injection: 500 mg of ganciclovir as lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

- Hypersensitivity to ganciclovir or valganciclovir. (4)

WARNINGS AND PRECAUTIONS

- Renal Impairment: Increased serum creatinine levels have been observed with the use of ganciclovir, particularly in elderly patients and transplant recipients receiving concomitant nephrotoxic drugs. Monitor renal function during therapy with ganciclovir, 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 Hikma Pharmaceuticals USA Inc. at 1-877-845-0689, 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 ganciclovir (8.2)

See 17 for PATIENT COUNSELING INFORMATION.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

BOXED WARNING
1 INDICATIONS AND USAGE
1.1 Treatment of CMV Retinitis
1.2 Prevention of CMV Disease in Transplant Recipients
2 DOSAGE AND ADMINISTRATION
2.1 Important Dosing and Administration Information
2.2 Testing Before and During Treatment
2.3 Recommended Dosage for Treatment of CMV Retinitis in Adult Patients with Normal Renal Function
2.4 Recommended Dosage for the Prevention of CMV Disease in Adult Transplant Recipients with Normal Renal Function
2.5 Recommended Dosage in Adult Patients with Renal Impairment
2.6 Preparation of Ganciclovir for Injection
2.7 Handling and Disposal
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hematologic Toxicity

5.2 Renal Impairment
5.3 Impairment of Fertility
5.4 Fetal Toxicity
5.5 Mutagenesis and Carcinogenesis
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience in Adult Patients
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility
14 CLINICAL STUDIES
14.1 Treatment of CMV Retinitis
14.2 Prevention of CMV Disease in Transplant Recipients
15 REFERENCES
16 HOW SUPPLIED
17 PATIENT COUNSELING INFORMATION
* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

BOXED WARNING

WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS

- **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 and limited human data, ganciclovir 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, ganciclovir has the potential to cause birth defects in humans *[see Warnings and Precautions (5.4)].***
- **Mutagenesis and Carcinogenesis: Based on animal data, ganciclovir has the potential to cause cancers in humans *[see Warnings and Precautions (5.5)].***

1 INDICATIONS AND USAGE

1.1 Treatment of CMV Retinitis

Ganciclovir for Injection, USP 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

Ganciclovir for Injection, USP 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

- To avoid phlebitis/pain at the infusion site, ganciclovir for injection must only be administered by intravenous infusion over 1 hour, preferably via plastic cannula, into a vein with adequate blood flow to permit rapid dilution and distribution.
- Do not administer ganciclovir for injection by rapid or bolus intravenous injection which may increase toxicity as a result of excessive plasma levels.
- The recommended dosage and infusion rate for ganciclovir should not be exceeded.
- Do not administer the reconstituted ganciclovir for injection solution intramuscularly or subcutaneously because it may result in severe tissue irritation due to high pH *[see Description (11)].*
- Administration of ganciclovir for injection should be accompanied by adequate hydration.

- 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 treatment with ganciclovir *[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 ganciclovir and dose 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 ganciclovir solution 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 ganciclovir 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 ganciclovir 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 the Prevention of CMV Disease in Adult Transplant Recipients with Normal Renal Function

Induction Dosage: The recommended initial dosage of ganciclovir 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 ganciclovir 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 impairment of renal function, refer to Table 1 for recommended doses of ganciclovir for induction and maintenance dosage for treatment of CMV retinitis and prevention of CMV disease in transplant recipients. Carefully monitor serum creatinine or creatinine clearance before and 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)	Ganciclovir Induction Dose (mg/kg)	Dosing Interval (hours) for Induction	Ganciclovir Maintenance Dose (mg/kg)	Dosing Interval (hours) for Maintenance
Greater than or equal to 70	5	12	5	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
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.

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 ganciclovir in patients undergoing hemodialysis should not exceed 1.25 mg/kg 3 times per week; and maintenance dosing should not exceed 0.625 mg/kg 3 times per week following each hemodialysis session. Ganciclovir 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 Preparation of Ganciclovir for Injection

Ganciclovir for injection must be reconstituted and diluted under the supervision of a healthcare provider and administered as intravenous infusion. Each 10 mL clear glass vial contains 543 mg ganciclovir sodium equivalent to 500 mg of ganciclovir. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the vial and the table after reconstitution. The contents of the vial should be prepared for administration in the following manner:

1. Reconstitution Instructions:
    1. Reconstitute lyophilized ganciclovir for injection by injecting 10 mL of Sterile Water for Injection, USP, into the vial. Do not use bacteriostatic water for injection containing parabens. It is incompatible with ganciclovir for injection and may cause precipitation.
    2. Gently swirl the vial in order to ensure complete wetting of the product. Continue swirling until a clear reconstituted solution is obtained.
    3. Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion. Discard the vial if particulate matter or discoloration is observed.

4. Reconstituted solution in the vial is stable at room temperature (25° C (77° F) for 12 hours. Do not refrigerate or freeze. Discard any unused portion of the reconstituted solution.

2. Infusion Instructions:
    1. Based on patient weight, the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) should be removed from the vial and added to an acceptable infusion fluid (typically 100 mL) for delivery over the course of 1 hour. Infusion concentrations greater than 10 mg/mL are not recommended. The following infusion fluids have been determined to be chemically and physically compatible with ganciclovir for injection solution: 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection and Lactated Ringer's Injection, USP.
    2. Ganciclovir for injection, when reconstituted with Sterile Water for Injection (non-bacteriostatic) and further diluted with 0.9% sodium chloride injection or other acceptable infusion fluid as specified above, should be used within 24 hours of dilution to reduce the risk of bacterial contamination. The diluted infusion solution should be refrigerated (2° to 8°C (36° to 46°F). Do not freeze.

2.7 Handling and Disposal

Caution should be exercised in the handling and preparation of solutions of ganciclovir. Solutions of ganciclovir are alkaline (pH 11). Avoid direct contact of the skin or mucous membranes with ganciclovir solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Wearing disposable gloves is recommended.

Because ganciclovir shares some of the properties of antitumor agents (i.e., carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs[1]*[see How Supplied/Storage and Handling (16)].*

3 DOSAGE FORMS AND STRENGTHS

For injection: Single dose vial containing 500 mg of ganciclovir as a sterile lyophilized white to off-white powder for reconstitution with 10 mL of preservative-free Sterile Water for Injection, USP for intravenous use. The concentration of ganciclovir in the reconstituted solution is 50 mg/mL *[see Dosage and Administration (2.6)].*

4 CONTRAINDICATIONS

Ganciclovir for injection 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)]*.

Ganciclovir is not recommended if the absolute neutrophil count is less than 500 cells/mL, hemoglobin is less than 8 g/dL, or the platelet count is less than 25,000 cells/mL. Ganciclovir should also be used with caution in patients with pre-existing cytopenias and in patients receiving myelosuppressive drugs or irradiation. Granulocytopenia (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 solution for treatment of CMV retinitis.

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving ganciclovir *[see Adverse Reactions (6.1)]*, 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/mL at the beginning of treatment *[see Dosage and Administration (2.2)]*.

5.2 Renal Impairment

Ganciclovir should be used with caution in patients with impaired renal function because the half-life and plasma/serum concentrations of ganciclovir will be increased due to reduced renal clearance. If renal function is impaired, dosage adjustments are recommended *[see Dosage and Administration (2.5), Use in Specific Populations (8.5, 8.6)]*.

Increased serum creatinine levels have been reported in elderly patients and in transplant recipients receiving concomitant nephrotoxic medications (i.e., cyclosporine and amphotericin B). Monitoring renal function during therapy with ganciclovir 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 and limited human data, ganciclovir 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 the use of ganciclovir *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)].*

5.4 Fetal Toxicity

Ganciclovir 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 ganciclovir. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir *[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. Ganciclovir should therefore be considered a potential carcinogen in humans *[see Dosage and Administration (2.7), Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

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

- Hematologic Toxicity *[see Warnings and Precautions (5.1)]*
- Renal Impairment *[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 Trial 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 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 ganciclovir for injection are summarized below, according to the participating study patient population.

Adverse Reactions in Patients with CMV Retinitis: Three controlled, randomized, phase 3 trials comparing ganciclovir for injection and ganciclovir capsules for maintenance treatment of CMV retinitis have been completed. During these trials, ganciclovir for injection or ganciclovir capsules were prematurely discontinued in 9% of subjects 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 (14.1)]*.

Table 2. Pooled Selected Adverse Reactions Reported in ³ 5% of Subjects Comparing Ganciclovir for Injection to Ganciclovir Capsules for Maintenance Treatment of CMV Retinitis

Adverse Reaction	**Maintenance Treatment Studies**	
	Ganciclovir for Injection (n=179)	**Ganciclovir Capsules (n=326)**
Pyrexia		
Diarrhea		
Leukopenia	48%	38%
Anemia	44%	41%
Total catheter	41%	29%

events	25%	19%
Catheter infection	22%	6%
Catheter sepsis	9%	4%
Other catheter related events	8%	1%
Sepsis	5%	1%
Decreased appetite	15%	4%
Vomiting	14%	15%
Infection	13%	13%
Hyperhidrosis	13%	9%
Chills	12%	11%
Neuropathy peripheral	10%	7%
Thrombocytopenia	9%	8%
Pruritus	6%	6%
	5%	6%

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

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

	CMV Retinitis Treatment*	
Laboratory Abnormalities	**Ganciclovir for Injection † 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 to <749	14%	17%
750 to <1000	26%	19%
Anemia with Hemoglobin (g/dL):		
<6.5 g/dL	5%	2%
6.5 to <8	16%	10%
8.0 to <9.5	26%	25%
Serum Creatinine (mg/dL):		
³2.5	2%	1%
³1.5 to <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 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 (14.2)]*.

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

	Ganciclovir			
	Heart Allograft*		**Bone Marrow Allograft†**	
	Ganciclovir (n=76)	Placebo (n=73)	Ganciclovir (n=57)	Control (n=55)
Neutropenia				
Absolute Neutrophil Count (ANC) per mL <500 500 to 1000	 4% 3%	 3% 8%	 12% 29%	 6% 17%
Total ANC £1000/mL	7%	11%	41%	23%
Thrombocytopenia				
Platelet count per mL <25,000 25,000 to 50,000	 3% 5%	 1% 3%	 32% 25%	 28% 37%
Total Platelet Count £50,000/mL	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 Ganciclovir or Placebo

Serum	**Heart Allograft ICM 1496**		**Bone Marrow Allograft ICM 1570**		**Bone Marrow Allograft ICM 1689**	
Creatinine Levels (mg/dL)	Ganciclovir (n=76)	Placebo (n=73)	Ganciclovir (n=20)	Control (n=20)	Ganciclovir (n=37)	Placebo (n=35)
≥2.5						

≥2.5 mg/dL	18%	4%	20%	0%	0%	0%
≥1.5 to <2.5	58%	69%	50%	35%	43%	44%

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

Adverse drug reactions with ganciclovir for injection or ganciclovir capsules in controlled clinical studies 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: arrhythmia

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 infection, 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, seizure, 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 ganciclovir for injection 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 ganciclovir 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 ganciclovir is coadministered 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 ganciclovir 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	Ganciclovir 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 in at least one case report in a pregnant woman, no adequate human data are available to establish whether ganciclovir poses a risk to pregnancy outcomes. The background risk of major birth defects and miscarriage for the indicated populations 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 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

Most maternal CMV infections are asymptomatic or they may be associated with a self-limited mononucleosis-like syndrome. However, in immunocompromised patients (i.e., transplant patients or patients with AIDS), CMV infections may be symptomatic and may result in significant maternal morbidity and mortality. The transmission of CMV to the fetus is a result of maternal viremia and transplacental infection. Perinatal infection can also occur from exposure of the neonate to CMV shedding in the genital tract. 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 morbidity, including mental retardation, sensorineural hearing loss, microcephaly, seizures, and other medical problems. The risk of congenital CMV infection resulting from primary maternal CMV infection may be higher and of greater severity than that resulting from maternal 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 ganciclovir

because of the potential for serious adverse reactions in nursing infants *[see Warnings and Precautions (5.1, 5.3, 5.4, 5.5), Nonclinical toxicology (13.1)]*. Furthermore, the Centers for Disease Control and Prevention recommends that HIV-infected mothers not breastfeed their infants to avoid potential postnatal transmission of HIV.

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 ganciclovir *[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 ganciclovir for injection *[see Dosage and Administration (2.2), 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 ganciclovir *[see Warnings and Precautions (5.4), Nonclinical Toxicology (13.1)].*

Infertility

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

Data

Human Data

In a small, open-label, non-randomized clinical study, adult male renal transplant patients receiving valganciclovir (the prodrug of ganciclovir) for CMV prophylaxis for up to 200 days post-transplantation were compared to an untreated control group. Patients were followed-up for six months after valganciclovir discontinuation. Among 24 evaluable patients in the valganciclovir group, the mean sperm density at the end of treatment visit decreased by 11 million/mL from baseline, whereas, among 14 evaluable patients in the control group the mean sperm density increased by 33 million/mL. However, at the follow-up visit among 20 evaluable patients in the valganciclovir group, the mean sperm density was comparable to that observed among 10 evaluable patients in the untreated control group (the mean sperm density at the end of follow-up visit increased by 41 million/mL from baseline in the valganciclovir group and by 43 million/mL in the untreated group).

8.4 Pediatric Use

Safety and efficacy of ganciclovir for injection 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 ganciclovir for injection 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 ± 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 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 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 renal clearance decreases with age, ganciclovir should be administered to elderly patients with special consideration of their renal status. 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 ganciclovir to patients with renal impairment *[see Dosage and Administration (2.5), Warnings and Precautions (5.2)]*.

8.7 Hepatic Impairment

The safety and efficacy of ganciclovir have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

Reports of adverse reactions after overdoses with ganciclovir, some with fatal outcomes, have been received from clinical trials and during postmarketing 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 kidney injury, elevated creatinine

Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting

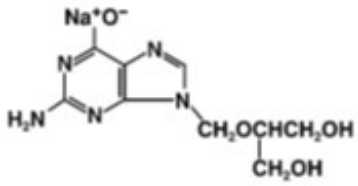
Neurotoxicity: seizure

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of ganciclovir *[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

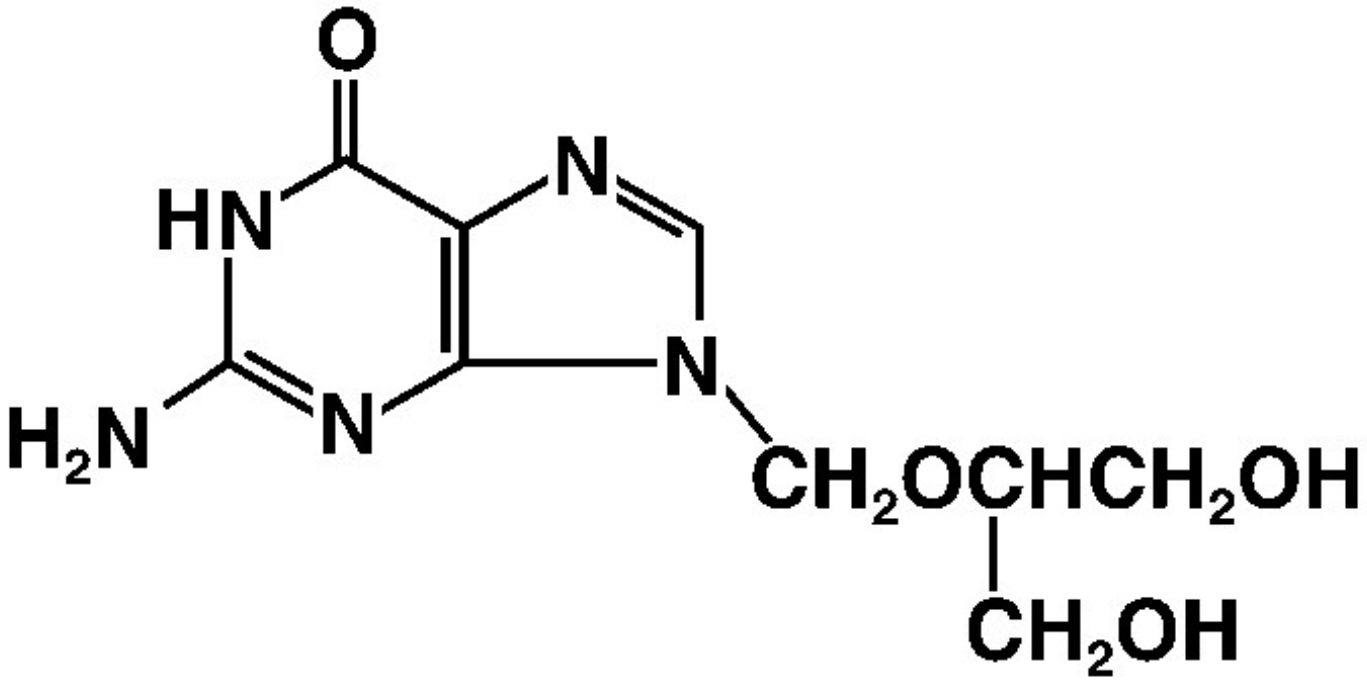
Ganciclovir for Injection, USP contains ganciclovir, in the form of the sodium salt for intravenous injection. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).

Chemically, ganciclovir is 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine and ganciclovir sodium is 9-[[2 hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine, monosodium salt. The chemical structures of ganciclovir sodium and ganciclovir are:



Ganciclovir Sodium Structural Formula

ganciclovir sodium
$C_9H_{12}N_5NaO_4$, M.W. =277.22



Ganciclovir Structural Formula

ganciclovir
$C_9H_{13}N_5O_4$
M.W. =255.23

Ganciclovir is a white to off-white crystalline powder. 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 pKas for ganciclovir are 2.2 and 9.4.

Ganciclovir, formulated as monosodium salt, using sodium hydroxide as a salt forming agent, is a sterile white to off-white lyophilized powder. The lyophilized powder has an aqueous solubility of greater than 50 mg/mL at 25°C. At physiological pH, ganciclovir sodium exists as the un-ionized form with a solubility of approximately 6 mg/mL at 37°C.

Each vial contains 543 mg ganciclovir sodium equivalent to 500 mg ganciclovir.

Inactive ingredients may include hydrochloric acid (QS) and sodium hydroxide (QS) added to adjust the pH.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ganciclovir is an antiviral drug with activity against 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 ± 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

When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6 to 5 mg/kg. 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). Half-life was 3.5 ± 0.9 hours (n=98) following intravenous administration.

Specific Populations

Pharmacokinetics in Patients with Renal Impairment

The pharmacokinetics following intravenous administration of ganciclovir for injection solution were evaluated in 10 immunocompromised patients with renal impairment who received doses ranging from 1.25 to 5 mg/kg. Decreased renal function results in decreased clearance of ganciclovir (Table 7).

Table 7. Ganciclovir Pharmacokinetics in Patients with Renal Impairment

Estimated Creatinine Clearance (mL/min)	**n**	**Dose**	**Clearance (mL/min) Mean ± SD**	**Half-life (hours) Mean ± SD**
50 to 79	4	3.2 to 5 mg/kg	128 ± 63	4.6 ± 1.4
25 to 49	3	3 to 5 mg/kg	57 ± 8	4.4 ± 0.4
<25	3	1.25 to 5 mg/kg	30 ± 13	10.7 ± 5.7

Plasma concentrations of ganciclovir are reduced by about 50% during a 4 hour hemodialysis session**.**

Pharmacokinetics in Geriatric Patients

The pharmacokinetic profiles of 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 Table 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	AUC0-12 70 ± 40% (range: 3% to 121%) Cmax49 ± 48% (range: -28% to 125%)
Didanosine 200 mg every 12 hours	5 mg/kg IV once daily	11	AUC0-12 50 ± 26% (range: 22% to 110%) Cmax 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 (CC50 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 [CC50 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 597600, 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 981982, 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 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 sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.

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

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 to 742) and III (codons 805 to 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 and Mutagenesis and 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 mg/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 mg/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 ganciclovir for injection solution 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 ganciclovir for injection 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 study conducted between February 1989 and December 1990, immediate treatment with 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 AVI 034, which were performed comparing ganciclovir for injection 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 to 62	37 22 to 56	39 23 to 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 CD4 Count Range		9.5 0 to 141	7 0 to 80	10 0 to 320
Mean (SD) Observation Time (days)		107.9 (43)	97.6 (42.5)	80.9 (47)

Trial ICM 1653: In this randomized, open-label, parallel group trial, conducted between March 1991 and November 1992, patients with AIDS and newly diagnosed CMV retinitis received a 3-week induction course of ganciclovir for injection solution, 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 ganciclovir for injection solution, 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 ganciclovir for injection solution were randomized to receive maintenance treatment with ganciclovir for injection solution, 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 ganciclovir for injection, 5 mg/kg twice daily, were randomized to receive 20 weeks of maintenance treatment with either ganciclovir capsules, 500 mg 6 times daily or ganciclovir for injection solution, 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 IV 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 Trial ICM 1653: Time to Progression of CMV Retinitis

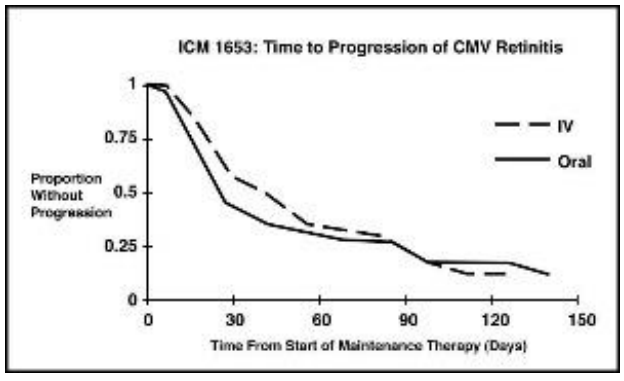


Figure 1

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

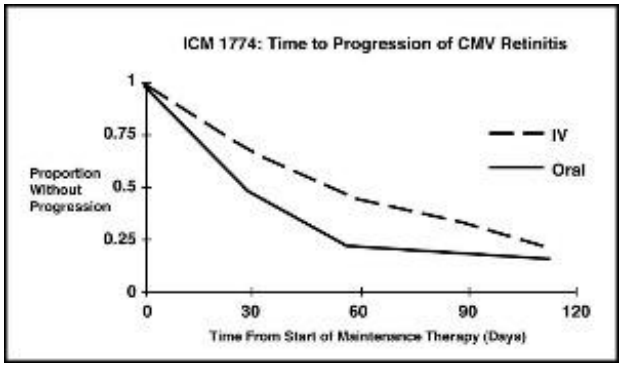


Figure 2

Figure 3 Trial AVI 034: Time to Progression of Retinitis

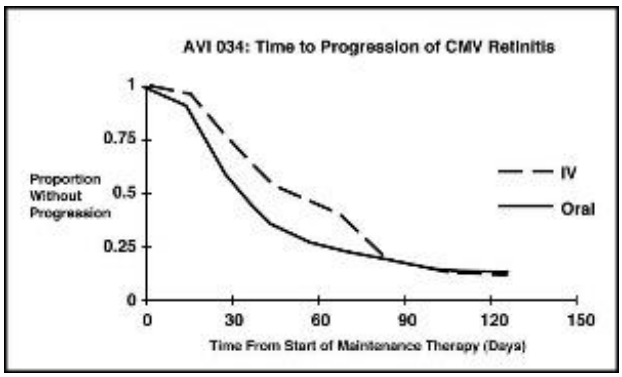


Figure 3

14.2 Prevention of CMV Disease in Transplant Recipients

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 ganciclovir. Immediately post-transplant, patients received ganciclovir for injection solution 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 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 ganciclovir following successful hematopoietic engraftment. Patients with virologic evidence of CMV infection received ganciclovir for injection solution 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 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 ganciclovir. Six of 37 (16%) patients treated with 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 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 ganciclovir *[*see *Adverse Reactions (6.1)]*.

Trial ICM 1570: This was a randomized, unblinded study 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 ganciclovir for injection solution (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 ganciclovir and 14 of 20 (70%) control patients developed interstitial pneumonia. The incidence of CMV disease was lower in the group treated with ganciclovir, consistent with the results observed in ICM 1689.

15 REFERENCES

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

16 HOW SUPPLIED

How Supplied

Ganciclovir for Injection, USP is supplied in 10 mL sterile single-dose vials, each containing 543 mg ganciclovir sodium equivalent to 500 mg of ganciclovir as a white to off-white powder. The concentration of ganciclovir in the reconstituted solution is 50 mg/mL. Because ganciclovir shares some of the properties of antitumor agents (i.e., carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. Ganciclovir for Injection, USP is supplied in cartons of 10 single-dose vials (NDC 0143-9299-10).

Storage

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Store reconstituted solution in the vial at 25°C (77°F) for no longer than 12 hours. Do not refrigerate or freeze. Discard any unused portion of the reconstituted solution.

Store diluted infusion solution under refrigeration at 2° to 8°C (36° to 46°F) for no longer than 24 hours. Do not freeze.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For Product Inquiry call 1-877-845-0689.

17 PATIENT COUNSELING INFORMATION

Hematologic Toxicity

Inform patients that ganciclovir may cause hematologic toxicity, including granulocytopenia (neutropenia), anemia, and thrombocytopenia. Inform patients that their blood counts and platelet counts should be closely monitored while on treatment *[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 should be monitored while on treatment to allow for dosage adjustment in patients with renal impairment *[see Warnings and Precautions (5.2)].*

Impairment of Fertility

Inform patients that ganciclovir may cause temporary or permanent infertility in humans *[see Warnings and Precautions (5.3), Use in Specific Populations (8.3)]*.

Pregnancy and Contraception

Advise female patients to use effective contraception during and for at least 30 days following treatment with ganciclovir. Similarly, advise men to practice barrier contraception during and for at least 90 days following treatment with ganciclovir *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Carcinogenicity

Inform patients that ganciclovir should be considered a potential carcinogen *[see Warnings and Precautions (5.5)]*.

Drug Interactions

Inform patients that ganciclovir 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 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 ganciclovir 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 follow-up examinations while being treated with ganciclovir. Some patients may require more frequent ophthalmological follow-up *[see Dosage and Administration (2.2), Adverse Reactions (6.1)].*

Lactation

Advise nursing mothers not to breastfeed if they are receiving ganciclovir because of the potential for serious adverse events in nursing infants and because HIV can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)].*

Manufactured by

THYMOORGAN PHARMAZIE GmbH,

Schiffgraben 23, 38690 Goslar, Germany

Distributed by

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07992

Revised February 2021

127.207.032/01

VIAL LABEL

Ganciclovir for Injection, USP 500 mg per vial Container Label

NDC 0143-**9299**-01 Rx only

Ganciclovir for Injection, USP

500 mg/vial

For Intravenous Infusion ONLY

Handle this drug product with great care because it is a potent cytotoxic agent and suspected carcinogen.

CARTON LABEL

Ganciclovir for Injection, USP 500 mg per vial Carton Labeling

NDC 0143-**9299**-10

10 Single-Dose Vials

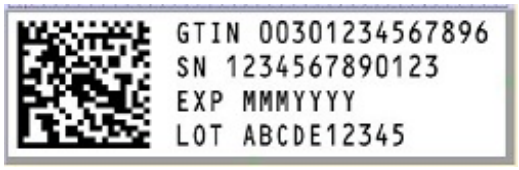
Ganciclovir for Injection, USP

500 mg/vial

For Intravenous Infusion ONLY

Handle this drug product with great care because it is a potent cytotoxic agent and suspected carcinogen.

SERIALIZATION IMAGE



Representative Serialization Image

GANCICLOVIR

ganciclovir sodium injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-9299
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
GANCICLOVIR SODIUM (UNII: 02L083W284) (GANCICLOVIR - UNII:P9G3CKZ4P5)	GANCICLOVIR	50 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0143-9299-10	10 in 1 BOX	06/17/2021	
1	NDC:0143-9299-01	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076222	06/17/2021	

Labeler - Hikma Pharmaceuticals USA Inc. (001230762)

Revised: 2/2021 Hikma Pharmaceuticals USA Inc.