

PRODUCT MONOGRAPH,  
INCLUDING PATIENT MEDICATION INFORMATION

Mar-Cidofovir

Cidofovir for Injection, USP

75 mg / mL cidofovir (as cidofovir dihydrate);

375 mg cidofovir (as cidofovir dihydrate) / vial  
USP standard

Antiviral Agent

Marcen Pharmaceuticals Inc.  
77 Auriga Drive, Unit #4  
Ottawa, Ontario K2E 7Z7

Date of Revision:  
March 13, 2018

Submission Control No. 200865

## TABLE OF CONTENTS

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
<b>1 INDICATIONS .....</b>	<b>3</b>
1.1 Pediatrics.....	3
1.2 Geriatrics.....	3
<b>2 CONTRAINDICATIONS .....</b>	<b>3</b>
<b>3 SERIOUS WARNINGS AND PRECAUTIONS BOX .....</b>	<b>4</b>
<b>4 DOSAGE AND ADMINISTRATION .....</b>	<b>4</b>
4.1 Dosing Considerations .....	4
4.2 Recommended Dose and Dosage Adjustment .....	5
4.3 Administration .....	6
<b>5 OVERDOSAGE .....</b>	<b>6</b>
<b>6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.....</b>	<b>7</b>
<b>7 WARNINGS AND PRECAUTIONS .....</b>	<b>7</b>
7.1 Special Populations.....	9
7.1.1 Pregnant Women.....	9
7.1.2 Breast-feeding .....	9
7.1.3 Pediatrics .....	9
7.1.4 Geriatrics .....	9
<b>8 ADVERSE REACTIONS.....</b>	<b>9</b>
8.1 Adverse Reaction Overview.....	9
8.2 Clinical Trial Adverse Reactions .....	10
8.3 Less Common Clinical Trial Adverse Reactions .....	11
<b>9 DRUG INTERACTIONS.....</b>	<b>13</b>
9.1 Overview .....	13
9.2 Drug-Drug Interactions .....	13
<b>10 ACTION AND CLINICAL PHARMACOLOGY .....</b>	<b>14</b>
10.1 Mechanism of Action .....	14
10.2 Pharmacodynamics.....	14
10.3 Pharmacokinetics .....	14
<b>11 STORAGE, STABILITY AND DISPOSAL .....</b>	<b>15</b>
<b>12 SPECIAL HANDLING INSTRUCTIONS.....</b>	<b>16</b>
<b>PART II: SCIENTIFIC INFORMATION .....</b>	<b>167</b>
<b>13 PHARMACEUTICAL INFORMATION.....</b>	<b>17</b>
<b>14 CLINICAL TRIALS.....</b>	<b>18</b>
<b>15 MICROBIOLOGY.....</b>	<b>21</b>
<b>16 NON-CLINICAL TOXICOLOGY .....</b>	<b>22</b>
<b>PATIENT MEDICATION INFORMATION .....</b>	<b>24</b>

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

Mar-Cidofovir is indicated for the treatment of cytomegalovirus (CMV) retinitis in adult patients having acquired immunodeficiency syndrome (AIDS).

#### 1.1 Pediatrics

**Pediatrics (< 18 years of age):** The safety and efficacy of Mar-Cidofovir has not been established in these patients. Use is not recommended in pediatric patients.

#### 1.2 Geriatrics

**Geriatrics (> 60 years of age):** The safety and efficacy of Mar-Cidofovir has not been established in these patients. Since elderly patients frequently have reduced glomerular function, particular attention should be paid to assessing renal function before and during administration of Mar-Cidofovir.

### 2 CONTRAINDICATIONS

Mar-Cidofovir is contraindicated in patients with renal impairment having a creatinine clearance  $\leq 55$  mL/min, or having proteinuria  $\geq 2+$  proteinuria ( $\geq 100$  mg/dL).

Mar-Cidofovir must be used concomitantly with probenecid to diminish its nephrotoxic effects. Patients must be well hydrated during Mar-Cidofovir administration (see DOSAGE AND ADMINISTRATION).

Mar-Cidofovir is contraindicated in patients unable to receive probenecid because of clinically significant hypersensitivity to the drug or to other sulpha-containing medications.

Concomitant administration of Mar-Cidofovir with potentially nephrotoxic agents is contraindicated. Patients must discontinue such agents at least 7 days before starting treatment with Mar-Cidofovir (see SERIOUS WARNINGS AND PRECAUTIONS BOX).

Direct intraocular injection of Mar-Cidofovir is contraindicated. Direct injection may be associated with significant decreases in intraocular pressure and impairment of vision.

Mar-Cidofovir is contraindicated in patients who are hypersensitive to cidofovir or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

### 3 **SERIOUS WARNINGS AND PRECAUTIONS BOX**

#### **Serious Warnings and Precautions**

- Renal impairment is the major toxicity of Mar-Cidofovir.
- Cases of acute renal failure resulting in need for dialysis and/or contributing to death have occurred with as few as one or two doses of cidofovir. To reduce possible nephrotoxicity, intravenous pre-hydration with normal saline and administration of probenecid must be used with each Mar-Cidofovir infusion.
- Renal function (serum creatinine and urine protein) must be determined within 48 hours prior to administration of every dose of Mar-Cidofovir. The dose of Mar-Cidofovir to be given should be modified for changes in renal function, as appropriate (see DOSAGE AND ADMINISTRATION).
- Mar-Cidofovir is contraindicated in patients who are receiving other nephrotoxic agents.
- Neutropenia has been observed in association with cidofovir treatment. Therefore, neutrophil counts should be monitored during Mar-Cidofovir therapy.
- Mar-Cidofovir is indicated only for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS).
- In animal studies, cidofovir was carcinogenic, teratogenic and caused hypospermia (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis, and Sexual Health/Reproduction).

### 4 **DOSAGE AND ADMINISTRATION**

#### 4.1 **Dosing Considerations**

**Before each administration of Mar-Cidofovir, serum creatinine and urine protein levels must be determined to confirm adequate renal function.**

**The recommended dosage, frequency, or infusion rate of Mar-Cidofovir must not be exceeded.**

**Mar-Cidofovir must be diluted in 100 ml 0.9% (normal) saline prior to administration.**

**To minimise potential nephrotoxicity, oral probenecid and intravenous saline prehydration must be administered with each Mar-Cidofovir infusion (see 4.2 Recommended Dose and Dosage Adjustment).**

Mar-Cidofovir is indicated for use in adults only.

#### 4.2 Recommended Dose and Dosage Adjustment

The recommended induction dose of Mar-Cidofovir for adult patients having a creatinine clearance > 55 mL/min, without ≥ 2+ proteinuria (≥ 100 mg/dL), is 5 mg/kg of cidofovir, given as an intravenous infusion at a constant rate over 1 hour, to be administered once weekly for two consecutive weeks (see Table 1).

**Table 1** Mar-Cidofovir (cidofovir) dosing recommendations

Treatment	Dosage	Frequency	Administration
Induction Regimen	5 mg/kg	Given once weekly for two weeks	Constant intravenous infusion over 1 hour
Maintenance Regimen	3-5 mg/kg, depending on renal function	Given once every two weeks	Constant intravenous infusion over 1 hour

Because serum creatinine in patients with AIDS and CMV retinitis may not provide an accurate representation of the patient's underlying renal status, it is recommended that renal function be assessed by calculating estimated creatinine clearance (eCrCl) using the Cockcroft-Gault formula, as follows:

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

$$\text{Creatinine clearance for females} = \frac{[140 - \text{age (years)}] \times [\text{body wt (kg)}] \times 0.85}{72 \times [\text{serum creatinine (mg/dL)}]}$$

Starting two weeks after completion of induction treatment, the recommended maintenance dose of Mar-Cidofovir is 5 mg/kg of cidofovir once every two weeks, given as an intravenous infusion at a constant rate over 1 hour.

**Probenecid:** Probenecid must be given orally with each dose of Mar-Cidofovir. Administer 2 grams probenecid 3 hours before each Mar-Cidofovir infusion. Administer an additional 1 gram at 2 hours and 1 gram at 8 hours after completion of the 1-hour Mar-Cidofovir infusion, for a total of 4 grams. Based on experience in clinical trials, ingestion of food prior to each dose of probenecid may reduce drug-related nausea and vomiting. The use of an antiemetic may also be necessary. In patients who develop allergic or hypersensitivity symptoms to probenecid, e.g., rash, fever, chills, the prophylactic or therapeutic use of an appropriate antihistamine and/or acetaminophen should be considered.

**Hydration:** Patients must receive at least one liter of 0.9% (normal) saline solution intravenously with each infusion of Mar-Cidofovir. The saline solution should be infused over a 1-2 hour period immediately before Mar-Cidofovir infusion. Patients who can tolerate the additional fluid load should then receive a second liter. If administered, the second liter of saline should be initiated either at the start of the Mar-Cidofovir infusion or immediately afterwards, and infused over a 1-3 hour period. Since patients with chronic diarrhea or AIDS-related wasting may have intravascular volume depletion, special attention should be given to repletion of fluids in these patients.

**Dose Adjustment based on Renal Function during < PRODUCT NAME > Therapy:** The maintenance dose of Mar-Cidofovir must be reduced from 5 mg/kg to 3 mg/kg for an increase in serum creatinine of 27-35  $\mu\text{mol/L}$  (0.3 to 0.4 mg/dL) above baseline. Mar-Cidofovir therapy must be discontinued for an increase in serum creatinine of  $\geq 44 \mu\text{mol/L}$  ( $\geq 0.5 \text{ mg/dL}$ ) above baseline or for the development of  $\geq 2+$  proteinuria.

**Pre-existing Renal Impairment:** Mar-Cidofovir is contraindicated in patients having a creatinine clearance  $\leq 55 \text{ mL/min}$ , or having proteinuria  $\geq 2+$  proteinuria ( $\geq 100 \text{ mg/dL}$ ) (see CONTRAINDICATIONS).

**Patient Monitoring:** Serum creatinine and urine protein must be monitored within 48 hours prior to each dose of Mar-Cidofovir being administered. White blood cell counts with differential should also be monitored prior to each dose. In patients with proteinuria, intravenous hydration should be administered, and the test repeated. Intraocular pressure, visual acuity and ocular symptoms should be monitored periodically.

### 4.3 Administration

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

With a syringe, transfer under aseptic conditions the appropriate dose of Mar-Cidofovir from the vial to a PVC infusion bag containing 100 mL 0.9% (normal) saline solution, and mix thoroughly. The entire volume should be infused intravenously into the patient at a constant rate over a period of 1 hour by use of a standard infusion pump.

If not intended for use immediately after preparation, Mar-Cidofovir infusion admixtures may be stored temporarily for up to 24 hours in a refrigerator (2-8°C), when reconstitution is performed under aseptic conditions. Storage beyond 24 hours or freezing is not recommended. Refrigerated solutions should be allowed to warm to room temperature prior to use.

No data are available to support the addition of other drugs or supplements to be recommended admixture for intravenous infusion. Compatibility with Ringer's solution, Lactated Ringer's solution or bacteriostatic infusion fluids has not been evaluated.

## 5 OVERDOSAGE

Two cases of cidofovir overdose have been reported. These patients received single doses of cidofovir, given intravenously, at 16.3 mg/kg and 17.4 mg/kg, respectively, with concomitant oral probenecid and intravenous hydration. In both cases, the patients were hospitalised and received oral probenecid (one gram three times daily) and vigorous intravenous hydration with normal saline for 3 to 5 days. Significant changes in renal function were not observed in either patient.

For management of a suspected drug overdose, contact your regional poison control centre.
---

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 2 Dosage Forms, Strengths, Composition and Packaging**

<b>Route of Administration</b>	<b>Dosage Form / Strength/Composition</b>	<b>Non-medicinal Ingredients</b>
Intravenous	75 mg/mL cidofovir (as cidofovir dihydrate); 375 mg cidofovir (as cidofovir dihydrate)/vial	water for injection and sodium hydroxide and hydrochloric acid

### **Dosage form and strength and Composition:**

Mar-Cidofovir for Injection is supplied in a clear, single-use, 5 mL glass vial containing 375 mg cidofovir (as cidofovir dihydrate) as a sterile, preservative-free, colorless, aqueous solution at a concentration of 75 mg/mL cidofovir (as cidofovir dihydrate). Non-medicinal ingredients include: water for injection, sodium hydroxide, hydrochloric acid.

**Packaging:** Mar-Cidofovir injection is clear, colorless solution packed in a USP type I, clear glass vial, stoppered with dark grey bromobutyl rubber stopper and sealed with pink colored flip off aluminium seal having polypropylene button with matte finish.

## 7 WARNINGS AND PRECAUTIONS

**Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.**

**Please see Contraindications at the beginning of Part I: Health Professional Information.**

### **General**

Due to dose-dependent nephrotoxicity related to cidofovir, doses greater than the recommended dose of Mar-Cidofovir must not be administered and the frequency or rate of administration must not be exceeded (see DOSAGE AND ADMINISTRATION).

### **Carcinogenesis and Mutagenesis**

In animal studies, cidofovir was carcinogenic (rat), teratogenic (rat and rabbit), and caused hypospermia. In light of these pre-clinical safety data, Mar-Cidofovir should be considered a potential human carcinogen.

### **Endocrine and Metabolism**

Decreased serum bicarbonate associated with proximal tubule injury and renal wasting syndrome (including Fanconi's syndrome) have been reported in patients receiving cidofovir. Fatal cases of metabolic acidosis in association with liver dysfunction and pancreatitis have been reported in patients receiving cidofovir.

### **Hematologic**

Neutropenia has been observed in patients receiving cidofovir. Neutrophil count should be monitored while receiving Mar-Cidofovir therapy.

### **Monitoring and Laboratory Tests**

See DOSAGE AND ADMINISTRATION

### **Ophthalmologic**

Uveitis/iritis was reported in clinical trials and during post-marketing in patients receiving cidofovir. Treatment with topical corticosteroids, with or without topical cycloplegic agents, may be considered. Patients should be monitored for signs and symptoms of uveitis or iritis during Mar-Cidofovir therapy.

Decreased intraocular pressure has been reported during cidofovir therapy, and in some instances, has been associated with decreased visual acuity. Intraocular pressure should be monitored during Mar-Cidofovir therapy to exclude ocular hypotony.

### **Renal**

Dose-dependent nephrotoxicity is the major dose-limiting toxicity related to administration of cidofovir intravenously. Proteinuria, as measured by urinalysis in a clinical laboratory, may be an early indicator of cidofovir-related nephrotoxicity. Patients receiving Mar-Cidofovir must have their serum creatinine and urine protein levels determined within 48 hours prior to each Mar-Cidofovir infusion. In patients exhibiting only  $\geq 2+$  proteinuria, intravenous hydration should be performed and the test repeated. If following hydration,  $\geq 2+$  proteinuria is still observed, Mar-Cidofovir must be discontinued. During treatment, these parameters should be investigated prior to the administration of each infusion, and treatment should be stopped in case of abnormality. Renal function that did not return to baseline after drug discontinuation has been observed in clinical trials of cidofovir given intravenously. In case of complete recovery, the re-introduction of cidofovir has not been evaluated.

Intravenous normal saline hydration and oral probenecid must accompany each Mar-Cidofovir infusion. Probenecid is known to interact with the metabolism or renal tubular excretion of many drugs (see DRUG INTERACTIONS).

An interval of at least 7 days must elapse following the administration of agents with

---



nephrotoxic potential prior to the initiation of therapy with Mar-Cidofovir, and must not be used during the course of therapy. The safety of cidofovir has not been evaluated in patients receiving other known potentially nephrotoxic agents, such as intravenous aminoglycosides (e.g., tobramycin, gentamicin, and amikacin), amphotericin B, foscarnet, intravenous pentamidine, vancomycin, adefovir, tenofovir, and nonsteroidal anti-inflammatory agents.

## **Sexual Health/Reproduction**

Male patients should be advised that cidofovir caused reduced testes weight and hypospermia in animals. Although not observed in clinical studies of intravenous cidofovir, such changes may occur in humans and may cause infertility. Men should be advised to practice barrier contraceptive methods during and for 3 months after treatment with Mar-Cidofovir.

### **7.1 Special Populations**

#### **7.1.1 Pregnant Women**

Mar-Cidofovir should not be used during pregnancy, or in women of childbearing age not using contraception. There are no studies of cidofovir in pregnant women. However, passage of drug-related compounds through the placental barrier was observed in pregnant rats, and embryotoxicity was seen in rats and rabbits.

#### **7.1.2 Breast-feeding**

HIV-1-infected mothers should not breast-feed their infants to avoid risking post-natal transmission of HIV. It is not known whether cidofovir is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for adverse reactions as well as the potential for tumorigenicity shown for cidofovir in animal studies, nursing mothers should be instructed not to breast-feed if they are receiving Mar-Cidofovir.

#### **7.1.3 Pediatrics**

The safety and efficacy of cidofovir have not been established in patients less than 18 years of age. Therefore, **Mar-Cidofovir** is not recommended for use in children and neonates.

#### **7.1.4 Geriatrics**

The safety and efficacy of Mar-Cidofovir have not been established in patients over 60 years of age. Since elderly individuals frequently have reduced glomerular function, particular attention should be paid to assessing renal function before and during administration of Mar-Cidofovir.

## **8 ADVERSE REACTIONS**

### **8.1 Adverse Reaction Overview**

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be

compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following are the major noted adverse reactions to have occurred with cidofovir, when given intravenously.

**Nephrotoxicity:** Renal toxicity as manifested by  $\geq 2+$  proteinuria, serum creatinine elevations of  $\geq 0.4$  mg/dL, or decrease creatinine clearance  $\leq 55$  mL/min, occurred in 79 of 135 (59%) patients receiving cidofovir at a maintenance dose of 5 mg/kg intravenously every other week, and in 56 of 112 (50%) patients receiving cidofovir intravenously at a maintenance dose of 3 mg/kg every other week. Maintenance dose reductions from 5 mg/kg to 3 mg/kg, due to proteinuria or serum creatinine elevation, were made in 12 of 41 (29%) patients who had not received prior therapy for CMV retinitis (Study 106), and in 19 of 74 (26%) patients who had received prior therapy for CMV retinitis (Study 107). Prior foscarnet use has been associated with an increased risk of nephrotoxicity. Such patients must be monitored closely.

**Neutropenia:** In clinical trials, at the 5 mg/kg maintenance dose, a decrease in absolute neutrophil count to  $\leq 500$  cells/mm<sup>3</sup> occurred in 24% of patients. Granulocyte Colony Stimulating Factor (GCSF) was used in 39% of patients. At the 3 mg/kg maintenance dose, a decrease in absolute neutrophil count to  $\leq 500$  cells/mm<sup>3</sup> occurred in 25% of patients.

**Decreased intraocular pressure/ocular hypotony:** Among the subset of patients monitored for intraocular pressure changes, a  $\geq 50\%$  decrease from baseline intraocular pressure was reported in 17 of 70 (24%) patients at the 5 mg/kg maintenance dose. At the 3 mg/kg maintenance dose, a  $\geq 50\%$  decrease from baseline intraocular pressure was reported in 12 of 83 (14%). Severe hypotony (intraocular pressure of 0-1 mm/Hg) has been reported in 3 patients. Risk of ocular hypotony may be increased in patients with pre-existing diabetes mellitus.

**Metabolic acidosis:** A diagnosis of Fanconi's syndrome was reported in 1% of patients. Decreases in serum bicarbonate to  $\leq 16$  mEq/L occurred in 16% of cidofovir-treated patients. Fanconi's syndrome and decreases in serum bicarbonate with evidence of renal tubular damage have been reported in patients receiving cidofovir. Fatal cases of metabolic acidosis in association with liver dysfunction and pancreatitis have been reported in patients receiving cidofovir.

**Anterior uveitis/iritis:** Uveitis or iritis was reported in 15 of 135 (11 %) patients receiving 5 mg/kg maintenance dose, and in 5 of 112 (4%) patients receiving 3 mg/kg maintenance dose. Treatment with topical corticosteroids, with or without topical cycloplegic agents, may be considered. Patients should be monitored for signs and symptoms of uveitis/iritis during therapy with Mar-Cidofovir.

## 8.2 Clinical Trial Adverse Reactions

Three clinical trials have been conducted with cidofovir given intravenously to evaluate treatment in patients with AIDS having cytomegalovirus retinitis (see CLINICAL TRIALS).

In clinical trials, cidofovir treatment was withdrawn due to adverse events in 39% of patients treated with 5 mg/kg every other week as maintenance therapy, and in 26% of patients receiving 3 mg/kg as maintenance dose.

The incidence of serious adverse events (SAE) in these three controlled clinical studies, regardless of presumed relationship to drug, is listed in the following table.

**Table 3 Serious Adverse Events occurring in > 5% of patients**

	<b>5 mg/kg</b> <b>n=135* (%)</b>	<b>3 mg/kg</b> <b>n=112<sup>§</sup> (%)</b>
Proteinuria ( $\geq 100$ mg/dL)	68 (50)	41 (37)
Neutropenia ( $\leq 500$ cells/mm <sup>3</sup> )	33 (24)	28 (25)
Decreased ocular pressure	17 (24)	12 (14)
Decreased serum bicarbonate ( $\leq 16$ )	21 (16)	21 (19)
Fever	19 (14)	7 (6)
Infection	16 (12)	6 (5)
Creatinine elevation ( $\geq 2.0$ mg/dL)	16 (12)	6 (5)
Pneumonia	12 (9)	12 (11)
Dyspnea	11 (8)	5 (4)
Nausea with vomiting	10 (7)	4 (4)

\* Patients receiving 5 mg/kg maintenance regimen in Studies 105, 106 and 107

§ Patients receiving 3 mg/kg maintenance regimen in Studies 105 and 107

¶ Defined as decreased intraocular pressure (IOP) to  $\leq 50\%$  that at baseline. Based on 70 patients receiving 5 mg/kg maintenance dosing (Studies 105 and 107), and on 83 patients receiving 3 mg/kg maintenance regimen (Studies 105 and 107), with available baseline and follow-up IOP determinations

The most frequently reported adverse events regardless of relationship to study drugs (cidofovir or probenecid) or severity are shown in the following table.

**Table 4 All Adverse Events occurring in > 15% of patients**

	<b>5 mg/kg</b> <b>n=135** (%)</b>	<b>3 mg/kg</b> <b>n=112<sup>§</sup> (%)</b>
Any AE	133 (99)	109 (97)
Proteinuria ( $\geq 30$ mg/dL)	112 (83)	78 (70)
Nausea with vomiting	81 (60)	37 (34)
Fever	69 (51)	39 (35)
Neutropenia ( $\leq 750$ cells/mm <sup>3</sup> )	53 (39)	42 (38)
Asthenia	50 (37)	31 (28)
Headache	34 (25)	16 (14)
Rash	34 (25)	13 (12)
Infection	32 (24)	21 (19)
Alopecia	32 (24)	8 (7)
Diarrhea	30 (22)	14 (13)
Creatinine elevation ( $\geq 1.5$ mg/dL)	29 (21)	15 (13)

Pain	29 (21)	10 (9)
Anemia	28 (21)	21 (19)
Anorexia	26 (19)	13 (12)
Dyspnea	26 (19)	9 (8)
Chills	25 (19)	5 (4)
Increased cough	22 (16)	10 (9)
Oral candidiasis	21 (16)	13 (12)

\*Patients receiving 5 mg/kg maintenance regimen in Studies 105, 106 and 107

§Patients receiving 3 mg/kg maintenance regimen in Studies 105 and 107

### 8.3 Less Common Clinical Trial Adverse Reactions

The following additional list of adverse events or intercurrent illnesses have been observed in clinical studies of cidofovir when given intravenously, and are listed below regardless of causal relationship to cidofovir. Evaluation of these reports was confounded because of the diverse manifestations of the underlying disease and because most patients received numerous concomitant medicines.

*Body as a Whole:* abdominal pain, accidental injury, allergic reaction, back pain, catheter blocked, cellulitis, chest pain, chills and fever, cryptococcosis, cyst, death, face edema, flu-like syndrome, hypothermia, injection site reaction, malaise, mucous membrane disorder, neck pain, overdose, photosensitivity reaction, sarcoma, sepsis

*Cardiovascular System:* cardiomyopathy, cardiovascular disorder, congestive heart failure, hypertension, hypotension, migraine, pallor, peripheral vascular disorder, phlebitis, postural hypotension, shock, syncope, tachycardia, vascular disorder, edema

*Digestive System:* cholangitis, colitis, constipation, esophagitis, dyspepsia, dysphagia, fecal incontinence, flatulence, gastritis, gastrointestinal hemorrhage, gingivitis, hepatitis, hepatomegaly, hepatosplenomegaly, jaundice, abnormal liver function, liver damage, liver necrosis, melena, pancreatitis, proctitis, rectal disorder, stomatitis, aphthous stomatitis, tongue discoloration, mouth ulceration, tooth caries

*Endocrine System:* adrenal cortex insufficiency

*Hemic & Lymphatic System:* hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, lymphoma like reaction, pancytopenia, splenic disorder, splenomegaly, thrombocytopenia, thrombocytopenic purpura

*Metabolic & Nutritional System:* cachexia, dehydration, edema, hypercalcemia, hyperglycemia, hyperkalemia, hyperlipemia, hypocalcemia, hypoglycemia, hypoglycemic reaction, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypoproteinemia, increased alkaline phosphatase, increased BUN, increased lactic dehydrogenase, increased SGOT, increased SGPT, peripheral edema, respiratory alkalosis, thirst, weight loss, weight gain

*Musculoskeletal System:* arthralgia, arthrosis, bone necrosis, bone pain, joint disorder, leg cramps, myalgia, myasthenia, pathological fracture

*Nervous System:* abnormal dreams, abnormal gait, acute brain syndrome, agitation, amnesia, anxiety, ataxia, cerebrovascular disorder, confusion, convulsion, delirium, dementia, depression, dizziness, drug dependence, dry mouth, encephalopathy, facial paralysis, hallucinations, hemiplegia, hyperesthesia, hypertonia, hypotony, incoordination, increased libido, insomnia, myoclonus, nervousness, neuropathy, paresthesia, personality disorder, somnolence, speech disorder, tremor, twitching, vasodilatation, vertigo.

*Respiratory System:* asthma, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, hypoxia, increased sputum, larynx edema, lung disorder, pharyngitis, pneumothorax, rhinitis, sinusitis

*Skin & Appendages:* acne, angioedema, dry skin, eczema, exfoliative dermatitis, furunculosis, herpes simplex, nail disorder, pruritus, rash, seborrhea, skin discoloration, skin disorder, skin hypertrophy, skin ulcer, sweating, urticaria

*Special Senses:* abnormal vision, amblyopia, blindness, cataract, conjunctivitis, corneal lesion, corneal opacity, diplopia, dry eyes, ear disorder, ear pain, eye disorder, eye pain, hyperacusis, iritis, keratitis, miosis, otitis externa, otitis media, refraction disorder, retinal detachment, retinal disorder, taste perversion, tinnitus, uveitis, visual field defect, hearing loss

*Urogenital System:* decreased creatinine clearance, dysuria, glycosuria, hematuria, kidney stone, mastitis, metrorrhagia, nocturia, polyuria, prostatic disorder, toxic nephropathy, urethritis, urinary casts, urinary incontinence, urinary retention, urinary tract infection

## **9 DRUG INTERACTIONS**

### **9.1 Overview**

Concomitant administration of Mar-Cidofovir with agents having nephrotoxic potential, e.g., intravenous aminoglycosides, i.e., tobramycin, gentamicin, and amikacin; amphotericin B, foscarnet, intravenous pentamidine, vancomycin, and non-steroidal anti-inflammatory agents, is contraindicated. Such agents must be discontinued at least seven days prior to starting therapy with Mar-Cidofovir (see CONTRAINDICATIONS).

### **9.2 Drug-Drug Interactions**

In order to limit the nephrotoxic effects of cidofovir, probenecid must be taken with each administration of Mar-Cidofovir (see DOSAGE AND ADMINISTRATION).

Probenecid is known to interact with the metabolism or renal tubular secretion of many drugs, e.g., paracetamol, acyclovir, angiotensin-converting enzyme inhibitors, aminosalicic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, nonsteroidal anti-inflammatory agents, theophylline, and zidovudine.

As probenecid reduces the clearance of zidovudine, patients who are being treated with zidovudine should temporarily discontinue zidovudine administration or decrease their zidovudine dose by 50% on days of cidofovir injection administration only.

---

## 10 ACTION AND CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Cidofovir suppresses CMV replication by selective inhibition of viral DNA synthesis. Biochemical data support selective inhibition of HSV-1, HSV-2 and CMV DNA polymerases by cidofovir diphosphate, the active intracellular metabolite of cidofovir. Cidofovir diphosphate inhibits these viral polymerases at concentrations that are 8- to 600-fold lower than those needed to inhibit human cellular DNA polymerases alpha, beta, and gamma. Incorporation of cidofovir into viral DNA results in reductions in the rate of viral DNA synthesis.

### 10.2 Pharmacodynamics

#### *Animal Pharmacology*

Cidofovir was evaluated in a battery of acute *in vivo* and *in vitro* assays assessing the pharmacodynamic effects on the following physiological systems: central nervous system (mouse); acute toxicity (mouse and rat, single intraperitoneal injection up to 30 mg/kg); anti-inflammation (mouse, rat); lipid metabolism (mouse); glucose tolerance (mouse); gastrointestinal function (rat); *in vitro* antimicrobial properties; cardiovascular system function (mouse); immune system function (mouse); and endocrine antagonist activity *in vitro* and *in vivo*. Cidofovir produced no significant effects in these assays, except for a moderate anti-ulcerogenic activity. The effects on cardiovascular system function were evaluated in rats receiving a single intravenous injection of saline or cidofovir (5 mg/kg). Systolic/diastolic and mean arterial blood pressure and heart rate were measured in conscious animals via a femoral artery catheter at 3 minutes pre-dose and at 1-15 minutes, 30 minutes, 1 hour, 2 hours, 5 hours and 24 hours post-dose. No significant test article-related effects on systemic blood pressure or heart rate were observed.

### 10.3 Pharmacokinetics

Mar-Cidofovir must be administered with probenecid.

The pharmacokinetics of cidofovir without probenecid were evaluated in 27 HIV-infected patients, with or without asymptomatic CMV infection. Dose-independent pharmacokinetics were demonstrated after one hour infusions of 1.0 (n=5), 3.0 (n=10), 5.0 (n=2) and 10.0 (n=8) mg/kg. There was no evidence of cidofovir accumulation after 4 weeks of repeated administration of 3 mg/kg/week (n=5) without probenecid. In patients with normal renal function, approximately 80 to 100% of the cidofovir dose was recovered unchanged in urine within 24 hours (n=27). The renal clearance of cidofovir was greater than creatinine clearance, indicating renal tubular secretion contributes to the elimination of cidofovir.

The pharmacokinetics of cidofovir administered with probenecid were evaluated in 12 HIV-infected patients with or without asymptomatic CMV infection and 10 patients with relapsing CMV retinitis. Dose-independent pharmacokinetics were observed for cidofovir, administered with probenecid, after one hour infusions of 3 (n=12), 5.0 (n=6) and 7.5 (n=4) mg/kg. Approximately 70 to 85% of the cidofovir dose administered with concomitant probenecid was

excreted as unchanged drug within 24 hours. When cidofovir was administered with probenecid, the renal clearance of cidofovir was reduced to a level consistent with creatinine clearance, suggesting that probenecid blocks active renal tubular secretion of cidofovir.

For a comparison of pharmacokinetic (PK) parameters of cidofovir, at 3 mg/kg and 5 mg/kg, without and with probenecid, when administered by infusion, please refer to the Table below.

**Table 6 Cidofovir Pharmacokinetics, without and with Probenecid+**

	<b>CIDOFOVIR, ADMINISTERED WITHOUT PROBENECID</b>		<b>CIDOFOVIR, ADMINISTERED WITH PROBENECID</b>	
	3 mg/kg (n=10)	5 mg/kg (n=2)	3 mg/kg (n=12)	5 mg/kg (n=6)
AUC ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	20.0 $\pm$ 2.3	28.3	25.7 $\pm$ 8.5	40.8 $\pm$ 9.0
Cmax (end of infusion)( $\mu\text{g}/\text{mL}$ )	7.3 $\pm$ 1.4	11.5	9.8 $\pm$ 3.7	19.6 $\pm$ 7.2
Vdss (mL/kg)	537 $\pm$ 126 (n=12)		410 $\pm$ 102 (n=18)	
Total Clearance (mL/min/1.73 m <sup>2</sup> )	179 $\pm$ 23.1 (n=12)		148 $\pm$ 38.8 (n=18)	
Renal Clearance (mL/min/1.73 m <sup>2</sup> )	150 $\pm$ 26.9 (n=12)		98.6 $\pm$ 27.9 (n=11)	

<sup>+</sup>See DOSAGE AND ADMINISTRATION

*In vitro* protein binding of cidofovir to plasma or serum protein was less than 6% over the cidofovir concentration range 0.25 to 25  $\mu\text{g}/\text{mL}$ .

CSF concentrations of cidofovir following intravenous infusion of 5 mg/kg with concomitant probenecid and intravenous hydration were undetectable (<0.1  $\mu\text{g}/\text{mL}$ , assay detection threshold) at 15 minutes after the end of an hour infusion in one patient whose corresponding serum concentration was 8.7  $\mu\text{g}/\text{mL}$ .

## 11 STORAGE, STABILITY AND DISPOSAL

The storage condition recommended for Cidofovir injection 75 mg/ml is “Store at 15°- 25°C (59° - 77°F).”

Due to the mutagenic properties of cidofovir, adequate precautions including the use of appropriate safety equipment are recommended for the preparation, administration and disposal of cidofovir injection. Excess cidofovir injection and all other materials used in the admixture preparation and administration should be placed in a leak-proof, puncture-proof container for disposal. The recommended method of disposal is high temperature incineration.

## 12 SPECIAL HANDLING INSTRUCTIONS

With a syringe, transfer under aseptic conditions the appropriate dose of cidofovir injection from the vial to an infusion bag containing 100 mL 0.9% (normal) saline solution, and mix thoroughly. The entire volume should be infused intravenously into the patient at a constant rate over a period of 1 hour by use of a standard infusion pump. Cidofovir injection should be administered by health care professionals adequately experienced in the care of AIDS patients.

If not intended for use immediately after preparation, cidofovir injection infusion admixtures may be stored temporarily for up to 24 hours in a refrigerator (2-8°C) when reconstitution is performed under aseptic conditions. Storage beyond 24 hours or freezing is not recommended. Refrigerated solutions should be allowed to warm to room temperature prior to use.

- 1) Do not use if seal over the bottle opening is broken or missing.
- 2) Visually inspect Cidofovir for Injection and examine for particulate matter and discoloration prior to administration.
- 3) Once the PVC infusion bag containing diluted cidofovir solution has been prepared, visually inspect the resulting solution to ensure it is clear and free from visible evidence of particulates. As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.
- 4) Any unused Cidofovir solution (concentrate in vials or the diluted solution) should be discarded immediately.



## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: Cidofovir

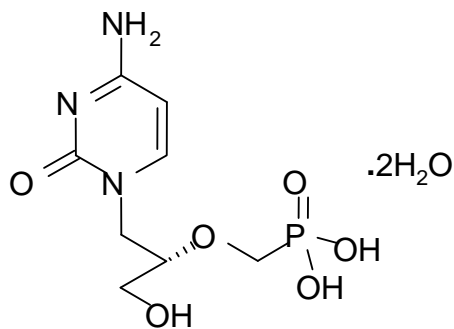
Chemical name:

[[[(1S)-2-(4-Amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl) Ethoxy] methyl] phosphonic acid dihydrate

(S)-1-[3-Hydroxy-2-(Phosphonylmethoxy) Propyl] Cytosine dihydrate

Molecular formula and molecular mass:  $C_8H_{14}N_3O_6P \cdot 2H_2O$ ; 315.22 dihydrate (279.19 anhydrous)

Structural formula:



Physicochemical properties:

Sparingly soluble in water, soluble in 0.1 M sodium hydroxide, Practically insoluble in methanol and in ethanol.

Solubility profile of Cidofovir Dihydrate in different solvents is tabulated below:

Solvent	Observation
Water	Sparingly soluble
Ethanol (96%)	Practically insoluble
Methanol	Practically insoluble

Dimethyl Formamide	Practically insoluble
Ethyl Acetate	Practically insoluble
Dimethyl sulfoxide	Practically insoluble
Chloroform	Practically insoluble
Acetone	Practically insoluble

Aqueous solubility of Cidofovir Dihydrate at pH buffers is summarized below:

Buffer pH	Solubility in mg/mL	Observation
1.2	6 mg/mL	Slightly soluble
6.0	5 mg/mL	Slightly soluble
8.0	11 mg/mL	Sparingly soluble

**Product Characteristics**  
**pH (1% Aq. Suspension)**

About 3.5

**pKa**

Strongest Acidic - 1.19

Strongest base - 2.15

**Log P:-3.9**

**Melting Point**

About 259.0°C

**Hygroscopicity:**

Cidofovir dihydrate is Non- Hygroscopic in nature

**Molar Absorptivity**

Molar absorptivity of Cidofovir Dihydrate is 9953 Lmol<sup>-1</sup>cm<sup>-1</sup>

**14 CLINICAL TRIALS**

Three Phase II/III controlled trials of cidofovir, given by intravenous infusion, have been conducted in HIV-infected patients with CMV retinitis.

### **Delayed Versus Immediate Therapy (Study 105)**

In Stage 1 of this open-label trial, conducted by the Studies of the Ocular Complications of AIDS (SOCA) Clinical Research Group, 29 previously untreated patients having peripheral CMV retinitis were randomised, to either, immediate treatment with cidofovir (5 mg/kg once a week for

2 weeks, then 3 mg/kg every other week), or to, have cidofovir treatment delayed until progression of CMV retinitis was observed. In Stage 2 of this trial, an additional 35 previously untreated patients with peripheral CMV retinitis were randomised to either immediate treatment with cidofovir (5 mg/kg once a week for 2 weeks, then 5 mg/kg every other week), immediate treatment with cidofovir (5 mg/kg once a week for 2 weeks, then 3 mg/kg every other week), or to have cidofovir treatment delayed until progression of CMV retinitis. Of the 64 patients in this study, 12 were randomised to 5 mg/kg maintenance therapy, 26 to 3 mg/kg maintenance therapy, and 26 to delayed therapy.

Of the 12 patients enrolled in the 5 mg/kg maintenance group, 5 patients progressed, 5 patients discontinued therapy, and 2 patients had no progression at study completion. Based on masked readings of retinal photographs, the median [95% confidence interval (CI)] time to retinitis progression was not reached (25, not reached) for the 5 mg/kg maintenance group. Median (95% CI) time to the alternative endpoint of retinitis progression or study drug discontinuation was 44 days (24, 207) for the 5 mg/kg maintenance group.

Patients receiving 5 mg/kg maintenance were observed to have had delayed time to retinitis progression, compared to patients receiving 3 mg/kg maintenance or deferred therapy.

### **Delayed Versus Immediate Therapy (Study 106)**

In an open-label trial, 48 previously untreated patients with peripheral CMV retinitis were randomised to either immediate treatment with cidofovir (5 mg/kg once a week for 2 weeks, then 5 mg/kg every other week), or to have cidofovir treatment delayed until progression of CMV retinitis. Patient baseline characteristics and disposition are shown in the Table, below.

**Table 7 Patient Characteristics and Disposition in Study 106**

	<b>Immediate Therapy</b>	<b>Delayed Therapy (n=23)</b>
Baseline Characteristics		
Age (years)	<b>38</b>	<b>38</b>
Sex (M/F)	<b>24/1</b>	<b>22/1</b>
Median CD4 cell count	<b>6</b>	<b>9</b>
Endpoints		
CMV retinitis progression	<b>10</b>	<b>18</b>
Discontinued due to adverse event	<b>6</b>	<b>0</b>
Withdrew consent	<b>3*</b>	<b>1</b>

Discontinued due to intercurrent illness	2 <sup>†</sup>	1 <sup>†</sup>
Discontinued based on ophthalmologic examination	1 <sup>‡</sup>	1 <sup>‡</sup>
No progression at study completion	1	0
Not evaluable at baseline	2	2

\* One patient died 2 weeks after withdrawing consent.

<sup>†</sup> Two patients on immediate therapy were diagnosed with CMV disease and discontinued from study. One patient on delayed therapy was diagnosed with CMV gastrointestinal disease.

<sup>‡</sup> CMV retinitis progression not confirmed by retinal photography.

Of 25 and 23 patients in the immediate- and delayed-treatment groups respectively, 23 and 21 were evaluable for retinitis progression, as determined by retinal photography. Based on masked readings of retinal photographs, the median [95% confidence interval (CI)] times to retinitis progression were 120 days (40, 134), and 22 days (10, 27) for the immediate and delayed therapy groups, respectively. This difference was statistically significant.

However, because of the limited number of patients remaining on treatment over time (3 of 25 patients received cidofovir for 120 days or longer), the median time to progression for the immediate therapy group was difficult to precisely estimate. Median (95% CI) times to the alternative endpoint of retinitis progression or study drug discontinuation (including adverse events, withdrawn consent, and systemic CMV disease) were 52 days (37, 85), and 22 days (13, 27) for the immediate and delayed therapy groups, respectively. This difference was statistically significant. Time to progression estimates from this study may not be directly comparable to estimates reported for other therapies.

### Dose-response study of cidofovir (Study 107)

In an open-label trial, 100 patients with relapsing CMV retinitis were randomised to receive 5 mg/kg once a week for 2 weeks, and then either 5 mg/kg (n = 49) or 3 mg/kg (n = 51) every other week.

Enrolled patients had been diagnosed with CMV retinitis an average of 390 days prior to randomisation and had received a median of 3.8 prior courses of systemic CMV therapy. Eighty four of the 100 patients were considered evaluable for progression by serial retinal photographs (43 randomised to 5 mg/kg and 41 randomised to 3 mg/kg). Twenty-six and 21 patients discontinued therapy due to an adverse event, intercurrent illness, excluded medication, or withdrawn consent, in the 5 mg/kg and 3 mg/kg groups, respectively.

**Table 8 Patient Characteristics and Disposition in Study 107**

	5 mg/kg Maintenance	3 mg/kg Maintenance
<b>Baseline Characteristics</b>		
Age (years)	39.3	39.1

Sex (M/F)	74/1	74/1
Median CD4 Cell Count	7.0	5.0
<b>Endpoints</b>		
Progression of CMV Retinitis	20 (27%)	35 (47%)
Death	9 (12%)	4 (5%)
Discontinued (Adverse Event/Intercurrent Illnesses)	29 (39%)	21 (28%)
Lost to Follow-up	0 (0%)	0 (0%)
Still at Risk	4 (5%)	0 (0%)
Other*	13 (17%)	15 (20%)

\*Includes, but not limited to, discontinuation due to mental incapacity, generalised debilitation, withdrawal of consent

Thirty-eight of the 100 randomised patients had progressed according to masked assessment of serial retinal photographs (13 randomised to 5 mg/kg and 25 randomised to 3 mg/kg). Using retinal photographs, the median (95% CI) times to retinitis progression for the 5 mg/kg and 3 mg/kg groups were 115 days (70, not reached), and 49 days (35, 52), respectively. This difference was statistically significant. Similar to Study 106, the median time to retinitis progression for the 5 mg/kg group was difficult to precisely estimate due to the limited number of patients remaining on treatment over time (4 of the 49 patients in the 5 mg/kg group were treated for 115 days or longer).

Median (95% CI) times to the alternative endpoint of retinitis progression or study drug discontinuation were 49 days (38, 63), and 35 days (27, 39), for the 5 mg/kg and 3 mg/kg groups, respectively. This difference was statistically significant.

## 15 MICROBIOLOGY

**Antiviral Activity:** Cidofovir is active *in vitro* against laboratory and clinical isolates of CMV and other herpes viruses. Inhibition of multiplication of various CMV isolates in cell cultures by cidofovir is shown in the Table below. Antiviral activity was seen at concentrations significantly below those which cause death in cell monolayers.

**Table 9 Cidofovir Inhibition of Virus Multiplication in Cell Culture**

<b>Virus</b>	<b>IC<sub>50</sub> (µM)</b>
<b>Wild-type CMV isolates</b>	<b>0.7 (± 0.6)</b>
<b>Ganciclovir-resistant CMV isolates</b>	<b>7.5 (± 4.3)</b>
<b>Foscarnet-resistant CMV isolates</b>	<b>0.6 (± 0.07)</b>

**Resistance:** CMV isolates with reduced susceptibility to cidofovir have been selected *in vitro* in the presence of high concentrations of cidofovir. IC50 values for selected resistant isolates ranged from 7-15  $\mu$ M.

**Cross-resistance:** Cidofovir resistant isolates selected *in vitro* were cross-resistant to ganciclovir but susceptible to foscarnet. The majority of ganciclovir-resistant isolates are UL97 gene product (phosphokinase) mutants, and remain susceptible to cidofovir. Reduced susceptibility to cidofovir, however, has been reported for DNA polymerase mutants of CMV which are resistant to ganciclovir. To date, all clinical isolates which exhibit high level resistance to ganciclovir, due to mutations in both the DNA polymerase and UL97 genes, have been shown to be cross-resistant to cidofovir. Cidofovir is active against some, but not all, CMV isolates which are resistant to foscarnet.

A few triple-drug resistant isolates have been described. Genotypic analysis of two of these triple drug-resistant isolates revealed several point mutations in the CMV DNA polymerase gene. The clinical significance of the development of these cross-resistant isolates is not known.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicity

Nephrotoxicity, as manifest by renal tubular nephrosis, was the major dose-limiting toxicity observed in repeat-dose studies of durations up to 26 weeks, by several routes of exposure and in multiple species. Cidofovir-mediated nephrotoxicity was shown to decrease with a less frequent dosing schedule (mice, rats, rabbits and guinea pigs), and with co-administration of probenecid (rabbits and monkeys). Additional common target tissue toxicities noted were effects on bone marrow (erythroid and myeloid depletion), testes (hypospermia), and, at nephrotoxic doses, spleen and thymus (lymphoid depletion).

### Mutagenicity and Genotoxicity

Cidofovir was not mutagenic in *in vitro* bacterial tests, but was clastogenic in an *in vitro* human lymphocyte assay, and was positive, at toxic and/or lethal doses, in the mouse micronucleus assay.

### Carcinogenicity

Two year animal carcinogenicity studies have not been carried out. In chronic toxicity studies in Sprague-Dawley rats, cidofovir was administered at 0.6, 3 or 15 mg/kg once weekly by intravenous infusion. Mammary adenocarcinoma formation in female rats, and Zymbal's gland carcinomas in male and female rats, were only seen at the 15 mg/kg/week high dose following intravenous administration for 26 weeks, whereas subscapular subcutaneous administration for 19 weeks resulted in mammary adenocarcinoma at doses of 0.6 mg/kg/week and higher. The high dose, when extrapolated systemically, was equivalent to 1.1 times the human systemic exposure at the recommended dose of cidofovir. The low dose was equivalent to 0.6 times the human systemic exposure at the recommended dose of cidofovir. Subscapular subcutaneous administration in young female rats resulted in a concentrated, high cidofovir dose locally at mammary tissue, and a greater tumorigenic response than observed with the intravenous route.

However, in a 52-week chronic toxicity study of cidofovir in cynomolgus monkeys, no cidofovir-associated toxicity, whether gross or microscopic, including neoplastic lesions, occurred at doses up to approximately 0.7 times the human systemic exposure (2.5 mg/kg/week) in combination with orally administered probenecid. However, the study was not designed as a carcinogenicity study due to the small number of animals at each dose and the short duration of treatment.

### **Reproduction and Teratology**

Cidofovir caused reduced testes weight and hypospermia in rats and monkeys. However, there was no significant effect on fertility and reproductive performance in male rats, or on peri- and post-natal viability, behaviour, or fertility in rats. Embryotoxicity in a Segment II study in rats, and embryotoxicity and teratogenicity in a Segment II study in rabbits, occurred only at maternally toxic doses.

## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PATIENT MEDICATION INFORMATION

#### **Mar-Cidofovir Cidofovir for Injection USP 75 mg/mL**

Read this carefully before you start taking **Mar-Cidofovir** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Mar-Cidofovir**.

#### **Serious Warnings and Precautions**

- **Mar-Cidofovir may cause problems with your kidneys. Talk to your doctor if you suspect that you are having kidney issues. See “Serious side effects and what to do about them”, below.**
- **To avoid serious or fatal kidney problems, you will be given Probenecid and fluids with each dose of Mar-Cidofovir. See “How to take Mar-Cidofovir”, below.**
- **Your doctor will request blood and urine tests before each dose of Mar-Cidofovir.**
- **You should not take Mar-Cidofovir if you are taking any other medicines that may cause kidney problems. Talk to your healthcare professional about any other medicines that you are taking.**
- **Mar-Cidofovir may affect your blood cell count. Your doctor will order blood tests to monitor this.**
- **Mar-Cidofovir should only be used to treat CMV Retinitis (cytomegalovirus) if you have AIDS (Acquired Immunodeficiency Syndrome). See “What is Mar-Cidofovir used for?”, below.**
- **Mar-Cidofovir may cause cancer, birth defects or infertility. Talk to your doctor if you plan to have children.**

#### **What is Mar-Cidofovir used for?**

Mar-Cidofovir is used to treat an eye infection called CMV (cytomegalovirus) retinitis in patients with AIDS (Acquired Immunodeficiency Syndrome).

CMV retinitis is an eye infection caused by a virus. CMV attacks the retina of the eye and may cause loss of vision, and eventually lead to blindness. Patients with AIDS are at high risk of developing CMV retinitis. Treatment for CMV retinitis is necessary to reduce the potential for blindness.

Mar-Cidofovir will not cure CMV retinitis but may improve your condition by delaying progression of the disease.

#### **How does Mar-Cidofovir work?**

Mar-Cidofovir is an antiviral medicine. It stops CMV from multiplying.

#### **What are the ingredients in Mar-Cidofovir?**

Medicinal ingredients: cidofovir as the dehydrate

Non-medicinal ingredients: water for injection, sodium hydroxide, hydrochloric acid.

#### **Mar-Cidofovir comes in the following dosage forms:**

Solution for Injection 75 mg /mL (375 mg / Vial).



**Do not use Mar-Cidofovir if:**

- you ever had kidney disease.
- you are currently taking other medicine that can harm your kidneys.
- you are allergic to cidofovir or any other ingredients of this medicine. See “What are the ingredients in Mar-Cidofovir, above.
- you cannot take probenecid because of a serious allergy to probenecid or to other sulpha-containing medications.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Mar-Cidofovir. Talk about any health conditions or problems you may have, including if you:**

- Are pregnant or planning to become pregnant. Mar-Cidofovir may cause birth defects. Tell your doctor if you become pregnant while taking Mar-Cidofovir.
- Are breastfeeding or plan to breastfeed. It is not known if Mar-Cidofovir passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take Mar-Cidofovir.

**Other warnings you should know about:**

Male Patients

Using Mar-Cidofovir may cause birth defects or infertility. Talk your doctor if you are expecting a child or plan to have children. Male patients should practice barrier contraceptive methods (condom) while taking Mar-Cidofovir and for 3 months afterwards.

Eyesight

Mar-Cidofovir may affect your eyesight. Be sure to schedule regular eye exams while taking Mar-Cidofovir.

Kidney Health

Mar-Cidofovir may cause kidney problems. Your doctor may ask for blood and urine tests to monitor your kidney health. This will help your doctor determine your dose.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with Mar-Cidofovir or probenecid:**

- paracetamol
- acyclovir
- angiotensin-converting enzyme inhibitors
- aminosalicic acid
- barbiturates
- benzodiazepines
- bumetanide
- clofibrate
- methotrexate
- famotidine
- furosemide,
- nonsteroidal anti-inflammatory agents

- theophylline
- zidovudine

**How to take Mar-Cidofovir:**

Mar-Cidofovir will be given by a healthcare professional. To reduce possible kidney damage, you will be given another medicine called probenecid with each dose.

Be sure to eat food and drink lots of fluids on days that you receive Mar-Cidofovir.

Your doctor may prescribe other medication to help manage the side effects of your treatment.

**Usual dose:**

Your doctor will determine how much Mar-Cidofovir to give you based on your test results and body weight.

You will receive Mar-Cidofovir once weekly for the first two weeks and once every 2 weeks afterwards.

**Overdose:**

If you think you have taken too much Mar-Cidofovir, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

**What are possible side effects from using Mar-Cidofovir?**

The most common side effects of Cidofovir include:

- Lack of energy

If any of these side effects affect you severely, please tell your doctor or pharmacist immediately.

Serious side effects and what to do about them				
Symptom/effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
<b>VERY COMMON</b>	Rash, weakness/fatigue, fever, hair loss, nausea, vomiting, headache	√		
	changes in blood or urine tests results		√	
<b>COMMON</b>	diarrhea and chills.	√		
	Any pain, redness or itching of the eye or changes in your vision,		√	

	reduced pressure in the eyes, difficult or laboured breathing, shortness of breath, inflammation of the pancreas and hearing impairment			
	Kidney problems which may include symptoms such as: changes in urine output or colour, blood in the urine, weight gain (from retaining fluid), confusion, swelling of the eyes, hands, legs, and feet.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on [Adverse Reaction Reporting \(http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php\)](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

The storage condition recommended for Mar-Cidofovir injection 75 mg/ml is “Store at 15°-25°C (59° - 77°F).”

Keep out of reach and sight of children.

### If you want more information about Mar-Cidofovir:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer’s website [www.marcanpharma.com](http://www.marcanpharma.com), or by calling 1-855-627-2261 .

This leaflet was prepared by  
Marcan Pharmaceuticals Inc. 77 Auriga Drive, Unit # 4, Ottawa, Ontario, K2E 7Z7.

Last Revised <13-03-2018>