

(/drug-shortages/486)Cidofovir



Drug Information: AHFS Drug Information (comprehensive) AHFS DI Essentials (point-of-care)

AHFS Class: 8:18.32 (tofc-08) – Nucleosides and Nucleotides

VA Class: AM800 (<http://www.pbm.va.gov/PBM/NationalFormulary.asp>)

Cidofovir (Systemic) (*AHFS Essentials*)

Cidofovir

CAS Number: 149394-66-1

Chemical Name: (S)-[[2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy)methyl]phosphonic acid dihydrate

Molecular Formula: C₈H₁₄N₃O₆P•2H₂O

Investigational Number: GS-0504

Synonym: Vistide

Synonym: CDV

FDA Boxed Warning:

Nephrotoxicity

Major toxicity is renal impairment.¹ Acute renal failure resulting in dialysis and/or contributing to death has occurred with as few as 1 or 2 doses of cidofovir.¹

To reduce risk of nephrotoxicity, IV hydration with 0.9% sodium chloride *must* be given prior to each cidofovir dose and oral probenecid regimen *must* be used concomitantly with each cidofovir dose.¹ (See Hydration and see Concomitant Probenecid under Dosage and Administration.) Renal function (S_{cr} and urine protein) *must* be assessed within 48 hours prior to each cidofovir dose and dosage modified as appropriate based on any changes in renal function.¹

Contraindicated in patients receiving other nephrotoxic drugs.¹ (See Interactions.)

Neutropenia

Neutropenia has been observed in association with cidofovir; monitor neutrophil counts closely.¹

Other Warnings

The only FDA-labeled indication is treatment of cytomegalovirus (CMV) retinitis in HIV-infected patients.¹

In animal studies, cidofovir was carcinogenic, teratogenic, and caused hypospermia.¹ (See Cautions.)

Brands: ; also available generically

Introduction

Antiviral; acyclic nucleotide analog (acyclic nucleoside phosphonate); active against herpesviruses and certain other viruses.^{3, 7, 10, 18, 75, 76,}

Uses

■ Cytomegalovirus (CMV) Retinitis

Initial treatment (induction therapy) and maintenance therapy (secondary prophylaxis) of CMV retinitis in HIV-infected adults, including those with acquired immunodeficiency syndrome (AIDS).^{1, 21, 24, 25, 31, 155,} Also used for management of CMV retinitis in **HIV-infected adolescents and children [off-label]**†.^{155, 156,}

Safety and efficacy *not* established for treatment of other CMV infections (e.g., pneumonitis, gastroenteritis), congenital or neonatal CMV disease, or CMV disease in individuals not infected with HIV.^{1,}

Like other antivirals, cidofovir is not a cure for CMV retinitis; stabilization or improvement of ocular manifestations may occur, but relapse and/or progression of CMV retinitis possible during or following cidofovir therapy.^{1, 3, 17, 21, 24, 25, 31,}

Retinitis is the most common clinical manifestation of CMV end-organ disease in HIV-infected patients;^{155,} ideally should be managed in consultation with an ophthalmologist familiar with diagnosis and treatment of retinal diseases.^{155, 156,}

Select antiviral regimen for initial treatment of CMV retinitis in HIV-infected individuals based on location and severity of CMV retinal lesions, severity of underlying immunosuppression, concomitant drug therapy, and patient's ability to adhere to the treatment regimen.^{155, 156,} Select antiviral regimen for maintenance therapy based on location of the CMV retinal lesions, vision in contralateral eye, patient's immunologic and virologic status, and patient's response to antiretroviral therapy.^{155, 156,}

For management of immediate sight-threatening CMV lesions (i.e., within 1.5 mm of the fovea) in HIV-infected adults and adolescents, CDC, NIH, and IDSA state that the preferred regimen is initial treatment (induction therapy) with intravitreal ganciclovir or intravitreal foscarnet (1–4 doses over 7–10 days) in conjunction with oral valganciclovir (twice daily for 14–21 days) followed by maintenance therapy (secondary prophylaxis) with oral valganciclovir (once daily).^{155,} One alternative regimen recommended by these experts for sight-threatening CMV retinitis in HIV-infected adults and adolescents is intravitreal ganciclovir or intravitreal foscarnet (1–4 doses over 7–10 days) in conjunction with IV cidofovir (once weekly for 2 weeks) followed by maintenance therapy (secondary prophylaxis) with IV cidofovir (once every other week).^{155,} Systemic antivirals (without an intravitreal antiviral) usually adequate for management of CMV retinitis in patients with only small peripheral lesions.^{155,}

For management of CMV retinitis in HIV-infected pediatric patients, CDC, NIH, IDSA, and others state that IV ganciclovir is drug of choice for initial treatment (induction therapy) and one of several options for maintenance therapy (secondary prophylaxis).¹⁵⁶ These experts state that IV cidofovir has not been studied in children with CMV disease, but is a possible alternative for **management of CMV retinitis in HIV-infected children [off-label]**† when other options cannot be used.¹⁵⁶

Because of risk of relapse, chronic maintenance therapy (secondary prophylaxis) of CMV retinitis usually continued until immune reconstitution occurs as a result of effective antiretroviral therapy.^{155, 156} CDC, NIH, and IDSA state that discontinuance of maintenance therapy of CMV retinitis can be considered in HIV-infected adults and adolescents if CMV lesions have been treated for ≥ 3 –6 months and are inactive and there has been a sustained (i.e., 3–6 months) increase in CD4⁺ T-cell count to $>100/\text{mm}^3$ in response to antiretroviral therapy.¹⁵⁵ Although safety of discontinuing maintenance therapy of CMV retinitis in HIV-infected pediatric patients not well studied, discontinuance of such therapy can be considered in those receiving antiretroviral therapy who have a sustained (i.e., >6 months) increase in CD4⁺ T-cell percentage to $>15\%$ (children <6 years of age) or increase in CD4⁺ T-cell count to $>100/\text{mm}^3$ (children ≥ 6 years of age).¹⁵⁶

If maintenance therapy of CMV retinitis discontinued, continue regular ophthalmologic monitoring (optimally every 3–6 months) for early detection of CMV relapse or immune reconstitution uveitis.^{155, 156} If CD4⁺ T-cell count decreases to $<100/\text{mm}^3$ (adults, adolescents, children ≥ 6 years of age) or CD4⁺ T-cell percentage decreases to $<15\%$ (children <6 years of age), reinitiate CMV retinitis maintenance therapy.^{155, 156}

■ Mucocutaneous Herpes Simplex Virus (HSV) Infections

Management of mucocutaneous infections caused by acyclovir-resistant HSV types 1 and 2 (HSV-1 and HSV-2) [off-label]† in immunocompromised individuals, including HIV-infected patients.^{39, 40, 42, 75, 155, 156}

Drugs of choice for management of orolabial lesions or initial or recurrent genital lesions caused by HSV are valacyclovir, famciclovir, and acyclovir.^{155, 156, 344}

For management of mucocutaneous lesions caused by acyclovir-resistant HSV in HIV-infected adults and **adolescents [off-label]**†, CDC, NIH, and IDSA recommend IV foscarnet as drug of choice and state that IV cidofovir is a potential alternative.¹⁵⁵ For **HIV-infected children [off-label]**†, these experts recommend IV foscarnet as drug of choice for acyclovir-resistant HSV infections and state that IV cidofovir is recommended for infections caused by HSV resistant to acyclovir and foscarnet.¹⁵⁶

Has been used **topically [off-label]**† for **management of mucocutaneous HSV infections [off-label]**†, including **genital herpes [off-label]**†, caused by acyclovir-resistant strains.^{43, 75, 78, 155, 156, 344}

■ Adenovirus Infections

Has been used for **treatment of adenovirus infections [off-label]**† in immunocompromised patients (e.g., allogeneic hematopoietic stem cell transplant recipients, solid organ transplant recipients).⁷⁵ Safety and efficacy not established and data are limited.⁷⁵

■ Varicella-Zoster Virus (VZV) Infections

Has been recommended as a possible alternative for **management of VZV infections [off-label]**†.¹⁵⁵

Preferred antivirals for management of acute, localized herpes zoster (shingles) in HIV-infected adults and adolescents are acyclovir, famciclovir, and valacyclovir.¹⁵⁵ For **management of proven or suspected acyclovir-resistant VZV infections [off-label]**† in HIV-infected adults or adolescents, CDC, NIH, and IDSA recommend IV foscarnet and state that IV cidofovir is a possible alternative.¹⁵⁵

Although optimal regimens for **management of progressive outer retinal necrosis caused by VZV [off-label]**† not identified, CDC, NIH, and IDSA recommend that such infections in HIV-infected adults and adolescents be treated with at least one IV antiviral (acyclovir, ganciclovir, foscarnet, cidofovir) used in conjunction with at least one intravitreal antiviral (ganciclovir or foscarnet).¹⁵⁵ Prognosis for visual preservation in patients with progressive outer retinal necrosis caused by VZV is poor;¹⁵⁵ such infections should be managed in consultation with an ophthalmologist.¹⁵⁵

■ Smallpox

Alternative for **treatment of certain serious complications of smallpox vaccination [off-label]**†, including eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, and aberrant vaccinia infection caused by inadvertent autoinoculation (if severe because of large numbers of lesions, toxicity, or pain).^{63, 70} Safety and efficacy not determined and possible benefits not known.⁶³

Vaccinia immune globulin IV (VIGIV) considered first-line treatment for serious complications of smallpox vaccination.^{63, 70}

If VIGIV alone is inadequate or if VIGIV not readily available, may consider use of certain antivirals (e.g., cidofovir, tecovirimat, brincidofovir) for treatment of complications of smallpox vaccination after consultation with CDC.⁷⁰

Contact state or local health department or CDC Emergency Operations Center at 770-488-7100 for assistance with diagnosis and management of suspected complications of smallpox vaccination.⁷⁰

Suggested as a possible alternative for **treatment of smallpox [off-label]**†.^{49, 50, 51} Although cidofovir is active in vitro against poxviruses, including variola virus (causative agent of smallpox), and has in vivo activity in mice against cowpox and vaccinia virus,^{53, 54, 55, 59, 60, 64} possible role, if any, for treatment of smallpox not determined.^{49, 50, 51}

■ Monkeypox

Although efficacy not established for treatment of **human monkeypox [off-label]**†,⁷¹ cidofovir is active in vitro against monkeypox and has in vivo activity against the virus in animal models.^{53, 66, 67, 68, 71, 75}

Monkeypox virus is an orthopoxvirus closely related to the causative agent of smallpox.^{50, 71} Although no specific treatments are available for human monkeypox infection, CDC states that monkeypox outbreaks can be controlled through use of smallpox vaccine, VIGIV, and certain antivirals (e.g., cidofovir, tecovirimat, brincidofovir).⁷¹

If an outbreak of monkeypox occurs in the US, CDC will establish updated guidelines for use of smallpox vaccine, VIGIV, or antivirals for treatment and/or postexposure prophylaxis of exposed individuals.⁷¹

Dosage and Administration

■ General

Assess renal function prior to initiation of cidofovir and monitor during therapy with the drug.¹ *Must* not be initiated in patients with $S_{cr} > 1.5$ mg/dL, calculated $Cl_{cr} \leq 55$ mL/minute, or urine protein concentration ≥ 100 mg/dL (equivalent to $\geq 2+$).¹ (See Renal Impairment under Dosage and Administration.)

To reduce risk of cidofovir-induced nephrotoxicity, patient *must* receive adequate hydration prior to each cidofovir dose and *must* receive a regimen of oral probenecid concomitantly with each cidofovir dose.¹

Must not exceed recommended cidofovir dosage and recommended frequency and rate of administration.¹

Hydration

All patients *must* receive ≥ 1 L of 0.9% sodium chloride infused IV over 1–2 hours immediately prior to each IV infusion of cidofovir.¹

For patients who can tolerate additional fluid, administer an additional 1 L of 0.9% sodium chloride; initiate second infusion of 0.9% sodium chloride either concomitantly with or immediately after the cidofovir IV infusion and administer over 1–3 hours.¹

Volume repletion and maintenance are particularly important in patients with potential volume depletion secondary to conditions such as chronic diarrhea, poor fluid intake, or HIV-related wasting.²⁹

Concomitant Probenecid

All patients *must* receive a regimen of oral probenecid concomitantly with each cidofovir dose.^{1, 3, 7} Cidofovir undergoes renal tubular secretion, suggesting that use of probenecid may reduce risk of cidofovir renal toxicity by decreasing concentrations of the drug within proximal tubular cells.^{1, 4, 7} For each dose of IV cidofovir, the recommended regimen of *oral probenecid* is 2 g given 3 hours prior to initiation of the cidofovir infusion, followed by 1-g doses 2 and 8 hours after completion of the cidofovir infusion, for a total *probenecid* dose of 4 g.¹

To reduce risk of nausea and/or vomiting associated with oral probenecid, food can be ingested prior to each probenecid dose and concomitant administration of an effective antiemetic can be considered.¹

For patients who develop allergic or other hypersensitivity manifestations with probenecid, appropriate prophylactic or therapeutic use of antihistamines and/or acetaminophen can be considered.¹ Because concomitant probenecid is required, cidofovir is contraindicated in patients with a history of severe hypersensitivity to probenecid or other sulfa-containing drugs.^{1, 30}

Because probenecid can affect the pharmacokinetics of many drugs, carefully assess other drugs that the patient may be receiving.¹ (See Specific Drugs under Interactions.)

■ Administration

Administer by slow IV infusion using a controlled-infusion device (e.g., pump).¹

Has been administered by **intravitreal injection [off-label]†**,^{6, 20, 24, 25, 26}, but a preparation specifically for intravitreal administration not commercially available in US.¹ Direct intraocular injection of the IV preparation (even if diluted) is *contraindicated* since such administration has been associated with iritis, ocular hypotony, and permanent visual impairment.^{1, 30}

Has been administered **topically [off-label]†** as a gel or cream for management of certain mucocutaneous viral infections (e.g., acyclovir-resistant HSV infections).^{43, 75, 78, 155, 156, 344} Although topical preparations not commercially available in US, a topical gel containing 1% cidofovir has been prepared extemporaneously using the IV preparation.^{75, 78, 155, 156, 344}

IV Infusion

Must be administered using a controlled-infusion device (e.g., pump).¹

Commercially available as a concentrate for injection containing 75 mg of cidofovir per mL that *must* be diluted prior to IV infusion.¹

Concentrate should appear clear and colorless;¹ do not use if discolored or contains particles.¹

Exercise caution when preparing, administering, and discarding solutions of cidofovir according to guidelines for handling mutagenic substances.¹ If cidofovir concentrate or a diluted solution of the drug comes in contact with skin or mucosa, wash affected area immediately and thoroughly with soap and water.¹ Discard partially used vials of cidofovir and diluted solutions of the drug by high-temperature incineration.¹

Dilution.

For IV infusion, withdraw appropriate dose of cidofovir concentrate from the vial and dilute in 100 mL of 0.9% sodium chloride injection in a compatible infusion container (e.g., PVC, glass, ethylene/propylene copolymer).¹ Administer entire volume of diluted solution within 24 hours after preparation.¹ (See Storage under Stability.)

Compatibility with Ringer's, lactated Ringer's, or bacteriostatic infusion solutions not evaluated.¹

Rate of Administration.

IV infusions should be given at a constant rate over 1 hour using a controlled-infusion device (e.g., pump).¹

To minimize risk of nephrotoxicity, IV dose must *not* be infused over a shorter time period.^{1, 29}

■ Dosage

Available as cidofovir dihydrate; dosage is expressed in terms of anhydrous cidofovir.¹

Pediatric Patients

CMV Retinitis in HIV-infected Adolescents [off-label]†.

IV– Initial treatment (induction therapy): 5 mg/kg once weekly for 2 consecutive weeks.¹⁵⁵

Maintenance therapy (secondary prophylaxis): 5 mg/kg once every 2 weeks (i.e., every other week).¹⁵⁵ If renal function declines, reduce maintenance dosage or discontinue cidofovir depending on the degree of impairment.^{1, 155} (See Renal Impairment under Dosage and Administration.)

Make decisions regarding discontinuance of CMV retinitis maintenance therapy in consultation with an ophthalmologist.¹⁵⁵ (See Cytomegalovirus [CMV] Retinitis under Uses.)

Mucocutaneous HSV Infections [off-label]†.

> Mucocutaneous Acyclovir-resistant HSV Infections in HIV-infected Adolescents [off-label]†.

IV– CDC, NIH, IDSA, and others recommend 5 mg/kg once weekly for ≥ 2 –4 weeks until a response is obtained.¹⁵⁵

Topical [off-label]†– Extemporaneously prepared gel containing cidofovir 1% [off-label]†: Has been applied to affected area once daily for 5 days.^{43, 344} In HIV-infected patients, treatment duration ≥ 3 –4 weeks recommended depending on clinical response.¹⁵⁵

Adults

CMV Retinitis in HIV-infected Adults.

IV— Initial treatment (induction therapy): 5 mg/kg once weekly for 2 consecutive weeks.^{1, 21, 24, 31, 155} If patient has immediate sight-threatening CMV retinal lesions, CDC, NIH, and IDSA recommend that initial treatment also include an intravitreal antiviral.¹⁵⁵ (See Cytomegalovirus [CMV] Retinitis under Uses.)

Maintenance therapy (secondary prophylaxis): 5 mg/kg once every 2 weeks (i.e., every other week).^{1, 24, 155} If renal function declines, reduce maintenance dosage or discontinue cidofovir depending on the degree of impairment.^{1, 155} (See Renal Impairment under Dosage and Administration.)

Make decisions regarding discontinuance of CMV retinitis maintenance therapy in consultation with an ophthalmologist.¹⁵⁵ (See Cytomegalovirus [CMV] Retinitis under Uses.)

Mucocutaneous HSV Infections [off-label]†.

> Mucocutaneous Acyclovir-resistant HSV Infections in immunocompromised Adults [off-label]†.

IV— 5 mg/kg once weekly for ≥ 2 –4 weeks until a response is obtained.^{39, 40, 155}

Topical [off-label]†— Extemporaneously prepared gel containing cidofovir 1% [off-label]†: Has been applied to affected area once daily for 5 days.^{43, 344} In HIV-infected patients, treatment duration ≥ 3 –4 weeks recommended depending on clinical response.¹⁵⁵

■ Special Populations

Dosage in Hepatic Impairment

Manufacturer makes no specific recommendation for dosage in patients with hepatic impairment;³⁰ effect on cidofovir pharmacokinetics not evaluated.³⁰

Dosage in Renal Impairment

Assess renal function prior to initiation of cidofovir and monitor during therapy with the drug.¹ (See Renal Effects under Cautions.)

Initiation of cidofovir contraindicated in patients with $S_{Cr} > 1.5$ mg/dL, calculated $Cl_{Cr} \leq 55$ mL/minute, or urine protein concentration ≥ 100 mg/dL (equivalent to $\geq 2+$).¹

If S_{Cr} increases by 0.3–0.4 mg/dL above baseline, reduce dose to 3 mg/kg.^{1, 155}

If S_{Cr} increases by ≥ 0.5 mg/dL above baseline or if proteinuria $\geq 3+$ develops, discontinue cidofovir.^{1, 155,}

If 2+ proteinuria develops in the face of a stable S_{Cr} , observe closely (including close monitoring of S_{Cr} and urinary protein) to detect potential deterioration that would warrant dose reduction or discontinuance of cidofovir.^{29, 30,}

CMV Retinitis in HIV-infected Adults and Adolescents [off-label]†.

IV— If S_{Cr} increases by 0.3–0.4 mg/dL above baseline, reduce maintenance dosage to 3 mg/kg once every 2 weeks (i.e., every other week).^{1, 155,}

If S_{Cr} increases by ≥ 0.5 mg/dL above baseline or if proteinuria $\geq 3+$ develops, discontinue cidofovir.^{1, 155,}

Geriatric Patients

Select dosage with caution because of age-related decreases in renal function.¹ (See Geriatric Use under Cautions.)

Cautions

■ Contraindications

Initiation in patients with $S_{Cr} > 1.5$ mg/dL, calculated $Cl_{Cr} \leq 55$ mL/minute, or urine protein concentration ≥ 100 mg/dL (equivalent to $\geq 2+$).¹

Concomitant use with other nephrotoxic drugs.¹ (See Interactions.)

Hypersensitivity to cidofovir.¹

History of clinically severe hypersensitivity to probenecid or other sulfa-containing drugs.¹

Direct intraocular injection of the IV preparation.¹

■ Warnings/Precautions

Warnings

Renal Effects.

Dose-dependent nephrotoxicity is the major dose-limiting toxicity.¹ In clinical trials in adults with CMV retinitis, renal toxicity (manifested by increase in S_{Cr} of ≥ 0.4 mg/dL, decrease in Cl_{Cr} to ≤ 55 mL/minute, or proteinuria $\geq 2+$) occurred in 59% of patients receiving recommended cidofovir maintenance dosage.¹

Acute renal failure resulting in dialysis and/or contributing to death has occurred with as few as 1 or 2 doses.^{1, 29, 35} In some cases, patients had risk factors for nephrotoxicity, such as preexisting mild renal insufficiency or cidofovir administration proximal to completion of aminoglycoside therapy.²⁹

Proteinuria may be an early sign of cidofovir-induced nephrotoxicity.¹ If proteinuria develops, manufacturer recommends that IV hydration be administered and the test repeated.¹

If renal function deteriorates, dosage reduction or discontinuance of cidofovir may be required.^{1, 29} (See Renal Impairment under Dosage and Administration.) Continued cidofovir may lead to additional proximal tubular cell injury, which may result in glycosuria; decreases in serum phosphate, uric acid, and bicarbonate concentrations; increases in S_{cr} concentrations; and/or acute renal failure which may require dialysis.¹

Occasionally, renal function may not return to baseline following discontinuance of cidofovir.¹

Fanconi syndrome manifested by multiple abnormalities of proximal renal tubular function reported.¹ (See Metabolic Acidosis under Cautions.)

To reduce risk of nephrotoxicity, IV hydration with 0.9% sodium chloride is required prior to each cidofovir dose and a regimen of oral probenecid is required with each cidofovir dose.¹ (See General under Dosage and Administration.)

Concomitant use with potentially nephrotoxic drugs is contraindicated;¹ discontinue such drugs ≥ 7 days prior to administration of cidofovir.^{1, 29} (See Interactions.)

Prior to initiation of cidofovir therapy, *must* assess renal function.¹ Cidofovir is contraindicated and should *not* be initiated in patients with $S_{cr} > 1.5$ mg/dL, calculated $Cl_{cr} \leq 55$ mL/minute, or urine protein concentration ≥ 100 mg/dL (equivalent to proteinuria of $\geq 2+$).¹ Because S_{cr} may not provide accurate assessment of renal function in patients with severe AIDS and CMV retinitis, use Cockcroft-Gault calculations initially to estimate Cl_{cr} more precisely when determining eligibility to receive cidofovir;^{1, 29} for subsequent assessments, S_{cr} should be used.^{29, 30}

During cidofovir therapy, *must* assess renal function (S_{cr} and urine protein) within 48 hours prior to *each* cidofovir dose and adjust dosage or withhold the drug as appropriate based on any changes in renal function.¹ (See Renal Impairment under Dosage and Administration.)

Hematologic Effects.

Neutropenia ($\leq 500/\text{mm}^3$) reported in 24% of adults in clinical trials receiving cidofovir maintenance therapy for CMV retinitis.¹

Monitor neutrophil counts during cidofovir therapy.¹

Carcinogenic and Mutagenic Potential.

Cidofovir should be considered a potential carcinogen in humans.¹ Has caused tumors (principally mammary adenocarcinomas) in rats.¹

In vitro, cidofovir induced chromosomal aberrations in human peripheral blood lymphocytes without metabolic activation, but there was no evidence of mutagenicity in microbial mutagenicity assays in the presence or absence of metabolic activation.¹

Effects on Fertility.

In animals, cidofovir has caused reduced testes weight and hypospermia.¹ Possibility exists that such effects could occur in humans and cause infertility.¹

Advise women of childbearing potential and men to use an effective method of contraception during cidofovir therapy and for certain periods of time after the drug is discontinued.¹ (See Pregnancy under Cautions.)

Selection and Use of Antivirals.

Cidofovir is labeled by FDA *only* for treatment of CMV retinitis in HIV-infected patients, including those with AIDS.¹

Safety and efficacy not established for treatment of other CMV infections or for treatment of CMV disease in individuals not infected with HIV.¹

Other Warnings/Precautions

Administration Precautions.

Administer cidofovir *only* by IV infusion;¹ do *not* administer IV preparation by intraocular injection.¹ (See Administration under Dosage and Administration.)

Patients *must* receive adequate IV hydration prior to each cidofovir dose and *must* receive a regimen of oral probenecid concomitantly with each cidofovir dose.¹ (See General under Dosage and Administration.)

Because of the potential for nephrotoxicity, recommended cidofovir dose, frequency, and rate of administration *must* not be exceeded.¹

Ophthalmologic Effects.

Decreased IOP may occur and may be associated with decreased visual acuity.¹ In adults in clinical trials receiving cidofovir maintenance therapy for CMV retinitis and whose IOP was monitored, 24% experienced $\geq 50\%$ decrease in IOP from baseline;¹ severe hypotony (i.e., IOP of 0–1 mm Hg) was reported in 3 patients.¹ Risk of ocular hypotony may be increased in patients with preexisting diabetes mellitus.¹

Uveitis or iritis reported in 11% of adults in clinical trials receiving cidofovir maintenance therapy for CMV retinitis.¹

Patients should receive periodic ophthalmic examinations to monitor IOP and visual acuity and to monitor for symptoms of uveitis or iritis.^{1, 35, 36,}

If anterior uveitis or iritis develops, consider appropriate therapy (topical corticosteroids with or without cycloplegic therapy) as indicated.^{1, 35,}

Metabolic Acidosis.

Decreased serum bicarbonate associated with proximal tubule injury and renal wasting syndrome (including Fanconi syndrome) reported.¹

Metabolic acidosis in association with liver dysfunction and pancreatitis has resulted in death.¹

Specific Populations

Pregnancy.

No adequate and well-controlled studies to date in pregnant women.¹ Use during pregnancy only if potential benefits justify potential risks to fetus.¹

In rats and rabbits, embryotoxicity (reduced fetal body weights) and maternal toxicity observed.¹ In rabbits, maternal toxicity and increased incidence of fetal external, soft tissue, and skeletal anomalies (meningocele, short snout, and short maxillary bones) observed.¹

Inform women of childbearing potential that cidofovir is embryotoxic in animals.¹ Advise women of childbearing potential to use an effective method of contraception during and for 1 month after cidofovir therapy.¹

Advise men to use a reliable method of barrier contraception during and for 3 months after cidofovir therapy.¹

For more information, see DART (<https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+dart:%22Cidofovir%22>) (Developmental and Reproductive Toxicology Database).

Lactation.

Not known whether distributed into human milk.¹

Discontinue nursing or the drug.¹

Instruct HIV-infected women not to breast-feed because of risk of HIV transmission.¹

Pediatric Use.

Safety and efficacy not established in pediatric patients < 18 years of age.^{1, 30}

Because of risks of potential long-term carcinogenic and reproductive toxicity, manufacturer states use with extreme caution in **children [off-label]**† with AIDS and *only* after careful evaluation and *only* when potential benefits outweigh risks.¹

Some experts state cidofovir has not been studied in children with CMV disease, but can be considered for management of CMV retinitis in HIV-infected **children [off-label]**† if other options cannot be used.¹⁵⁶

Geriatric Use.

Safety and efficacy not evaluated in adults >60 years of age.¹

Because geriatric patients frequently have reduced GFR, pay particular attention to monitoring renal function prior to and during cidofovir therapy in this age group and modify dosage as indicated.¹ (See Renal Impairment under Dosage and Administration.)

Renal Impairment.

Initiation of cidofovir contraindicated in patients with $S_{cr} > 1.5$ mg/dL, calculated $Cl_{cr} \leq 55$ mL/minute, or urine protein concentration ≥ 100 mg/dL (equivalent to $\geq 2+$).¹ (See Renal Impairment under Dosage and Administration.)

Pharmacokinetic data in individuals with renal impairment (Cl_{cr} as low as 11 mL/minute) indicate cidofovir clearance decreases proportionally with Cl_{cr} .¹

High-flux hemodialysis reduces serum cidofovir concentrations by approximately 75%.¹

■ Common Adverse Effects

Nephrotoxicity (proteinuria, elevated S_{cr}), nausea and/or vomiting, fever, neutropenia, asthenia, headache, rash, infection, alopecia, diarrhea, pain, anemia, decreased IOP, anorexia, dyspnea, chills, increased cough, oral moniliasis, decreased serum bicarbonate.¹

Interactions

■ Nephrotoxic Drugs

Concomitant use with other nephrotoxic drugs is contraindicated since it may increase risk of nephrotoxicity.¹ Other nephrotoxic agents *must* be discontinued ≥ 7 days prior to initiating cidofovir.¹

■ Specific Drugs

Drug	Interaction	Comments
Acetaminophen	Probenecid may affect metabolism or renal tubular excretion of acetaminophen ¹	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of acetaminophen ¹
Acyclovir	Probenecid may affect metabolism or renal tubular excretion of acyclovir ¹	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of acyclovir ¹
Aminoglycosides (amikacin, gentamicin, tobramycin)	Possible increased risk of nephrotoxicity ¹	Concomitant use contraindicated; ¹ discontinue ≥ 7 days prior to initiating cidofovir ¹
Aminosalicylic acid	Probenecid may affect metabolism or renal tubular excretion of aminosalicylic acid ¹	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of aminosalicylic acid ¹
Amphotericin B	Possible increased risk of nephrotoxicity ¹	Concomitant use contraindicated; ¹ discontinue ≥ 7 days prior to initiating cidofovir ¹
Angiotensin-converting enzyme (ACE) inhibitors	Probenecid may affect metabolism or renal tubular excretion of ACE inhibitors ¹	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of ACE inhibitors ¹
Barbiturates	Probenecid may affect metabolism or renal tubular excretion of barbiturates ¹	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of barbiturates ¹
Benzodiazepines	Probenecid may affect metabolism or renal tubular excretion of benzodiazepines ¹	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of benzodiazepines ¹

Drug	Interaction	Comments
Bumetanide	Probenecid may affect metabolism or renal tubular excretion of bumetanide ¹ ,	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of bumetanide ¹ ,
Famotidine	Probenecid may affect metabolism or renal tubular excretion of famotidine ¹ ,	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of famotidine ¹ ,
Foscarnet	Possible increased risk of nephrotoxicity ¹ ,	Concomitant use contraindicated; ¹ , discontinue ≥7 days prior to initiating cidofovir and monitor closely ¹ ,
Furosemide	Probenecid may affect metabolism or renal tubular excretion of furosemide ¹ ,	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of furosemide ¹ ,
Methotrexate	Probenecid may affect metabolism or renal tubular excretion of methotrexate ¹ ,	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of methotrexate ¹ ,
Nonsteroidal anti-inflammatory agents (NSAIDs)	Possible increased risk of nephrotoxicity ¹ , Probenecid may affect metabolism or renal tubular excretion of NSAIDs ¹ ,	Concomitant use contraindicated; ¹ , discontinue ≥7 days prior to initiating cidofovir ¹ ,
Pentamidine	IV pentamidine: Possible increased risk of nephrotoxicity ¹ ,	IV pentamidine: Concomitant use contraindicated; ¹ , discontinue ≥7 days prior to initiating cidofovir ¹ ,
Probenecid	Decreased renal clearance of cidofovir; ¹ , can also affect pharmacokinetics of other drugs patient is receiving ¹ ,	Used concomitantly with cidofovir for therapeutic advantage to reduce risk of cidofovir-associated nephrotoxicity; ¹ , ⁷⁵ , consider possible interactions with other drugs patient is receiving ¹ ,
Theophylline	Probenecid may affect metabolism or renal tubular excretion of theophylline ¹ ,	Since probenecid regimen must be used with each cidofovir dose, carefully assess concomitant use of theophylline ¹ ,
Vancomycin	Possible increased risk of nephrotoxicity ¹ ,	Concomitant use contraindicated; ¹ , discontinue ≥7 days prior to initiating cidofovir ¹ ,
Zidovudine	No evidence of pharmacokinetic interactions with cidofovir; ¹ , concomitant probenecid reduces metabolic clearance of zidovudine ¹ ,	Temporarily discontinue zidovudine or decrease zidovudine dosage by 50% on days patient receives probenecid ¹ ,

Pharmacokinetics

■ Absorption

Bioavailability

Low concentrations of cidofovir are absorbed systemically following topical application of **extemporaneously prepared gel containing cidofovir 1% [off-label]**† to mucocutaneous HSV lesions.⁴³

■ Distribution

Extent

Undetectable in CSF following IV administration in one patient.¹

Not known whether distributed into human milk.¹

Plasma Protein Binding

<6%.¹

■ Elimination

Metabolism

Cidofovir is converted via cellular enzymes to the pharmacologically active diphosphate metabolite.^{1, 2, 3, 5, 7, 11, 12, 13, 15, 16, 18, 24}

Elimination Route

When administered with usual concomitant probenecid regimen (see Concomitant Probenecid under Dosage and Administration), 70–85% of an IV cidofovir dose is eliminated unchanged in urine within 24 hours.¹ If administered without probenecid, 80–100% of the IV cidofovir dose is eliminated unchanged in urine within 24 hours.¹

Removed by hemodialysis.¹

Stability

■ Storage

Parenteral

Concentrate for IV Infusion.

20–25°C.¹

Following dilution with 0.9% sodium chloride, administer within 24 hours of preparation;¹ do not refrigerate or freeze to extend storage period beyond 24 hours.¹

If prepared in advance, diluted solution may be refrigerated at 2–8°C but should be administered within 24 hours of preparation;¹ allow solution to reach room temperature before administration.¹

■ Compatibility

Parenteral

Compatibility with Ringer's, lactated Ringer's, or bacteriostatic infusion fluids not evaluated.¹

Solution Compatibility^{HID}.

Compatible

Dextrose 5% in sodium chloride 0.45%

Dextrose 5% in water

Sodium chloride 0.9%

Actions and Spectrum

Cidofovir is a prodrug with no antiviral activity until converted via cellular enzymes to the pharmacologically active diphosphate metabolite.^{2, 3, 13, 15, 16, 18, 20, 75,}

Cidofovir diphosphate is a viral DNA polymerase inhibitor that interferes with viral DNA synthesis and inhibits viral replication^{1, 6, 10, 11, 13, 14, 16, 20, 75,} by competitive inhibition of viral DNA polymerase^{6, 14, 16, 75,} and incorporation and termination of the growing viral DNA chain.^{1, 3, 75,} The inhibitory activity of cidofovir diphosphate is highly selective^{1, 9, 10, 11, 12, 20,} because of its greater affinity for viral DNA polymerases than for human DNA polymerases.^{1, 3, 5, 75,}

Active against various herpesviruses, including CMV, HSV-1 and HSV-2, VZV, and Epstein-Barr virus (EBV).^{1, 3, 16, 24, 33, 75,} Also active in vitro against adenovirus,^{3, 16, 24, 75,} human papillomavirus (HPV),^{3, 24, 33, 75,} and human polyomavirus.^{1, 2, 3, 7, 11, 13, 15, 16, 18, 24, 34, 75,}

Has in vitro activity against poxviruses, including vaccinia virus (cowpox), monkeypox, and variola virus (causative agent of smallpox).^{45, 46, 47, 53, 57, 67, 68, 71, 75,} Also has in vivo activity against monkeypox in animal models^{53, 66, 67, 68, 71,} and against vaccinia virus in mice.^{47, 48, 53, 54, 55, 56,}

May be active against some ganciclovir-resistant CMV^{1, 2, 9, 27,} and some acyclovir-resistant HSV;^{2, 18,} active against some, but not all, CMV isolates resistant to foscarnet.¹

CMV isolates with reduced susceptibility to cidofovir have been selected in vitro.¹ Consider possibility of cidofovir-resistant CMV in patients with CMV retinitis who fail to respond to cidofovir or experience recurrent CMV retinitis progression during cidofovir therapy.^{1, 3,}

Some cidofovir-resistant CMV isolates selected in vitro have been cross-resistant to ganciclovir, but remained susceptible to foscarnet.^{1, 75,} Ganciclovir-resistant or ganciclovir- and foscarnet-resistant isolates that were cross-resistant to cidofovir have been obtained from drug-naïve patients and patients who were treated with ganciclovir with or without foscarnet.¹

Advice to Patients

The following information contains important points for the clinician to discuss with patients during counseling. For more comprehensive monographs suitable for distribution to the patient, please refer to the *AHFS Patient Medication Information* monographs available from MedlinePlus (<https://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?v:project=medlineplus&query=Cidofovir>) (in English and Spanish; written at a 6th- to 8th-grade reading level).

Advise patients that cidofovir is not a cure for CMV retinitis; they may continue to experience progression of retinitis during or following treatment.¹ Regular ophthalmologic examinations are necessary.¹ Other manifestations of CMV disease may also occur.¹

Advise HIV-infected patients who are receiving zidovudine to temporarily discontinue zidovudine or decrease the zidovudine dose by 50% on days cidofovir is administered because the probenecid regimen used with each cidofovir dose reduces metabolic clearance of zidovudine.¹

Inform patients that the major toxicity of cidofovir is renal impairment; dosage modifications, including reduction, interruption, and, possibly, discontinuance of the drug may be required.¹

Importance of close monitoring of renal function (routine urinalysis, S_{cr}) during cidofovir therapy.¹

Importance of receiving IV hydration prior to each cidofovir dose and importance of taking the recommended regimen of oral probenecid with each cidofovir dose to minimize risk of cidofovir-associated nephrotoxicity.¹

Inform patients of possible adverse effects associated with the probenecid regimen, including headache, nausea, vomiting, and hypersensitivity reactions (e.g., rash, fever, chills, anaphylaxis).¹

Advise patients that taking probenecid after a meal or concomitant use of an antiemetic may decrease nausea;¹ antihistamines and/or acetaminophen can be used to ameliorate hypersensitivity reactions.¹

Inform patients that cidofovir has caused tumors (principally mammary adenocarcinomas) in rats and the drug should be considered a potential carcinogen in humans.¹

Inform patients that cidofovir has caused reduced testes weight and hypospermia in animals and such effects may occur in humans and cause infertility.¹

Importance of informing clinician of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses.¹

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.¹ Inform women of childbearing potential that cidofovir is embryotoxic in animals and should not be used during pregnancy.¹

Advise women of childbearing potential to use effective contraception during and for 1 month after cidofovir therapy.¹ Advise men to practice barrier contraceptive methods during and for 3 months after cidofovir treatment.¹

Importance of advising patients of other important precautionary information.¹ (See Cautions.)

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

For the **treatment of serious complications of smallpox vaccination [off-label]**† or the **treatment of human monkeypox [off-label]**†, cidofovir is stored in the US Strategic National Stockpile (SNS).^{70, 71} The SNS ensures that certain drugs and medical supplies are readily available to prevent or treat specific diseases, including during public health emergencies, and is managed by the US Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR).⁷² To request a drug from the SNS, state health departments can contact the CDC Emergency Operations Center at 770-488-7100 or the HHS Secretary's Operations Center at 202-619-7800.⁷³

[Cidofovir \(https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm?sugg=NonProprietaryName&ApptName=Cidofovir&collapse=1\)](https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm?sugg=NonProprietaryName&ApptName=Cidofovir&collapse=1)

Parenteral

Concentrate, for injection, for IV infusion only

75 mg (of anhydrous cidofovir) per mL*

Cidofovir Injection

* available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Related Resources

AHFS Patient Medication Information (<https://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?v:project=medlineplus&query=Cidofovir>) and other related patient health topics (MedlinePlus)

ASHP Drug Shortages Resource Center (<https://www.ashp.org/Drug-Shortages>)

CCRIS (<https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:%22Cidofovir%22>) (Chemical Carcinogenesis Research Information System)

ChemIDplus (<https://chem.nlm.nih.gov/chemidplus/name/Cidofovir>)

Biochemical Data Summary ([http://www.drugbank.ca/unearth/q?](http://www.drugbank.ca/unearth/q?utf8=%E2%9C%93&query=Cidofovir&searcher=drugs&approved=1&vet_approved=1&nutraceutica)

[utf8=%E2%9C%93&query=Cidofovir&searcher=drugs&approved=1&vet_approved=1&nutraceutica](http://www.drugbank.ca/unearth/q?utf8=%E2%9C%93&query=Cidofovir&searcher=drugs&approved=1&vet_approved=1&nutraceutica) (US and Canada)

Clinical Trials (<https://www.clinicaltrials.gov/ct/search?submit=Search&term=Cidofovir>)

DailyMed (<https://dailymed.nlm.nih.gov/dailymed/search.cfm?query=Cidofovir>) (drug labels)

DART (<https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+dart:%22Cidofovir%22>)

(Developmental and Reproductive Toxicology Database)

Drugs@FDA ([https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?](https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchType=BasicSearch&SearchTerm=Cidofovir)

[fuseaction=Search.SearchAction&SearchType=BasicSearch&SearchTerm=Cidofovir](https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchType=BasicSearch&SearchTerm=Cidofovir)) (approval information)

European Medicines Agency ([https://www.ema.europa.eu/en/search/search?](https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=Cidofovir)

[search_api_views_fulltext=Cidofovir](https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=Cidofovir))

FDA National Drug Code Directory (<https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm?sugg=NonProprietaryName&ApptName=Cidofovir&collapse=1>)

FDA Recalls, Market Withdrawals, and Safety Alerts

(<https://www.fda.gov/Safety/Recalls/default.htm>)

HSDB (<https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:%22Cidofovir%22>) (Hazardous Substances Data Bank)

Inxight Drugs (<https://drugs.ncats.io/substances?q=%22Cidofovir%22>) (National Center for Advancing Translational Sciences)

LactMed (drug effects on breastfeeding) (<https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@or+%28@na+%22Cidofovir%22+%29>)

New Drug Approvals (<http://ahfs.ashp.org/drug-assignments.aspx>)

Orange Book ([https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?](https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?panel=0&drugname=Cidofovir)

[panel=0&drugname=Cidofovir](https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?panel=0&drugname=Cidofovir)) (therapeutic equivalence)

PharmGKB (<https://www.pharmgkb.org/search?connections&gaSearch=Cidofovir&query=Cidofovir&type=chemical>) (Pharmacogenomic data from PharmGKB)
 Pillbox (*beta*) (https://pillbox.nlm.nih.gov/pillimage/search_results.php?submit=Search&splid=&getingredient=Cidofovir) (drug identification and images)
 PubMed (<https://www.ncbi.nlm.nih.gov/pubmed?DB=pubmed&term=Cidofovir%5BAll+Fields%5D>) (scientific journals)
 Safety-related Labeling Changes (<https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges>) (FDA/CDER)
 ToxLine (<https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+toxline:%22Cidofovir%22>) (Toxicology Literature Online)

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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ASHP represents pharmacists who serve as patient care providers in acute and ambulatory settings. The organization's nearly 55,000 members include pharmacists, student pharmacists, and pharmacy technicians. For more than 75 years, ASHP has been at the forefront of efforts to improve medication use and enhance patient safety. For more information about the wide array of ASHP activities and the many ways in which pharmacists advance healthcare, visit ASHP's website (<https://www.ashp.org>), or its consumer website (<https://www.safemedication.com>).

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