Cidofovir (AHFS DI)

Boxed Warning:

Nephrotoxicity
1. 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]

2. 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] Renal function (Scr 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]

3. Contraindicated in patients receiving other nephrotoxic drugs.[1]

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

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

2. In animal studies, cidofovir was carcinogenic, teratogenic, and caused hypospermia.[1]

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
Treatment of cytomegalovirus (CMV) retinitis in adults with HIV infection, including those with acquired immunodeficiency syndrome (AIDS).[1,21,24,31,155] 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]

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]

The National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (IDSA) have developed guidelines for the management of opportunistic infections in adults and adolescents with HIV.[155] The guidelines state that first-line therapies for the treatment of immediate sight-threatening CMV retinal lesions in HIV-infected adults and adolescents include oral valganciclovir, IV ganciclovir, or IV ganciclovir induction followed by oral valganciclovir maintenance.[155] While IV foscarnet and IV cidofovir are also effective treatments, these drugs are less-preferred options because of substantial toxicity, including nephrotoxicity.[155]

The CDC, IDSA, Pediatric Infectious Diseases Society, and the US Department of Health and Human Services (HHS) have developed guidelines for the management of opportunistic Infections in children with HIV.[156] These experts state that IV ganciclovir is the drug of choice for initial treatment (induction therapy) in infants and children with HIV and acquired CMV disease, including CMV retinitis; oral valganciclovir and foscarnet may be considered as alternative options.[156] Cidofovir has not been studied in children with CMV disease, but can be considered when other options cannot be used.[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.[3,9,40,42,75,155,156]

Generally not considered a drug of choice, but an alternative therapy.[155,156,344]

Although topical formulation not commercially available, has been used topically (off-label) for management of mucocutaneous HSV infections+ 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]

Smallpox

Has been used for management of adverse reactions to vaccinia virus vaccines (smallpox vaccine) (off-label).[63,70] While antiviral activity demonstrated in animals, limited data in humans.[55,63,64,70,77]

Vaccinia immune globulin IV (VIGIV) considered first-line treatment for complications of smallpox vaccination; antivirals may be considered as a secondary treatment after consultation with CDC.[63,70]

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]

Mpox

Has been used in the treatment of mpox infection (off-label).[71] Although efficacy not established,[71] cidofovir is active in vitro against mpox and has in vivo activity against the virus in animal models.[53,66,67,68,71,75]

Mpox virus is an orthopoxvirus closely related to the causative agent of smallpox.[50,71] Although no specific treatments are available for human mpox infection, drugs that have shown to be effective against other orthopoxviruses (e.g., cidofovir, tecovirimat, brincidofovir, VIGIV) have been used to treatment severe mpox.[71]

Supportive care and pain control usually sufficient for most patients with an intact immune system who do not have a skin disease.[71] In patients who require more than supportive care, tecovirimat is typically the first therapy that should be considered.[71] Brincidofovir and VIGIV are additional therapeutics available from the Strategic National Stockpile (SNS) that can be considered in patients who need an additional or alternative treatment to tecovirimat; cidofovir can also be considered.[71] Treatment decisions should be individualized.[71] Healthcare providers may request a clinical consultation with CDC at poxvirus@cdc.gov or 770-488-7100.[71]

Dosage and Administration

General

Pretreatment Screening

1. Assess patient's renal function prior to initiating therapy.[1] The drug is contraindicated in patients with serum creatinine concentration >1.5 mg/dL, calculated creatinine clearance ≤55 mL/minute, or urine protein concentration ≥100 mg/dL (equivalent to ≥2+ proteinuria).[1]

Patient Monitoring

1. Monitor renal function (serum creatinine and urine protein) within 48 hours prior to each dose.[1]
2. Monitor white blood cell counts with differential prior to each dose.[1]
3. Monitor intraocular pressure, visual acuity, and ocular symptoms periodically.[1]
4. Monitor for signs and symptoms of uveitis/iritis during therapy.[1]

Premedication and Prophylaxis

1. Patients must receive adequate hydration prior to each dose of cidofovir to reduce the risk of cidofovir-induced nephrotoxicity.[1] Patients should receive at least 1 L of 0.9% sodium chloride infused IV over 1–2 hours immediately before each IV infusion of cidofovir.[1] For patients who can tolerate additional fluid, an additional 1 L of 0.9% sodium chloride should be administered; this second IV infusion of 0.9% sodium chloride should be initiated either concomitantly with or immediately after the cidofovir IV infusion and should be administered over 1–3 hours.[1]

Other General Considerations

1. To reduce the risk of cidofovir-induced nephrotoxicity, a regimen of oral probenecid must be administered concomitantly with each dose of cidofovir. [1,3,7]
2. For each dose of cidofovir, the recommended regimen of oral probenecid is 2 g given 3 hours prior to initiation of the cidofovir IV infusion, followed by 1-g doses given 2 and 8 hours after completion of the cidofovir IV infusion, for a total probenecid dose of 4 g.[1]
3. To reduce the 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 since probenecid is contraindicated in such patients.[1,30]
4. Because probenecid can affect the pharmacokinetics of many drugs, a careful assessment should be made of other drugs that the patient may be receiving.[1]

Administration and Preparation

Administer by IV infusion.[1] Has been administered by intravitreal injection+,[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

Administration using a controlled-infusion device (e.g., pump) recommended by manufacturer.[1]

Commercially available as an injection concentrate containing 75 mg of cidofovir per mL that must be diluted prior to IV infusion.[1] Concentrate should appear clear and colorless; 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 the drug comes in contact with skin or mucosa, wash affected area and flush thoroughly with water.[1] Discard partially used vials.[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]

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 and Children (off-label):

Initial treatment (induction therapy) in HIV-infected adolescents: 5 mg/kg IV once weekly for 2 consecutive weeks.[155]

Maintenance therapy (secondary prophylaxis): 5 mg/kg IV 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]

If cidofovir is used as an alternative for secondary prophylaxis in HIV-infected children (off-label), a dosage of 5 mg/kg IV every other week has been recommended.[156]

Make decisions regarding discontinuance of CMV retinitis maintenance

therapy in consultation with an ophthalmologist.[155,156]

Mucocutaneous HSV Infections (off-label):
Mucocutaneous Acyclovir-resistant HSV Infections in HIV-infected Adolescents (off-label):
CDC, NIH, IDSA, and others recommend 5 mg/kg IV once weekly for ≥2–4 weeks until a response is obtained.[155]

Extemporaneously prepared gel containing cidofovir 1% (off-label):
Has been applied to affected area topically 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:
Initial treatment (induction therapy): 5 mg/kg IV once weekly for 2 consecutive weeks.[1,21,24,31,155]

Maintenance therapy (secondary prophylaxis): 5 mg/kg IV 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]

Make decisions regarding discontinuance of CMV retinitis maintenance therapy in consultation with an ophthalmologist.[155]

Mucocutaneous HSV Infections (off-label):
Mucocutaneous Acyclovir-resistant HSV Infections in immunocompromised Adults (off-label):
5 mg/kg IV once weekly for ≥2–4 weeks until a response is obtained.[39,40,155]

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

Special Populations
Hepatic Impairment
Manufacturer makes no specific recommendation for dosage in patients with hepatic impairment; effect on cidofovir pharmacokinetics not evaluated.[30]

Renal Impairment
Assess renal function prior to initiation of cidofovir and monitor during therapy with the drug.[1]

Initiation of cidofovir contraindicated in patients with Scr >1.5 mg/dL, calculated Clcr ≤55 mL/minute, or urine protein concentration ≥100 mg/dL (equivalent to ≥2+)[1]

If Scr increases by 0.3–0.4 mg/dL above baseline, reduce dose to 3 mg/kg.[1,155]

If Scr increases by ≥0.5 mg/dL above baseline or if proteinuria ≥3+ develops, discontinue cidofovir.[1,155]

If 2+ proteinuria develops in the face of a stable Scr, observe closely (including close monitoring of Scr 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):
If Scr increases by 0.3–0.4 mg/dL above baseline, reduce maintenance dosage to 3 mg/kg IV once every 2 weeks (i.e., every other week).[1,155] If Scr increases by ≥0.5 mg/dL above baseline or if proteinuria ≥3+ develops, discontinue cidofovir.[1,155]

Geriatric Patients
Select dosage with caution because of age-related decreases in renal function.[1]

Cautions
Contraindications
1. Initiation in patients with Scr >1.5 mg/dL, calculated Clcr ≤55 mL/minute, or urine protein concentration ≥100 mg/dL (equivalent to ≥2+ proteinuria).[1]
2. Concomitant use with other nephrotoxic drugs.[1] Such agents must be discontinued at least 7 days prior to starting therapy with cidofovir injection.[1]
3. Hypersensitivity to cidofovir.[1]
4. History of clinically severe hypersensitivity to probenecid or other sulfa-containing drugs.[1]
5. Direct intraocular injection of the IV preparation.[1]

Warnings and Precautions
Renal Effects
Dose-dependent nephrotoxicity is the major dose-limiting toxicity (see Boxed Warning).[1] In clinical trials in adults with CMV retinitis, renal toxicity (manifested by increase in Scr of ≥0.4 mg/dL, decrease in Clcr to ≤55 mL/minute, or proteinuria ≥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] 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 Scr 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]

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]

Concomitant use with potentially nephrotoxic drugs is contraindicated;[1] discontinue such drugs ≥7 days prior to administration of cidofovir.[1,29]

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

During cidofovir therapy, must assess renal function (Scr 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]

Hematologic Effects
Neutropenia (≤500/mm3) reported in 24% of adults in clinical trials receiving cidofovir maintenance therapy for CMV retinitis (see Boxed Warning).[1] Monitor neutrophil counts during cidofovir therapy.[1]

Carcinogenic and Mutagenic Potential
Cidofovir should be considered a potential carcinogen in humans (see Boxed Warning).[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 (see Boxed Warning).[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]

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]

Administration Precautions
Administer cidofovir only by IV infusion; do not administer IV preparation by intraocular injection.[1]

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] 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 ≥50% decrease in IOP from baseline; 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 adults 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 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]

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]

The HHS perinatal HIV transmission guideline provides updated recommendations on infant feeding.[202] The guideline states that patients with HIV should receive evidence-based, patient-centered counseling to support shared decision making about infant feeding.[202] During counseling, patients should be informed that feeding with appropriate formula or pasteurized donor human milk from a milk bank eliminates the risk of postnatal HIV transmission to the infant.[202] Additionally, achieving and maintaining viral suppression with antiretroviral therapy during pregnancy and postpartum reduces the risk of breastfeeding HIV transmission to <1%, but does not completely eliminate the risk.[202] Replacement feeding with formula or banked pasteurized donor milk is recommended when patients with HIV are not on antiretroviral therapy and/or do not have a suppressed viral load during pregnancy (at a minimum throughout the third trimester), as well as at delivery.[202]

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]

Renal Impairment

Initiation of cidofovir contraindicated in patients with Scr >1.5 mg/dL, calculated Clcr ≤55 mL/minute, or urine protein concentration ≥100 mg/dL (equivalent to ≥2+)[1]

Pharmacokinetic data in individuals with renal impairment (Clcr as low as 11 mL/minute) indicate cidofovir clearance decreases proportionally with Clcr.[1] High-flux hemodialysis reduces serum cidofovir concentrations by approximately 75%[1]

Common Adverse Effects
Most common adverse effects (≥15%): nephrotoxicity (proteinuria, elevated Scr), 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]

Drug 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]

Please refer to the full prescribing information for additional information regarding drug interactions with cidofovir.

Pharmacokinetics
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]

Extent
Undetectable in CSF following IV administration in one patient.[1]
Not known whether distributed into human milk.[1]

Plasma Protein Binding
<6%[1]

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, 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

Concentrate for IV Infusion: 20–25°C.[1]

Following dilution with 0.9% sodium chloride, administer within 24 hours of preparation; 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; allow solution to reach room temperature before administration.[1]

Actions

1. 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]
2. 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]
3. 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]
4. 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]
5. 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]
6. 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]
7. 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-naive patients and patients who were treated with ganciclovir with or without foscarnet.[1]

Advice to Patients

1. 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]
2. 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]
3. 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] Stress importance of close monitoring of renal function (routine urinalysis, Scr) during cidofovir therapy.[1]
4. Stress importance of receiving IV hydration prior to each cidofovir dose and of taking the recommended regimen of oral probenecid with each cidofovir dose to minimize risk of cidofovir-associated nephrotoxicity.[1]
5. Advise patients of the importance of completing a full course of probenecid with each cidofovir injection. 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; antihistamines and/or acetaminophen can be used to ameliorate hypersensitivity reactions.[1]
6. Inform patients that cidofovir has caused tumors (principally mammary adenocarcinomas) in rats and the drug should be considered a potential carcinogen in humans.[1]
7. Inform patients that cidofovir has caused reduced testes weight and hypospermia in animals and such effects may occur in humans and cause infertility.[1]
8. Stress importance of informing clinician of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses.[1]
9. Stress 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]
10. 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]
11. Inform patients of other important precautionary information.[1]

Preparations

Restricted Distribution

For the treatment of smallpox (off-label), cidofovir is stored in the US Strategic National Stockpile (SNS).[79]

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

Cidofovir
Concentrate, for injection, for IV infusion only
75 mg (of anhydrous cidofovir) per mL

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