Cidofovir (Vistide®)

Class:
Cidofovir is an acyclic phosphonate nucleotide analog.

Antiviral Activity:
Cidofovir has activity against herpesviruses, adenoviruses, and papillomaviruses.

Mechanism of Action:
Cidofovir undergoes two stages of phosphorylation, via monophosphate kinase and pyruvate kinase respectively, to form an active metabolite, cidofovir diphosphate. Cidofovir diphosphate acts as a competitive inhibitor and an alternate substrate for cytomegalovirus (CMV) DNA polymerase. It is incorporated into the growing CMV DNA strand and blocks further viral DNA synthesis leading to non-productive infection.

The mechanism of action in cells infected with HPV differs from that of CMV, because HPV utilizes host cell DNA polymerase instead of a virally encoded polymerase. Infected cells are trapped in the S phase, which indicates a halt of DNA synthesis. Cidofovir also induces DNA fragmentation and caspase-3 protease activity, an early event in the induction of apoptosis, in HPV-positive cells.

Mechanism of Resistance:
Cidofovir-resistant strains of HSV-1 and HSV-2 have been created under selective pressure *in vitro*. However, precise mutations leading to resistance have not been fully elucidated. *In vivo,* various regimens of cidofovir have failed to produce drug-resistant viruses.

Pharmacodynamics:
Cidofovir is metabolized intracellularly to mono- and diphosphate moieties, as well as to cidofovir monophosphate choline. The long intracellular half-lives of the diphosphate and choline derivatives (17 and > 48 hours, respectively) contribute to long-acting activity. Therefore, once-weekly dosing regimens are justified even though actual plasma concentrations of cidofovir may not be detectable shortly after the infusion.

Pharmacokinetics:
Following oral administration, the absolute bioavailability of cidofovir ranges from 5 to 22%. The primary route of elimination is renal, with approximately 90% of the total dose cleared by the kidneys. Active tubular secretion appears to play a role in the elimination of cidofovir.

Adverse Effects:
Nephrotoxicity is the most common adverse effect and the risk increases with increasing dose and frequency. Neutropenia, asthenia, alopecia, ocular hypotony, Fanconi syndrome, anterior uveitis/iritis, hearing loss, neoplasms, and cardiomyopathy have also been seen with cidofovir. Application site reactions, such as inflammation, erosion and burning sensation are common and can occasionally be severe.
Postinflammatory hyperpigmentation and transient alopecia on the bearded area have also been observed.

Adverse events reported with cidofovir and concurrent probenecid include constitutional reactions, such as fever, chills, nausea, vomiting, fatigue, headache, gastrointestinal upset and rash.

Dosage:
Solution for Injection (75 mg/ml)

Adults:
CMV retinitis:
induction therapy – 5 mg/kg intravenously once weekly for two consecutive weeks
maintenance therapy – 5 mg/kg every other week

Administer each dose of cidofovir with a total of 4 gm of probenecid:
2 gm, 3 hours before cidofovir infusion and 1 gm at 2 and 8 hours after infusion.
Administer 1 liter of 0.9% sodium chloride immediately before each cidofovir infusion and, if additional fluid can be tolerated, give 1 liter of 0.9% sodium chloride with or immediately following the cidofovir infusion.

Probenecid and prehydration helps to provide renal protection. Tubular secretion of cidofovir is blocked by probenecid, leading to less accumulation in renal tubular cells, faster elimination of the drug from the kidney, and overall decreased exposure of the kidney to the drug.

Children: Only use when the potential benefits of the drug outweigh the risks (long-term carcinogenic and reproductive toxicity)

Disease state based dosing:
Renal Impairment:
Increase in serum creatinine of 0.3–0.4 mg/dL – reduce dose to 3 mg/kg
Increase in serum creatinine of 0.5 mg/dL or more, or 3+ or higher proteinuria – discontinue therapy
Preexisting serum creatinine exceeding 1.5 mg/dL, or creatinine clearance < 55 mL/min, or preexisting urine protein concentration of > 100 mg/dL (equivalent to > 2+ proteinuria) – contraindicated
Hepatic Impairment:
No specific recommendation for dosage adjustment

Contraindications/Warnings/ Precautions:
Cidofovir use is contraindicated with preexisting serum creatinine exceeding 1.5 mg/dL, or creatinine clearance < 55 mL/min, or preexisting urine protein concentration of > 100 mg/dL (equivalent to > 2+ proteinuria) as well as use with or within 7 days of nephrotoxic agents.

Drug Interactions:
Probenecid – inhibits the active tubular secretion of cidofovir.
Amphotericin B, aminoglycosides, pentamidine, and other nephrotoxic agents – increase the risk of nephrotoxicity and are contraindicated

Pregnancy:
Category C: Risk unknown. Human studies inadequate

Monitoring Requirements:
Serum creatinine and urine protein (within 48 hours prior to each dose), CBC and regular ophthalmologic examinations.

Brand names/Manufacturer:
Vistide®/ Gilead Sciences Inc