Valganciclovir

Brand Name: Valcyte
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Valganciclovir hydrochloride is a hydrochloride salt of the L-valyl ester of ganciclovir that exists as a mixture of two diastereomers. Ganciclovir is a synthetic analogue of 2-deoxyguanosine. [1]

HIV/AIDS-Related Uses

Valganciclovir hydrochloride was approved by the FDA on March 29, 2001, for the treatment of cytomegalovirus (CMV) retinitis in patients with weakened immune systems, including individuals with HIV and AIDS.[2] It is currently being investigated to determine its efficacy in preventing CMV end-organ disease in HIV infected patients.[3] It is also being investigated for safety and efficacy in treating congenital CMV disease in neonates.[4]

Non-HIV/AIDS-Related Uses

Valganciclovir was approved by the FDA on September 12, 2003, for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk (donor CMV seropositive/recipient CMV seronegative).[5] It is being investigated for its efficacy in treating and preventing CMV disease in stem cell transplant recipients.[6]

Pharmacology

Valganciclovir is a prodrug of ganciclovir; it is converted rapidly to ganciclovir by intestinal and hepatic esterases. Subsequent intracellular phosphorylation converts ganciclovir to ganciclovir triphosphate, which inhibits viral DNA synthesis by competing with deoxyguanosine for incorporation into viral DNA, thus terminating DNA synthesis at the point of incorporation. Because initial phosphorylation depends largely on the presence of the viral protein kinase pUL97, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.[7]

The absolute bioavailability of ganciclovir following oral administration of valganciclovir is approximately 60%, about 10-fold higher than that following oral administration of ganciclovir. The mean 24-hour area under the plasma concentration-time curve (AUC24) for ganciclovir following once-daily administration of 900 mg of oral valganciclovir is comparable to that for once-daily administration of 5 mg/kg intravenous (IV) ganciclovir and exceeds the AUC24 for 1 g of oral ganciclovir administered three times daily.[8] Peak plasma concentration of ganciclovir is approximately 5.6 mcg/ml, and time to peak concentration following administration of 450 mg to 2,625 mg valganciclovir tablets is from 1 to 3 hours.[9] [10]

Valganciclovir is in FDA Pregnancy Category C. There have been no adequate or well-controlled studies in pregnant women; however, data obtained using an ex vivo human placental model show that ganciclovir crosses the placenta, likely through simple diffusion. Because valganciclovir is rapidly converted to ganciclovir in vivo, it is expected to have reproductive toxicity similar to ganciclovir. It is not known whether valganciclovir is excreted in human milk; however, valganciclovir caused granulocytopenia, anemia, and thrombocytopenia in clinical trials, and ganciclovir was mutagenic and carcinogenic in animal studies. Because of the potential for HIV transmission and for serious adverse events from valganciclovir to breastfed infants, women should be instructed not to breastfeed while taking valganciclovir.[11] [12]

Due to valganciclovir's rapid conversion to ganciclovir following oral administration, protein binding of valganciclovir has not been established. Plasma protein binding of ganciclovir is 1% to 2% over concentrations of 0.5 and 51 mcg/ml. In one study, the steady state volume of IV ganciclovir was reported to be 0.703 +/- 0.134 l/kg.[13]

Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected. For a single 1,000 mg dose of radiolabeled oral ganciclovir, no metabolite accounts for more than 1% to 2% of the radioactivity recovered in the feces or urine. The terminal half-life of ganciclovir following oral administration of valganciclovir is approximately 4.08 hours.[14]

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Pharmacology (cont.)

Valganciclovir is eliminated as ganciclovir via renal excretion through both glomerular filtration and active tubular secretion. Renal impairment decreases the clearance of ganciclovir and increases terminal half-life.[15]

Viral resistance can arise after prolonged treatment with valganciclovir. Selection of mutations in the viral protein kinase gene UL97 results in resistance to ganciclovir only, whereas mutations in the viral polymerase gene UL54 may show cross resistance to other antivirals with a similar mechanism of action. Viral resistance has been observed in patients receiving prolonged treatment for CMV retinitis with ganciclovir. CMV resistance to ganciclovir has also been observed in individuals with both AIDS and CMV retinitis who have never received ganciclovir therapy.[16]

Adverse Events/Toxicity

In animal studies, ganciclovir caused aspermatogenesis and was found to be carcinogenic, mutagenic, and teratogenic. Valganciclovir should therefore be considered a potential teratogen and carcinogen in humans. Women of childbearing age should use effective contraception during treatment, and men should practice barrier contraception during treatment and for at least 90 days following treatment.[17]

The most frequent and clinically significant adverse effects of valganciclovir are fever; retinal detachment; and hematologic reactions, including anemia, neutropenia, and thrombocytopenia. Other frequently reported but less serious adverse effects include abdominal pain, diarrhea, headache, insomnia, nausea and vomiting, paresthesia, and peripheral neuropathy.[18]

Drug and Food Interactions

Because valganciclovir is rapidly and extensively converted to ganciclovir, drug interactions associated with ganciclovir would be expected for valganciclovir. Concurrent administration of valganciclovir with nephrotoxic medications (or if valganciclovir is administered to individuals with renal impairment) increases the chance of renal function impairment and may cause toxic accumulation of ganciclovir in the body. Patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.[19] Drugs with potential for clinically significant interactions with ganciclovir include didanosine, myelosuppressive agents or irradiation, mycophenolate, probenecid, and zidovudine.[20]

Contraindications

Valganciclovir is contraindicated in patients with hypersensitivity to valganciclovir or ganciclovir. Valganciclovir should not be administered to patients undergoing hemodialysis because the appropriate daily dose for these patients is lower than 450 mg, which would require breaking a tablet. Broken valganciclovir tablets pose a hazard to skin and mucous membranes.[21]

Clinical Trials

For information on clinical trials that involve Valganciclovir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Valganciclovir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[22]

Dosage Form: Tablets containing valganciclovir HCl 496.3 mg (corresponding to valganciclovir 450 mg).[23]

Storage: Store tablets at 25 C (77 F); excursions permitted between 15 C to 30 C (59 F to 86 F).[24]

Chemistry

CAS Name: L-Valine, 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-3-hydroxypropyl ester, monohydrochloride[25]

CAS Number: 175865-60-8[26]

Molecular formula: C14-H22-N6-O5.Cl-H[27]

C43.02%, H5.93%, N21.51%, O20.47%, Cl9.07%[28]

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Chemistry (cont.)

Molecular weight: 390.83[29]

Physical Description: White to off-white crystalline powder.[30]

Solubility: 70 mg/ml in water at 25 C and pH of 7.0.[31]

Other Names

RO 107-9070/194[32]

RS-079070-194[33]

Valcyt[34]

Valganciclovir hydrochloride[35]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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