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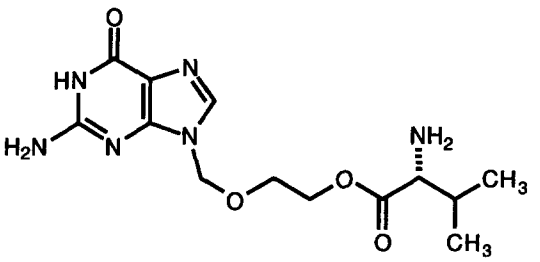
New Drugs—Reports of New Drugs Recently Approved by the FDA

Valacyclovir



Structure
$C_{13}H_{20}N_6O_4$ MW 324.34
[CAS 124832-26-4]

L-Valine 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester

Supply: Hydrochlorides, [CAS 124832-27-5], crystalline solid as hydrate.

VALTREX®
256U, 256U87, BW-256 Valacyclovir HCl, Zelitrex, ValACV

Mechanism of action: Terminates production of viral DNA.

Therapeutic category: Antiviral.

Synthesis: Valacyclovir was prepared in two steps. The carbobenzyloxy (Cbz) protected amino acid was coupled with acyclovir using the coupling reagent, dicyclohexylcarbodiimide (DCC) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in DMF. Deprotection by catalytic hydrogenation in the presence of HCl gave the desired aminoacyl ester as the hydrochloride salt. Minor racemization during the ester formation was observed.[1]

Summary: Valacyclovir is the L-valyl ester prodrug of acyclovir and exhibits similar potency, but has more favorable pharmacokinetic characteristics, requiring a less frequent dosing schedule and achieving higher blood plasma levels than acyclovir. With the acyclovir prodrugs, the physical properties such as water or lipid solubilities (log P) are not major determinants of the most effective bioavailability. The structure–activity relationship of the amino acid esters suggests the involvement of a stereospecific transport process. The common branched chain amino acids, L-valine and L-isoleucine, are favored by this proposed transporter.[2] Acyclovir is a derivative of guanosine. A critical step in its activation is phosphorylation by viral thymidine kinase. The affinity of acyclovir for herpes virus-encoded thymidine kinase is approximately 200 times greater than for human thymidine kinase, and phosphorylation of acyclovir by the human enzyme occurs at a negligible rate. This selective affinity results in the activation and concentration of acyclovir in virus-infected cells. After phosphorylation to acyclovir monophosphate (acyclo-GMP), normal cellular enzymes catalyze the sequential phosphorylation to acyclovir diphosphate (acyclo-GDP) and acyclovir triphosphate (acyclo-GTP). Acyclovir triphosphate terminates the production of viral DNA by inhibiting DNA polymerase via competition with deoxyguanosine triphosphate; it has selective affinity for viral DNA polymerase. In addition, acyclo-GTP is incorporated into the elongating viral DNA, where it causes termination of the viral DNA strand.[3,4,5] After oral administration, valacyclovir is rapidly absorbed and extensively converted to acyclovir via first-pass metabolism. Acyclovir has been detected in plasma as early as 15 min after the valacyclovir administration. Oral administration results in plasma acyclovir concentrations approximately 3- to 5-fold greater than those achievable with comparable oral doses of acyclovir.[6,7,8] The elimination half-life of acyclovir is

approximately 3 h; acyclovir is primarily excreted unchanged in the urine. Valacyclovir appears to be a significant development in antiviral therapy. Its significantly greater oral bioavailability results in plasma acyclovir levels comparable to those seen with intravenous acyclovir. Although acyclovir has been effective in immunocompetent patients with mucocutaneous herpes simplex virus (HSV) infection, the need for multiple daily dosing has been problematic. With a higher C_{max} after valacyclovir administration, less frequent dosing may be equally effective, both for acute treatment and for suppression. In the treatment of recurrent genital herpes simplex infections, valacyclovir 1,000 mg orally twice a day for 5 days has been effective. In patients receiving the drug within 24 h of initiation of signs and symptoms, valacyclovir was as effective as acyclovir in reducing time to lesion healing and length of episode.[9] Herpes zoster (shingles) patients treated with oral valacycyclovir report complete cessation of postherpetic pain in a statistically shorter time than patients treated with oral acyclovir; the two drugs have a similar time to rash healing. Valacyclovir has been approved for marketing in the U.S.A. as a treatment for shingles in immunocompetent patients. Valacyclovir was first launched in the U.K. and Ireland in January 1995, and has since been launched in Sweden.

Manufacturer: Glaxo Wellcome.

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