CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVED LABELING

Final Printed Labeling

VALTREX® (valacyclovir hydrochloride) Caplets

PRODUCT INFORMATION

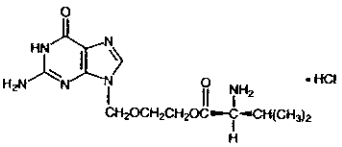
VALTREX®
(valacyclovir hydrochloride)
Caplets

JAN 13 1997
APPROVED

DESCRIPTION: VALTREX (valacyclovir hydrochloride) is the hydrochloride salt of L-valyl ester of the antiviral drug acyclovir (ZOVIRAX® Brand, Glaxo Wellcome Inc.).

VALTREX Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

The chemical name of valacyclovir hydrochloride is *L*-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl ester, monohydrochloride. It has the following structural formula:



Valacyclovir hydrochloride is a white to off-white powder with the molecular formula $C_{13}H_{20}N_6O_4 \cdot HCl$ and a molecular weight of 360.80. The maximum solubility in water at 25°C is 174 mg/mL. The pk_a's for valacyclovir hydrochloride are 1.90, 7.47, and 9.43.

MICROBIOLOGY: Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV) both in vitro and in vivo. In cell culture, acyclovir's highest antiviral activity is against HSV-1, followed in decreasing order of potency against HSV-2 and VZV.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV, VZV, and EBV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities: The quantitative relationship between the in vitro susceptibility of herpesviruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 µg/mL for HSV-1 and from 0.01 to 9.9 µg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 µg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 µg/mL.

Drug Resistance: Resistance of VZV to antiviral nucleoside analogues can result from qualitative or quantitative changes in the viral TK or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to acyclovir have been recovered from patients with AIDS. In these cases, TK-deficient mutants of VZV have been recovered.

Resistance of HSV to antiviral nucleoside analogues occurs by the same mechanisms as resistance to VZV. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to valacyclovir (and therefore acyclovir) should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY: After oral administration, valacyclovir is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism.

Pharmacokinetics: The pharmacokinetics of valacyclovir and acyclovir after oral administration of VALTREX have been investigated in 12 volunteer studies involving 253 adults.

Absorption and Bioavailability: The absolute bioavailability of acyclovir after administration of VALTREX is 54.5% ± 9.1% as determined following a 1-gram oral dose of VALTREX and a 350-mg intravenous acyclovir dose to 12 healthy volunteers. Acyclovir bioavailability from the administration of VALTREX is not altered by administration with food (30 minutes after an 873 Kcal breakfast, which included 51 grams of fat).

There was a lack of dose proportionality in acyclovir maximum concentration (C_{max}) and area under the acyclovir concentration-time curve (AUC) after single-dose administration of 100 mg, 250 mg, 500 mg, 750 mg, and 1 gram of VALTREX to eight healthy volunteers. The mean C_{max} (± S.D.) was 0.83 (± 0.14), 2.15 (± 0.50), 3.28 (± 0.83), 4.17 (± 1.14), and 5.65 (± 2.37) µg/mL, respectively; and the mean AUC (± S.D.) was 2.28 (± 0.40), 5.76 (± 0.60), 11.59 (± 1.79), 14.11 (± 3.54), and 19.52 (± 6.04) hr•µg/mL, respectively.

There was also a lack of dose proportionality in acyclovir C_{max} and AUC after the multiple-dose administration of 250 mg, 500 mg, and 1 gram of VALTREX administered four times daily for 11 days in parallel groups of eight healthy volunteers. The mean C_{max} (± S.D.) was 2.11 (± 0.33), 3.69 (± 0.87), and 4.96 (± 0.64) µg/mL, respectively, and the mean AUC (± S.D.) was 5.66 (± 1.09), 9.88 (± 2.01), and 15.70 (± 2.27) hr•µg/mL, respectively.

There is no accumulation of acyclovir after the administration of valacyclovir at the recommended dosage regimens in healthy volunteers with normal renal function.

Distribution: The binding of valacyclovir to human plasma proteins ranged from 13.5% to 17.9%.

Metabolism: After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract. Valacyclovir is rapidly and nearly completely converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism. Acyclovir is converted to a small extent to inactive metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither valacyclovir nor acyclovir metabolism is associated with liver microsomal enzymes. Plasma concentrations of unconverted valacyclovir are low and transient, generally becoming non-quantifiable by 3 hours after administration. Peak plasma valacyclovir concentrations are generally less than 0.5 µg/mL at all doses. After single-dose administration of 1 gram of VALTREX, average plasma valacyclovir concentrations observed were 0.5, 0.4, and 0.8 µg/mL in patients with hepatic dysfunction, renal insufficiency, and healthy volunteers who received concomitant cimetidine and probenecid, respectively.

Elimination: The pharmacokinetic disposition of acyclovir delivered by valacyclovir is consistent with previous experience from intravenous and oral acyclovir. Following the oral administration of a single 1-gram dose of radiolabeled valacyclovir to four healthy subjects, 45.60% and 47.12% of administered radioactivity was recovered in urine and feces over 96 hours, respectively. Acyclovir accounted for 88.60% of the radioactivity excreted in the urine. Renal clearance of acyclovir following the administration of a single 1-gram dose of VALTREX to 12 healthy volunteers was approximately 255 ± 86 mL/min which represents 41.9% of total acyclovir apparent plasma clearance.

The plasma elimination half-life of acyclovir typically averaged 2.5 to 3.3 hours in all studies of VALTREX in volunteers with normal renal function.

End-Stage Renal Disease (ESRD): Following administration of VALTREX to volunteers with ESRD, the average acyclovir half-life is approximately 14 hours. During hemodialysis, the acyclovir half-life is approximately 4 hours. Approximately one-third of acyclovir in the body is removed by dialysis during a 4-hour hemodialysis session. Apparent plasma clearance of acyclovir in dialysis patients was 86.3 ± 21.3 mL/min/1.73 m^2, compared to 679.16 ± 162.76 mL/min/1.73 m^2 in healthy volunteers.

Reduction in dosage is recommended in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Geriatrics: After single-dose administration of 1 gram of VALTREX in healthy geriatric volunteers (n = 9, mean age ± S.D. = 74.0 ± 5.4 years), the half-life of acyclovir was 3.11 ± 0.51 hours, compared to 2.91 ± 0.63 hours in healthy volunteers (n = 33, mean age ± S.D. = 41.2 ± 10.1 years). Dosage modification may be necessary in geriatric patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Pediatrics: Valacyclovir pharmacokinetics have not been evaluated in pediatric patients.

Liver Disease: Administration of VALTREX to patients with moderate (biopsy-proven cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver disease indicated that the rate but not the extent of conversion of valacyclovir to acyclovir is reduced, and the acyclovir half-life is not affected. Dosage modification is not recommended for patients with cirrhosis.

HIV Disease: In nine patients with advanced HIV disease (CD4 cell counts <150 cells/mm^3) who received VALTREX at a dosage of 1 gram four times daily for 30 days, the pharmacokinetics of valacyclovir and acyclovir were not different from that observed in healthy volunteers (see WARNINGS).

Drug Interactions: The administration of cimetidine and probenecid, separately or together, reduced the rate but not the extent of conversion of valacyclovir to acyclovir. Acyclovir C_{max} was increased 8.4% ± 27.8%, 22.5% ± 25.3%, and 29.6% ± 27.5% by cimetidine, probenecid, and combination treatment (concomitant cimetidine and probenecid administration), respectively. Acyclovir AUC (0 to 24) was increased 31.9% ± 22.9%, 49.0% ± 27.9%, and 77.9% ± 38.6% by cimetidine, probenecid, and combination treatment, respectively. The renal clearance of acyclovir was reduced by approximately 23.5% ± 9.6%, 33.0% ± 10.4%, and 46% ± 11.2% with cimetidine, probenecid, and combination treatment, respectively, resulting in higher plasma acyclovir concentrations. Thiazide diuretics did not affect acyclovir pharmacokinetics after administration of VALTREX in a geriatric population.

Clinical Trials: ***Herpes Zoster Infections:*** Two randomized double-blind clinical trials in immunocompetent patients with localized herpes zoster were conducted. VALTREX was compared to placebo in patients less than 50 years of age, and to ZOVIRAX in patients greater than 50 years of age. All patients were treated within 72 hours of appearance of zoster rash. In patients less than 50 years of age, the median time to cessation of new lesion formation was 2 days for those treated with VALTREX compared to 3 days for those treated with placebo. In patients greater than 50 years of age, the median time to cessation of new lesions was 3 days in patients treated with either VALTREX or ZOVIRAX. In patients less than 50 years of age, no difference was found with respect to the duration of pain after rash healing (post-herpetic neuralgia) between the recipients of VALTREX and placebo. In patients greater than 50 years of age, among the 83% who reported pain after healing (post-herpetic neuralgia), the median duration of pain after healing [95% confidence interval] in days was: 40 [31, 51], 43 [36, 55], and 59 [41, 77] for 7-day VALTREX, 14-day VALTREX, and 7-day ZOVIRAX, respectively.

Initial Genital Herpes: In a randomized, double-blind trial, immunocompetent adults with first episode genital herpes who presented within 72 hours of symptom onset were randomized to receive for 10 days VALTREX 1 gram b.i.d. (n = 323) or ZOVIRAX 200 mg 5 times a day (n = 320). For both treatment groups: the median time to lesion healing was 9 days, the median time to cessation of pain was 5 days, the median time to cessation of viral shedding was 3 days.

Recurrent Genital Herpes: Two double-blind placebo-controlled trials in immunocompetent patients with recurrent genital herpes were conducted. Patients self-initiated therapy within 24 hours of the first sign or symptom of a recurrent genital herpes episode.

In one study, patients were randomized to receive 5 days of treatment with either VALTREX 500 mg b.i.d. (n = 360) or placebo (n = 259). The median time to lesion healing was 4 days in the group receiving VALTREX 500 mg versus 6 days in the placebo group, and the median time to cessation of viral shedding in patients with at least one positive culture (42% of the overall study population) was 2 days in the group receiving VALTREX 500 mg versus 4 days in the placebo group. The median time to cessation of pain was 3 days in the group receiving VALTREX 500 mg versus 4 days in the placebo group. Results supporting efficacy were replicated in a second trial.

ORIGINAL

Labeling: _____

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VALTREX® (valacyclovir hydrochloride) Caplets

INDICATIONS AND USAGE:
Herpes Zoster: VALTREX is indicated for the treatment of herpes zoster (shingles).
Genital Herpes: VALTREX is indicated for treatment of the initial episode and for the episodic treatment of recurrent genital herpes.

CONTRAINDICATIONS: VALTREX is contraindicated in patients with a known hypersensitivity or intolerance to valacyclovir, acyclovir, or any component of the formulation.

WARNINGS: Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), *in some cases resulting in death, has occurred in patients with* advanced HIV disease and also in allogeneic bone marrow transplant and renal transplant recipients participating in clinical trials of VALTREX at doses of 8 grams per day.

PRECAUTIONS: The efficacy of VALTREX has not been established for the treatment of disseminated herpes zoster, or suppression of recurrent genital herpes, or in immunocompromised patients.

Dosage adjustment is recommended when administering VALTREX to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Caution should also be exercised when administering VALTREX to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

Information for Patients: ***Herpes Zoster:*** There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes: Patients should be informed that VALTREX is not a cure for genital herpes. There are no data evaluating whether VALTREX will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

There are no data on the effectiveness of treatment initiated more than 72 hours after the onset of signs and symptoms of a first episode of genital herpes or more than 24 hours of the onset of signs and symptoms of a recurrent episode.

Drug Interactions: An additive increase in acyclovir AUC and C_{max} was observed when VALTREX was administered to healthy volunteers who were taking cimetidine, probenecid, or a combination of both cimetidine and probenecid (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to the steady-state acyclovir *AUC observed in humans treated with* 1 gram VALTREX given orally three times a day to treat herpes zoster. Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Valacyclovir was noncarcinogenic in lifetime carcinogenicity bioassays at single daily doses (gavage) of up to 120 mg/kg/day for mice and 100 mg/kg/day for rats. There was no significant difference in the incidence of tumors between treated and control animals, nor did valacyclovir shorten the latency of tumors. Plasma concentrations of acyclovir *were equivalent to human levels in the mouse bioassay and* 1.4 to 2.3 times human levels in the rat bioassay.

Valacyclovir was tested in five genetic toxicity assays. An Ames assay was negative in the absence or presence of metabolic activation. Also negative were an in vitro cytogenetic study with human lymphocytes and a rat cytogenetic study at a single oral dose of 3000 mg/kg (8 to 9 times human plasma levels).

In the mouse lymphoma assay, valacyclovir was negative in the absence of metabolic activation. In the presence of metabolic activation (76% to 88% conversion to acyclovir), valacyclovir was weakly mutagenic.

A mouse micronucleus assay was negative at 250 mg/kg but weakly positive at 500 mg/kg (acyclovir concentrations 26 to 51 times human plasma levels).

Valacyclovir did not impair fertility or reproduction in rats at 200 mg/kg/day (6 times human plasma levels).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Valacyclovir was not teratogenic in rats or rabbits given 400 mg/kg (which results in exposures of 10 and 7 times human plasma levels, respectively) during the period of major organogenesis. There are no adequate and well-controlled studies of VALTREX or ZOVIRAX in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy has been ongoing since 1984. As of December 1994, outcomes of live births have been documented in 380 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. VALTREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Exposure Registry: *To monitor maternal-fetal outcomes of pregnant* women exposed to VALTREX, Glaxo Wellcome Inc. maintains a Valacyclovir in Pregnancy Registry. Physicians are encouraged to register their patients by calling (800) 722-9292, ext. 39437.

Nursing Mothers: There is no experience with VALTREX. However, acyclovir concentrations have been documented in breast milk in two women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high *as 0.3 mg/kg/day. VALTREX should be administered to a nursing mother with caution* and only when indicated.

Pediatric Use: Safety and effectiveness of VALTREX in pediatric patients have not been established.

Geriatric Use: Of the total number of patients included in clinical studies of VALTREX, 810 were age 65 or older, and 339 were age 75 or older. A total of 34 volunteers age 65 or older completed a pharmacokinetic trial of VALTREX. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of VALTREX in geriatric volunteers varied with renal function. Dosage reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: The adverse events reported by greater than 2% of a given treatment group in *clinical trials of VALTREX are listed in Table 1.*

Table 1: Incidence (%) of Adverse Events in Herpes Zoster and Genital Herpes Study Populations

	Herpes Zoster			Genital Herpes			
Adverse Event	VALTREX 1 gram t.i.d. (n = 967)	ZOVIRAX 800 mg 5x daily (n = 376)	Placebo (n = 195)	VALTREX 1 gram b.i.d. (n = 1,194)	VALTREX 500 mg b.i.d. (n = 359)	ZOVIRAX 200 mg 5x daily (n = 822)	Placebo (n = 439)
Nausea	15	19	8	6	6	7	8
Headache	14	13	12	16	17	12	14
Vomiting	6	8	3	1	1	2	<1
Diarrhea	5	7	6	4	5	3	6
Constipation	4	5	3	<1	1	1	1
Asthenia	4	5	4	2	1	2	4
Dizziness	3	6	2	3	2	2	3
Abdominal Pain	3	3	2	2	3	2	3
Anorexia	2	3	2	<1	<1	<1	<1

OVERDOSAGE: There have been no reports of overdosage from the administration of VALTREX. However, it is known that precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION: VALTREX Caplets may be given without regard to meals.

Herpes Zoster: The recommended dosage of VALTREX for the treatment of herpes zoster is 1 gram (two 500-mg caplets) orally three times daily for 7 days. Therapy should be initiated at the earliest sign or symptom of herpes zoster and is most effective when started within 48 hours of the onset of zoster rash. No data are available on efficacy of *treatment started greater than 72 hours after rash onset.*

Genital Herpes: ***Initial Episodes:*** The recommended dosage of VALTREX for treatment of initial genital herpes is 1 gram twice daily for 10 days.

There are no data on the effectiveness of treatment with VALTREX when initiated more than 72 hours after the onset of signs and symptoms. Therapy was most effective when administered within 48 hours of the onset of signs and symptoms.

Recurrent Episodes: The recommended dosage of VALTREX for the treatment of recurrent genital herpes is 500 mg twice daily for 5 days. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode. There are no data on the effectiveness of treatment with VALTREX when initiated more than 24 hours after the onset of signs or symptoms.

Patients with Acute or Chronic Renal Impairment: In patients with reduced renal function, reduction in dosage is recommended (see Table 2).

Table 2: Dosages for Patients with Renal Impairment

Creatinine Clearance (mL/min)	Dosage for Herpes Zoster	Dosage for Genital Herpes	
		Initial Treatment	Recurrent Episodes
>50	1 g every 8 hours	1 g every 12 hours	500 mg every 12 hours
30 - 49	1 g every 12 hours	1 g every 12 hours	500 mg every 12 hours
10 - 29	1 g every 24 hours	1 g every 24 hours	500 mg every 24 hours
<10	500 mg every 24 hours	500 mg every 24 hours	500 mg every 24 hours

Hemodialysis: During hemodialysis, the half-life of acyclovir after administration of VALTREX is approximately 4 hours. About one-third of acyclovir in the body is removed by dialysis during a 4-hour hemodialysis session. Patients requiring hemodialysis should receive the recommended dose of VALTREX after hemodialysis.

Peritoneal Dialysis: There is no information specific to administration of VALTREX in patients receiving peritoneal dialysis. The effect of chronic ambulatory peritoneal dialysis (CAPD) and continuous arteriovenous hemofiltration/dialysis (CAVHD) on acyclovir pharmacokinetics has been studied. The removal of acyclovir after CAPD and CAVHD is less pronounced than with hemodialysis, and the pharmacokinetic parameters closely resemble those observed in patients with ESRD not receiving hemodialysis. Therefore, supplemental doses of VALTREX should not be required following CAPD or CAVHD.

HOW SUPPLIED: VALTREX Caplets (blue, film-coated, capsule-shaped tablets) containing valacyclovir hydrochloride equivatent to 500 mg valacyclovir and printed with "VALTREX 500 mg" - Bottle of 42 (NDC 0173-0933-03) and unit dose pack of 100 (NDC 0173-0933-56).

Store at 15° to 25°C (59° to 77°F).

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