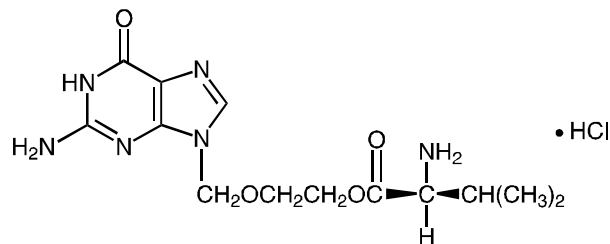


VALTRESX®
(valacyclovir hydrochloride)
Caplets

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

VALTRESX Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram 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:

Mechanism of Antiviral Action: 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 3 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,

VALTRESX[®] (valacyclovir hydrochloride) Caplets

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 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/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 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/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, to acyclovir) should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY: After oral administration, valacyclovir hydrochloride 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 VALTRESX have been investigated in 14 volunteer studies involving 283 adults.

Absorption and Bioavailability: The absolute bioavailability of acyclovir after administration of VALTRESX is $54.5\% \pm 9.1\%$ as determined following a 1-gram oral dose of VALTRESX and a 350-mg intravenous acyclovir dose to 12 healthy volunteers. Acyclovir bioavailability from the administration of VALTRESX 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 VALTRESX to 8 healthy volunteers. The mean C_{max} (\pm SD) was 0.83 (\pm 0.14), 2.15 (\pm 0.50), 3.28 (\pm 0.83), 4.17 (\pm 1.14), and 5.65 (\pm 2.37) mcg/mL, respectively; and the mean AUC (\pm SD) was 2.28 (\pm 0.40), 5.76 (\pm 0.60), 11.59 (\pm 1.79), 14.11 (\pm 3.54), and 19.52 (\pm 6.04) h•mcg/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 VALTRESX administered 4 times daily for 11 days in parallel groups of 8 healthy volunteers. The mean C_{max} (\pm SD) was 2.11 (\pm 0.33), 3.69 (\pm 0.87), and 4.96 (\pm 0.64) mcg/mL, respectively, and the mean AUC (\pm SD) was 5.66 (\pm 1.09), 9.88 (\pm 2.01), and 15.70 (\pm 2.27) h•mcg/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 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

VALTRESX[®] (valacyclovir hydrochloride) Caplets

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 mcg/mL at all doses. After single-dose administration of 1 gram of VALTRESX, average plasma valacyclovir concentrations observed were 0.5, 0.4, and 0.8 mcg/mL in patients with hepatic dysfunction, renal insufficiency, and in 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 4 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 VALTRESX 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 VALTRESX in volunteers with normal renal function.

End-Stage Renal Disease (ESRD): Following administration of VALTRESX 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 m², compared to 679.16 ± 162.76 mL/min/1.73 m² 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 VALTRESX in healthy geriatric volunteers (n = 9, mean age \pm SD = 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 \pm SD = 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 VALTRESX 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 9 patients with advanced HIV disease (CD4 cell counts <150 cells/mm³) who received VALTRESX at a dosage of 1 gram 4 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 pharmacokinetics of digoxin was not affected by coadministration of VALTRESX 1 gram 3 times daily, and the pharmacokinetics of acyclovir after a single dose of VALTRESX (1 gram) was unchanged by coadministration of digoxin (2 doses of 0.75 mg), single doses of antacids (Al³⁺ or Mg⁺⁺), or multiple doses of thiazide diuretics. Acyclovir C_{max} and AUC following a single dose of VALTRESX (1 gram) increased by 8% and 32%, respectively, after a single dose of cimetidine (800 mg), or by 22% and 49%, respectively, after probenecid (1 gram),

VALTREX® (valacyclovir hydrochloride) Caplets

or by 30% and 78%, respectively, after a combination of cimetidine and probenecid, primarily due to a reduction in renal clearance of acyclovir. These effects are not considered to be of clinical significance in subjects with normal renal function. Therefore, no dosage adjustment is recommended when VALTREX is coadministered with digoxin, antacids, thiazide diuretics, cimetidine, or probenecid in subjects with normal renal function.

Clinical Trials: Herpes Zoster Infections: Two randomized double-blind clinical trials in immunocompetent adults 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.

Genital Herpes Infections: Initial Episode: Six hundred and forty-three immunocompetent adults with first episode genital herpes who presented within 72 hours of symptom onset were randomized in a double-blind trial to receive 10 days of 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 Episodes: Two double-blind placebo-controlled trials in immunocompetent adults 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 1 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 1 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.

Suppressive Therapy: One thousand four hundred seventy-nine (1479) immunocompetent adults with a history of 6 or more recurrences per year were randomized into a double-blind, placebo-controlled study. Outcomes for the overall study population are shown in Table 1.

VALTREX® (valacyclovir hydrochloride) Caplets

Table 1: Proportions of Patients Recurrence-free at 6 and 12 Months

Treatment Arm	6 Months			12 Months		
	VALTREX 1 gram q.d. (n = 269)	ZOVIRAX 400 mg b.i.d. (n = 267)	Placebo (n = 134)	VALTREX 1 gram q.d. (n = 269)	ZOVIRAX 400 mg b.i.d. (n = 267)	Placebo (n = 134)
Recurrence-free (%)	55	54	7	34	34	4
Recurrences (%)	35	36	83	46	46	85
Unknowns (%)	10	10	10	19	19	10

Subjects with 9 or fewer recurrences per year showed comparable results with VALTREX 500 mg once daily.

INDICATIONS AND USAGE:

Herpes Zoster: VALTREX is indicated for the treatment of herpes zoster (shingles).

Genital Herpes: VALTREX is indicated for the treatment or suppression of 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: Dosage reduction is recommended when administering VALTREX to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Acute renal failure and central nervous system symptoms have been reported in patients with underlying renal disease who have received inappropriately high doses of VALTREX for their level of renal function. Similar caution should be exercised when administering VALTREX to geriatric patients (see Geriatric Use) and patients receiving potentially nephrotoxic agents.

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).

The efficacy of VALTREX has not been established for the treatment of disseminated herpes zoster or in immunocompromised patients.

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

VALTRESX[®] (valacyclovir hydrochloride) Caplets

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.

There are no data on the safety or effectiveness of chronic suppressive therapy of more than 1 year's duration.

Drug Interactions: 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 VALTRESX given orally 3 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 per day for mice and 100 mg/kg per 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 5 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 per 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 VALTRESX or ZOVIRAX in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 756 pregnancies followed in 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 or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. VALTRESX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: There is no experience with VALTRESX. However, acyclovir concentrations have been documented in breast milk in 2 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 per day. VALTRESX should be administered to a nursing mother with caution and only when indicated.

VALTREX® (valacyclovir hydrochloride) Caplets

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, 861 were age 65 or older, and 344 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: Frequently reported adverse events in clinical trials of VALTREX are listed in Table 2.

Table 2: Incidence (%) of Adverse Events in Herpes Zoster and Genital Herpes Study Populations

Adverse Event	Herpes Zoster		Genital Herpes Treatment			Genital Herpes Suppression		
	VALTREX 1 gram t.i.d. (n = 967)	Placebo (n = 195)	VALTREX 1 gram b.i.d. (n = 1194)	VALTREX 500 mg b.i.d. (n = 359)	Placebo (n = 439)	VALTREX 1 gram q.d. (n = 269)	VALTREX 500 mg q.d. (n = 266)	Placebo (n = 134)
Nausea	15	8	6	6	8	11	11	8
Headache	14	12	16	17	14	35	38	34
Vomiting	6	3	1	1	<1	3	3	2
Dizziness	3	2	3	2	3	4	2	1
Abdominal Pain	3	2	2	3	3	11	9	6
Dysmenorrhea	0	0	<1	1	1	8	5	4
Arthralgia	1	0	<1	1	<1	6	5	4
Depression	1	1	1	0	<1	7	5	5

Laboratory abnormalities reported in clinical trials of VALTREX are listed in Table 3.

VALTREX® (valacyclovir hydrochloride) Caplets

Table 3: Incidence (%) of Laboratory Abnormalities in Herpes Zoster and Genital Herpes Study Populations

Laboratory Abnormality	Herpes Zoster		Genital Herpes Treatment			Genital Herpes Suppression		
	VALTREX 1 gram t.i.d.	Placebo	VALTREX 1 gram b.i.d.	VALTREX 500 mg b.i.d.	Placebo	VALTREX 1 gram q.d.	VALTREX 500 mg q.d.	Placebo
Anemia	0.8	0	0.3	0.3	0	0	0.8	0.8
Leukopenia	1.3	0.6	0.7	0.8	0.2	0.7	0.8	1.5
Thrombocytopenia	1.0	1.2	0.3	0.6	0.7	0.4	1.1	1.5
AST (SGOT)	1.0	0	1.0	*	0.5	4.1	3.8	3.0
Serum Creatinine	0.2	0	0.7	0	0	0	0	0

*Data were not collected prospectively in this study.

Observed During Clinical Practice: The following events have been identified during post-approval use of VALTREX in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to VALTREX, or a combination of these factors.

General: Facial edema, hypertension, tachycardia.

Allergic: Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritus, rash, and urticaria.

CNS Symptoms: Confusion, agitation, hallucinations (auditory and visual), aggressive behavior, mania.

Gastrointestinal: Diarrhea.

Hepatobiliary Tract and Pancreas: Liver enzyme abnormalities, hepatitis.

Renal: Elevated creatinine, renal failure.

Hemic: Thrombocytopenia, aplastic anemia.

Skin: Erythema multiforme, rashes including photosensitivity.

Renal Impairment: Renal failure and CNS symptoms have been reported in patients with renal impairment who received VALTREX or acyclovir at greater than the recommended dose. **Dosage adjustment is recommended in this patient population (see DOSAGE AND ADMINISTRATION).**

OVERDOSAGE: Caution should be exercised to prevent inadvertent overdose (see PRECAUTIONS). 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 orally 3 times daily for 7 days. Therapy should be initiated at the earliest sign or symptom

VALTREX® (valacyclovir hydrochloride) Caplets

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.

Suppressive Therapy: The recommended dosage of VALTREX for chronic suppressive therapy of recurrent genital herpes is 1 gram once daily. In patients with a history of 9 or fewer recurrences per year, an alternative dose is 500 mg once daily. The safety and efficacy of therapy with VALTREX beyond 1 year have not been established.

Patients with Acute or Chronic Renal Impairment: In patients with reduced renal function, reduction in dosage is recommended (see Table 4).

Table 4: Dosages for Patients with Renal Impairment

Indications	Normal Dosage Regimen (Creatinine Clearance ≥50)	Creatinine Clearance (mL/min)		
		30-49	10-29	<10
Herpes zoster	1 gram every 8 hours	1 gram every 12 hours	1 gram every 24 hours	500 mg every 24 hours
Genital herpes				
Initial treatment	1 gram every 12 hours	no reduction	1 gram every 24 hours	500 mg every 24 hours
Recurrent episodes	500 mg every 12 hours	no reduction	500 mg every 24 hours	500 mg every 24 hours
Suppressive therapy	1 gram every 24 hours	no reduction	500 mg every 24 hours	500 mg every 24 hours
Suppressive therapy	500 mg every 24 hours	no reduction	500 mg every 48 hours	500 mg every 48 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.

VALTREX[®] (valacyclovir hydrochloride) Caplets

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 equivalent 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).

VALTREX Caplets (blue, film-coated, capsule-shaped tablets) containing valacyclovir hydrochloride equivalent to 1 gram valacyclovir and printed with "VALTREX 1 gram" - Bottle of 20 (NDC 0173-0565-00).

Store at 15° to 25°C (59° to 77°F).

GlaxoWellcome

Manufactured by
Catalytica Pharmaceuticals, Inc.
Greenville, NC 27834
for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent No. 4,957,924

©Copyright 1996, 1999, Glaxo Wellcome Inc. All rights reserved.

January 2000

RL-790