PRESCRIBING INFORMATION

VALTREX®

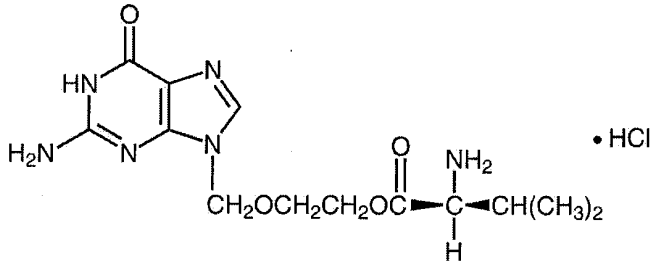
(valacyclovir hydrochloride)
Caplets

DESCRIPTION

VALTREX (valacyclovir hydrochloride) is the hydrochloride salt of *L*-valyl ester of the antiviral drug acyclovir (ZOVIRAX® Brand, GlaxoSmithKline).

VALTREX 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, hypromellose, 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 $C_{13}H_{20}N_6O_4$•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.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. 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 with 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 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 HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/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 and VZV to acyclovir occurs by the same mechanisms. 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 VALTREX have been investigated in 14 volunteer studies involving 283 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 8 healthy volunteers. The mean C_{max} (± SD) was 0.83 (± 0.14), 2.15 (± 0.50), 3.28 (± 0.83), 4.17 (± 1.14), and 5.65 (± 2.37) mcg/mL, respectively; and the mean AUC (± SD) was 2.28 (± 0.40), 5.76 (± 0.60), 11.59 (± 1.79), 14.11 (± 3.54), and 19.52 (± 6.04) hr•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 VALTREX administered 4 times daily for 11 days in parallel groups of 8 healthy volunteers. The mean C_{max} (± SD) was 2.11 (± 0.33), 3.69 (± 0.87), and 4.96 (± 0.64) mcg/mL, respectively, and the mean AUC (± SD) was 5.66 (± 1.09), 9.88 (± 2.01), and 15.70 (± 2.27) hr•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 aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither valacyclovir nor acyclovir is metabolized by cytochrome P450 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 VALTREX, 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 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 with 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, the half-life of acyclovir was 3.11 ± 0.51 hours, compared with 2.91 ± 0.63 hours in

healthy volunteers. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of VALTREX in geriatric volunteers varied with renal function. Dose reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see PRECAUTIONS and 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 9 patients with HIV disease and CD4 cell counts <150 cells/mm^3 who received VALTREX 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 VALTREX 1 gram 3 times daily, and the pharmacokinetics of acyclovir after a single dose of VALTREX (1 gram) was unchanged by coadministration of digoxin (2 doses of 0.75 mg), single doses of antacids (Al^{3+} or Mg^{++}), or multiple doses of thiazide diuretics. Acyclovir C_{max} and AUC following a single dose of VALTREX (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), 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: Two randomized double-blind clinical trials in immunocompetent adults with localized herpes zoster were conducted. VALTREX was compared with 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 with 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 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 twice daily (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: Three double-blind trials (2 of them placebo-controlled) 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 twice daily (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.

In a third study, patients were randomized to receive VALTREX 500 mg twice daily for 5 days (n = 398) or VALTREX 500 mg twice daily for 3 days (and matching placebo twice daily for 2 additional days) (n = 402). The median time to lesion healing was about 4½ days in both treatment groups. The median time to cessation of pain was about 3 days in both treatment groups.

Suppressive Therapy: Two clinical studies were conducted, one in immunocompetent adults and one in HIV-infected adults.

A double-blind, 12-month, placebo- and active-controlled study enrolled immunocompetent adults with a history of 6 or more recurrences per year. Outcomes for the overall study population are shown in Table 1.

Table 1. Recurrence Rates in Immunocompetent Adults at 6 and 12 Months

	6 Months			12 Months		
Treatment Arm	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%

*Includes lost to follow-up, discontinuations due to adverse events, and consent withdrawn.

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

In a second study, 293 HIV-infected adults on stable antiretroviral therapy with a history of 4 or more recurrences of ano-genital herpes per year were randomized to receive either VALTREX 500 mg twice daily (n = 194) or matching placebo (n = 99) for 6 months. The median duration of recurrent genital herpes in enrolled subjects was 8 years, and the median number of recurrences in the year prior to enrollment was 5. Overall, the median prestudy HIV-1 RNA was 2.6 $\log_{10}$ copies/mL. Among patients who received VALTREX, the prestudy median CD4 cell count was 336 cells/mm^3; 11% had <100 cells/mm^3, 16% had 100 to 199 cells/mm^3, 42% had 200 to 499 cells/mm^3, and 31% had ≥500 cells/mm^3. Outcomes for the overall study population are shown in Table 2.

Table 2. Recurrence Rates in HIV-Infected Adults at 6 Months

Treatment Arm	VALTREX 500 mg b.i.d. (n = 194)	Placebo (n = 99)
Recurrence free	65%	26%
Recurrences	17%	57%
Unknowns*	18%	17%

*Includes lost to follow-up, discontinuations due to adverse events, and consent withdrawn.

Reduction of Transmission of Genital Herpes: A double-blind, placebo-controlled study to assess transmission of genital herpes was conducted in 1,484 monogamous, heterosexual, immunocompetent adult couples. The couples were discordant for HSV-2 infection. The source partner had a history of 9 or fewer genital herpes episodes per year. Both partners were counseled on safer sex practices and were advised to use condoms throughout the study period. Source partners were randomized to treatment with either VALTREX 500 mg once daily or placebo once daily for 8 months. The primary efficacy endpoint was symptomatic acquisition of HSV-2 in susceptible partners. Overall HSV-2 acquisition was defined as symptomatic HSV-2 acquisition and/or HSV-2 seroconversion in susceptible partners. The efficacy results are summarized in Table 3.

Table 3. Percentage of Susceptible Partners Who Acquired HSV-2 Defined by the Primary and Selected Secondary Endpoints

	VALTREX* (n = 743)	Placebo (n = 741)
Symptomatic HSV-2 acquisition	4 (0.5%)	16 (2.2%)
HSV-2 seroconversion	12 (1.6%)	24 (3.2%)
Overall HSV-2 acquisition	14 (1.9%)	27 (3.6%)

* Results show reductions in risk of 75% (symptomatic HSV-2 acquisition), 50% (HSV-2 seroconversion), and 48% (overall HSV-2 acquisition) with VALTREX versus placebo. Individual results may vary based on consistency of safer sex practices.

Cold Sores (Herpes Labialis): Two double-blind, placebo-controlled clinical trials were conducted in 1,856 healthy adults and adolescents (≥12 years old) with a history of recurrent cold sores. Patients self-initiated therapy at the earliest symptoms and prior to any signs of a cold sore. The majority of patients initiated treatment within 2 hours of onset of symptoms. Patients were randomized to VALTREX 2 grams twice daily on Day 1 followed by placebo on Day 2, VALTREX 2 grams twice daily on Day 1 followed by 1 gram twice daily on Day 2, or placebo on Days 1 and 2.

The mean duration of cold sore episodes was about 1 day shorter in treated subjects as compared with placebo. The 2-day regimen did not offer additional benefit over the 1-day regimen.

No significant difference was observed between subjects receiving VALTREX or placebo in the prevention of progression of cold sore lesions beyond the papular stage.

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 in immunocompetent individuals and for the suppression of recurrent genital herpes in HIV-infected individuals.

When VALTREX is used as suppressive therapy in immunocompetent individuals with genital herpes, the risk of heterosexual transmission to susceptible partners is reduced. Safer sex practices should be used with suppressive therapy (see current Centers for Disease Control and Prevention (CDC) *Sexually Transmitted Diseases Treatment Guidelines*).

Cold Sores (Herpes Labialis): VALTREX is indicated for the treatment of cold sores (herpes labialis).

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.

Given the dosage recommendations for treatment of cold sores, special attention should be paid when prescribing VALTREX for cold sores in patients who are elderly or who have impaired renal function (see DOSAGE AND ADMINISTRATION and Geriatric Use). Treatment should not exceed 1 day (2 doses of 2 grams in 24 hours). Therapy beyond 1 day does not provide additional clinical benefit.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Adequate hydration should be maintained. 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 safety and efficacy of VALTREX have not been established in immunocompromised patients other than for the suppression of genital herpes in HIV-infected patients. The safety and efficacy of VALTREX for suppression of recurrent genital herpes in patients with advanced HIV disease (CD4 cell count <100 cells/mm^3) have not been established. The efficacy of VALTREX for the treatment of genital herpes in HIV-infected patients has not been established. The safety and efficacy of VALTREX have not been established for the treatment of disseminated herpes zoster.

The efficacy of VALTREX for reducing transmission of genital herpes has not been established in individuals with multiple partners and non-heterosexual couples.

Information for Patients: Patients should be advised to maintain adequate hydration.

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. 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 is frequently transmitted in the absence of symptoms through asymptomatic viral shedding. Therefore, patients should be counseled to use safer sex practices in combination with

suppressive therapy with VALTREX. Sex partners of infected persons should be advised that they might be infected even if they have no symptoms. Type-specific serologic testing of asymptomatic partners of persons with genital herpes can determine whether risk for HSV-2 acquisition exists.

VALTREX has not been shown to reduce transmission of sexually transmitted infections other than HSV-2.

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 after 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 in otherwise healthy patients. There are no data on the safety or effectiveness of chronic suppressive therapy of more than 6 months' duration in HIV-infected patients.

Cold Sores (Herpes Labialis): Patients should be advised to initiate treatment at the earliest symptom of a cold sore (e.g., tingling, itching, or burning). There are no data on the effectiveness of treatment initiated after the development of clinical signs of a cold sore (e.g., papule, vesicle, or ulcer). Patients should be instructed that treatment for cold sores should not exceed 1 day (2 doses) and that their doses should be taken about 12 hours apart. Patients should be informed that VALTREX is not a cure for cold sores (herpes labialis).

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 VALTREX 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 valacyclovir giving plasma acyclovir concentrations equivalent to human levels in the mouse bioassay and 1.4 to 2.3 times human levels in the rat bioassay. There was no significant difference in the incidence of tumors between treated and control animals, nor did valacyclovir shorten the latency of tumors.

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.

In the mouse lymphoma assay, valacyclovir was not mutagenic in the absence of metabolic activation. In the presence of metabolic activation (76% to 88% conversion to acyclovir), valacyclovir was mutagenic.

Valacyclovir was mutagenic in a mouse micronucleus assay.

Valacyclovir did not impair fertility or reproduction in rats at 6 times human plasma levels.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Valacyclovir was not teratogenic in rats or rabbits at 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 was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. 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. VALTREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Following oral administration of a 500-mg dose of VALTREX to 5 nursing mothers, peak acyclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 times (median 1.4) the corresponding maternal acyclovir serum concentrations. The acyclovir breast milk AUC ranged from 1.4 to 2.6 times (median 2.2) maternal serum AUC. A 500-mg maternal dosage of VALTREX twice daily would provide a nursing infant with an oral acyclovir dosage of approximately 0.6 mg/kg/day. This would result in less than 2% of the exposure obtained after administration of a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir to the nursing infant. Unchanged valacyclovir was not detected in maternal serum, breast milk, or infant urine. VALTREX should be administered to a nursing mother with caution and only when indicated.

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

Geriatric Use: Of the total number of subjects in clinical studies of VALTREX, 906 were 65 and over, and 352 were 75 and over. In a clinical study of herpes zoster, the duration of pain after healing (post-herpetic neuralgia) was longer in patients 65 and older compared with younger adults. Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have renal or CNS adverse events. With respect to CNS adverse events observed during clinical practice, agitation, hallucinations, confusion, delirium, and encephalopathy were reported more frequently in elderly patients (see CLINICAL PHARMACOLOGY, ADVERSE REACTIONS: Observed During Clinical Practice, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Frequently reported adverse events in clinical trials of VALTREX in healthy patients are listed in Tables 4 and 5.

Table 4. Incidence (%) of Adverse Events in Herpes Zoster Study Populations

Adverse Event	VALTREX 1 gram t.i.d. (n = 967)	Placebo (n = 195)
Nausea	15%	8%
Headache	14%	12%
Vomiting	6%	3%
Dizziness	3%	2%
Abdominal pain	3%	2%

Table 5. Incidence (%) of Adverse Events in Genital Herpes Study Populations

	Genital Herpes Treatment			Genital Herpes Suppression		
Adverse Event	VALTREX 1 gram b.i.d. (n = 1,194)	VALTREX 500 mg b.i.d. (n = 1,159)	Placebo (n = 439)	VALTREX 1 gram q.d. (n = 269)	VALTREX 500 mg q.d. (n = 266)	Placebo (n = 134)
Nausea	6%	5%	8%	11%	11%	8%
Headache	16%	15%	14%	35%	38%	34%
Vomiting	1%	<1%	<1%	3%	3%	2%
Dizziness	3%	2%	3%	4%	2%	1%
Abdominal pain	2%	1%	3%	11%	9%	6%
Dysmenorrhea	<1%	<1%	1%	8%	5%	4%
Arthralgia	<1%	<1%	<1%	6%	5%	4%
Depression	1%	0%	<1%	7%	5%	5%

Laboratory abnormalities reported in clinical trials of VALTREX in otherwise healthy patients are listed in Table 6.

Table 6. 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
Hemoglobin (<0.8 x LLN)	0.8%	0%	0.3%	0.2%	0%	0%	0.8%	0.8%
White blood cells (<0.75 x LLN)	1.3%	0.6%	0.7%	0.6%	0.2%	0.7%	0.8%	1.5%
Platelet count (<100,000/mm^3)	1.0%	1.2%	0.3%	0.1%	0.7%	0.4%	1.1%	1.5%
AST (SGOT) (>2 x ULN)	1.0%	0%	1.0%	*	0.5%	4.1%	3.8%	3.0%
Serum creatinine (>1.5 x ULN)	0.2%	0%	0.7%	0%	0%	0%	0%	0%

*Data were not collected prospectively.
LLN = Lower limit of normal.
ULN = Upper limit of normal.

Suppression of Genital Herpes in HIV-Infected Patients: In HIV-infected patients, frequently reported adverse events for VALTREX (500 mg twice daily; n = 194, median days on therapy = 172) and placebo (n = 99, median days on therapy = 59), respectively, included headache (13% vs. 8%), fatigue (8% vs. 5%), and rash (8% vs. 1%). Post-randomization laboratory abnormalities that were reported more frequently in valacyclovir subjects versus placebo included elevated alkaline phosphatase (4% vs. 2%), elevated ALT (14% vs. 10%), elevated AST (16% vs. 11%), decreased neutrophil counts (18% vs. 10%), and decreased platelet counts (3% vs. 0%).

Reduction of Transmission: In a clinical study for the reduction of transmission of genital herpes, the adverse events reported by patients receiving VALTREX 500 mg once daily (n = 743) or placebo once daily (n = 741) included headache (VALTREX 29%, placebo 26%), nasopharyngitis (VALTREX 16%, placebo 15%), and upper respiratory tract infection (VALTREX 9%, placebo 10%). In this 8-month study, there were no clinically significant changes from baseline laboratory parameters in subjects receiving VALTREX compared with placebo.

Cold Sores (Herpes Labialis): In clinical studies for the treatment of cold sores, the adverse events reported by patients receiving VALTREX (n = 609) or placebo (n = 609) included headache (VALTREX 14%, placebo 10%) and dizziness (VALTREX 2%, placebo 1%). The frequencies of abnormal ALT (>2 x ULN) were 1.8% for patients receiving VALTREX

compared with 0.8% for placebo. Other laboratory abnormalities (hemoglobin, white blood cells, alkaline phosphatase, and serum creatinine) occurred with similar frequencies in the 2 groups.

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: Aggressive behavior; agitation; ataxia; coma; confusion; decreased consciousness; dysarthria; encephalopathy; mania; and psychosis, including auditory and visual hallucinations; seizures, tremors (see PRECAUTIONS).

Eye: Visual abnormalities.

Gastrointestinal: Diarrhea.

Hepatobiliary Tract and Pancreas: Liver enzyme abnormalities, hepatitis.

Renal: Elevated creatinine, renal failure, renal pain (may be associated with renal failure).

Hematologic: Thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis, TTP/HUS.

Skin: Erythema multiforme, rashes including photosensitivity, alopecia.

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. **Dose reduction 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 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 3 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 normal immune function. 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.

In HIV-infected patients with CD4 cell count ≥100 cells/mm^3, the recommended dosage of VALTREX for chronic suppressive therapy of recurrent genital herpes is 500 mg twice daily. The safety and efficacy of therapy with VALTREX beyond 6 months in patients with HIV infection have not been established.

Reduction of Transmission: The recommended dosage of VALTREX for reduction of transmission of genital herpes in patients with a history of 9 or fewer recurrences per year is 500 mg once daily for the source partner. Patients should be counseled to use safer sex practices in combination with suppressive therapy with VALTREX. The efficacy of reducing transmission beyond 8 months in discordant couples has not been established.

Cold Sores (Herpes Labialis): The recommended dosage of VALTREX for the treatment of cold sores is 2 grams twice daily for 1 day taken about 12 hours apart. Therapy should be initiated at the earliest symptom of a cold sore (e.g., tingling, itching, or burning). There are no data on the effectiveness of treatment initiated after the development of clinical signs of a cold sore (e.g., papule, vesicle, or ulcer).

Patients with Acute or Chronic Renal Impairment: In patients with reduced renal function, reduction in dosage is recommended (see Table 7).

Table 7. 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
Genital herpes Recurrent episodes	500 mg every 12 hours	no reduction	500 mg every 24 hours	500 mg every 24 hours
Genital herpes Suppressive therapy	1 gram every 24 hours	no reduction	500 mg every 24 hours	500 mg every 24 hours
	500 mg every 24 hours	no reduction	500 mg every 48 hours	500 mg every 48 hours
Genital herpes Suppressive therapy in HIV-infected patients	500 mg every 12 hours	no reduction	500 mg every 24 hours	500 mg every 24 hours
Herpes labialis (cold sores) **Do not exceed 1 day of treatment.**	Two 2-gram doses taken about 12 hours apart	Two 1-gram doses taken about 12 hours apart	Two 500-mg doses taken about 12 hours apart	500-mg single dose

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 equivalent to 500 mg valacyclovir and printed with "VALTREX 500 mg."

Bottle of 30 (NDC 0173-0933-08).
Bottle of 90 (NDC 0173-0933-10).
Unit dose pack of 100 (NDC 0173-0933-56).
VALTREX Caplets (blue, film-coated, capsule-shaped tablets, with a partial scorebar on both sides) containing valacyclovir hydrochloride equivalent to 1 gram valacyclovir and printed with "VALTREX 1 gram."
Bottle of 30 (NDC 0173-0565-04).
Bottle of 90 (NDC 0173-0565-10).
Store at 15° to 25°C (59° to 77°F). Dispense in a well-closed container as defined in the USP.

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PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION
VALTREX® (VAL-trex)
(valacyclovir hydrochloride) Caplets

Read the Patient Information that comes with VALTREX before you start using it and each time you get a refill. There may be new information. This information does not take the place of

talking to your healthcare provider about your medical condition or treatment. Ask your healthcare provider or pharmacist if you have questions.

What is VALTREX?

VALTREX is a prescription antiviral medicine. VALTREX lowers the ability of herpes viruses to multiply in your body.

VALTREX is used:

- to treat cold sores (also called fever blisters or herpes labialis) in adults
- to treat shingles (also called herpes zoster) in adults
- to treat or control genital herpes outbreaks in adults with normal immune systems
- to control genital herpes outbreaks in adults infected with the human immunodeficiency virus (HIV) with CD4 cell count greater than 100 cells/mm^3
- with safer sex practices to lower the chances of spreading genital herpes to others.

Even with safer sex practices, it is still possible to spread genital herpes.

VALTREX used daily with the following safer sex practices can lower the chances of passing genital herpes to your partner.

- **Do not have sexual contact with your partner when you have any symptom or outbreak of genital herpes.**
- **Use a condom** made of latex or polyurethane whenever you have sexual contact.

VALTREX does not cure herpes infections (cold sores, shingles, or genital herpes).

VALTREX has not been studied in children who have not reached puberty.

What are cold sores, shingles, and genital herpes?

Cold sores are caused by a herpes virus that may be spread by kissing or other physical contact with the infected area of the skin. They are small, painful ulcers that you get in or around your mouth. It is not known if VALTREX can stop the spread of cold sores to others.

Shingles is caused by the same herpes virus that causes chickenpox. It causes small, painful blisters that happen on a certain area of your skin. Shingles occurs in people who have already had chickenpox. Shingles can be spread to people who have not had chickenpox or the chickenpox vaccine by contact with the infected areas of the skin. It is not known if VALTREX can stop the spread of shingles to others.

Genital herpes is a sexually transmitted disease. It causes small, painful blisters on your genital area. You can spread genital herpes to others, even when you have no symptoms. If you are sexually active, you can still pass herpes to your partner, even if you are taking VALTREX.

VALTREX, taken every day as prescribed and used with the following **safer sex practices**, can lower the chances of passing genital herpes to your partner.

- **Do not have sexual contact with your partner when you have any symptom or outbreak of genital herpes.**
- **Use a condom** made of latex or polyurethane whenever you have sexual contact.

Ask your healthcare provider for more information about safer sex practices.

Who should not take VALTREX?

Do not take VALTREX if you are allergic to any of its ingredients or to acyclovir. The active ingredient is valacyclovir. See the end of this leaflet for a complete list of ingredients in VALTREX.

Before taking VALTREX, tell your healthcare provider:

About all your medical conditions, including:

- **if you have had a bone marrow transplant or kidney transplant, or if you have advanced HIV disease or "AIDS".** Patients with these conditions may have a higher chance for getting a blood disorder called thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). TTP/HUS can result in death.
- **if you have kidney problems.** Patients with kidney problems may have a higher chance for getting side effects or more kidney problems with VALTREX. Your healthcare provider may give you a lower dose of VALTREX.
- **if you are 65 years of age or older.** Elderly patients have a higher chance of certain side effects. Also, elderly patients are more likely to have kidney problems. Your healthcare provider may give you a lower dose of VALTREX.
- if **you are pregnant or planning to become pregnant.** Talk with your healthcare provider about the risks and benefits of taking prescription drugs (including VALTREX) during pregnancy.
- **if you are breastfeeding.** VALTREX may pass into your milk and it may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking VALTREX.
- **about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. VALTREX may affect other medicines, and other medicines may affect VALTREX. This may happen if you have certain medical conditions such as kidney problems. It is a good idea to keep a complete list of all the medicines you take. Show this list to your healthcare provider and pharmacist any time you get a new medicine.

How should I take VALTREX?

Take VALTREX exactly as prescribed by your healthcare provider. Your dose of VALTREX and length of treatment will depend on the type of herpes infection that you have and any other medical problems that you have.

- Do not stop VALTREX or change your treatment without talking to your healthcare provider.
- VALTREX can be taken with or without food.
- If you are taking VALTREX to treat cold sores, shingles, or genital herpes, you should start treatment as soon as possible after your symptoms start. VALTREX may not help you if you start treatment too late.
- If you miss a dose of VALTREX, take it as soon as you remember and then take your next dose at its regular time. However, if it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time.
- Do not take more than the prescribed number of VALTREX Caplets each day. Call your healthcare provider right away if you take too much VALTREX.

What are the possible side effects of VALTREX?

Kidney failure and nervous system problems are not common, but can be serious in some patients taking VALTREX. Nervous system problems include aggressive behavior, unsteady movement, shaky movements, confusion, speech problems, hallucinations (seeing or hearing things that are really not there), seizures, and coma. Kidney failure and nervous system problems have happened in patients who already have kidney disease and in elderly patients whose kidneys do not work well due to age. **Always tell your healthcare provider if you have kidney problems before taking VALTREX. Call your doctor right away if you get a nervous system problem while you are taking VALTREX.**

Common side effects of VALTREX include headache, nausea, stomach pain, vomiting, and dizziness. Side effects in HIV-infected adults include headache, tiredness, and rash. These side effects are usually mild and usually do not cause patients to stop taking VALTREX.

Other less common side effects include painful periods in women, joint pain, depression, low blood cell counts, and changes in tests that measure how well the liver and kidneys work.

Talk to your healthcare provider if you develop any side effects that concern you.

These are not all the side effects of VALTREX. For more information ask your healthcare provider or pharmacist.

How should I store VALTREX?

- Store VALTREX at room temperature, 59° to 77°F (15° to 25°C).
- Keep VALTREX in a tightly closed container.

- Do not keep medicine that is out of date or that you no longer need.
- **Keep VALTREX and all medicines out of the reach of children.**

General information about VALTREX

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use VALTREX for a condition for which it was not prescribed. Do not give VALTREX to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about VALTREX. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about VALTREX that is written for health professionals. More information is available at www.VALTREX.com.

What are the ingredients in VALTREX?

Active Ingredient: valacyclovir hydrochloride

Inactive Ingredients: carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide.

Rx Only

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