# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 20-550/S-012

## FINAL PRINTED LABELING

# VALTREX®

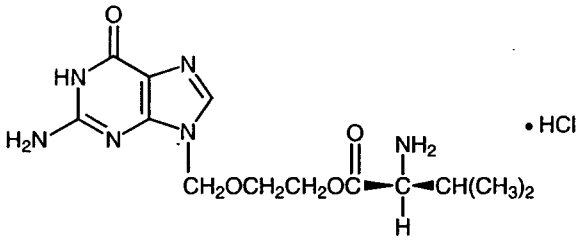
## (valacyclovir hydrochloride)

## Caplets

**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 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 $C_{13}H_{20}N_6O_4$•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 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 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) 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 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) 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 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 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, the half-life of acyclovir was 3.11 ± 0.51 hours, compared to 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 advanced HIV disease (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 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 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:*** 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 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.

In a third study, patients were randomized to receive VALTREX 500 mg b.i.d. for 5 days (n = 398) or VALTREX 500 mg b.i.d. for 3 days (and matching placebo b.i.d. 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:*** 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.

**Table 1: Proportions of Patients Recurrence Free 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 |

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 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 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 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 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 not mutagenic in a mouse micronucleus assay at 250 mg/kg but 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 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:** There is no experience with VALTREX. 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. 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, 852 were 65 and over, and 346 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 are listed in Tables 2 and 3.

**Table 2: 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 3: Incidence (%) of Adverse Events in Genital Herpes Study Populations**

| | Genital Herpes Treatment | | | Genital Herpes Suppression | | |
|---|---|---|---|---|---|---|
| Adverse Event | VALTREX 1 gram b.i.d. (n = 1194) | VALTREX 500 mg b.i.d. (n = 1159) | 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 are listed in Table 4.

**Table 4: Incidence (%) of Laboratory Abnormalities in Herpes Zoster and Genital Herpes Study Populations**

| | Herpes Zoster | | Genital Herpes Treatment | | | Genital Herpes Suppression | | |
|---|---|---|---|---|---|---|---|---|
| Laboratory Abnormality | 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% | 0.2% | 0% | 0% | 0.8% | 0.8% |
| Leukopenia | 1.3% | 0.6% | 0.7% | 0.6% | 0.2% | 0.7% | 0.8% | 1.5% |
| Thrombocytopenia | 1.0% | 1.2% | 0.3% | 0.1% | 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.

**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; coma; confusion; decreased consciousness; encephalopathy; mania; and psychosis, including auditory and visual hallucinations (see PRECAUTIONS).

*Eye:* Visual abnormalities.

*Gastrointestinal:* Diarrhea.

*Hepatobiliary Tract and Pancreas:* Liver enzyme abnormalities, hepatitis.

*Renal:* Elevated creatinine, renal failure.

*Hematologic:* 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. **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 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 5).

**Table 5: 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.

**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



Date of Issue

RL-no.