

ACYCLOVIR- acyclovir tablet

VALACYCLOVIR HYDROCHLORIDE- valacyclovir hydrochloride tablet, film coated

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DIRECT RX

VALACYCLOVIR HYDROCHLORIDE

1.1 Adult Patients

Cold Sores (Herpes Labialis): Valacyclovir tablets, USP are indicated for treatment of cold sores (herpes labialis). The efficacy of valacyclovir tablets, USP initiated after the development of clinical signs of a cold sore (e.g., papule, vesicle, or ulcer) has not been established.

Genital Herpes: Initial Episode: Valacyclovir tablets, USP are indicated for treatment of the initial episode of genital herpes in immunocompetent adults. The efficacy of treatment with valacyclovir tablets, USP when initiated more than 72 hours after the onset of signs and symptoms has not been established.

Recurrent Episodes: Valacyclovir tablets, USP are indicated for treatment of recurrent episodes of genital herpes in immunocompetent adults. The efficacy of treatment with valacyclovir tablets, USP when initiated more than 24 hours after the onset of signs and symptoms has not been established.

Suppressive Therapy: Valacyclovir tablets, USP are indicated for chronic suppressive therapy of recurrent episodes of genital herpes in immunocompetent and in HIV-infected adults. The efficacy and safety of valacyclovir tablets, USP for the suppression of genital herpes beyond 1 year in immunocompetent patients and beyond 6 months in HIV-infected patients have not been established.

Reduction of Transmission: Valacyclovir tablets, USP are indicated for the reduction of transmission of genital herpes in immunocompetent adults. The efficacy of valacyclovir tablets, USP for the reduction of transmission of genital herpes beyond 8 months in discordant couples has not been established. The efficacy of valacyclovir tablets, USP for the reduction of transmission of genital herpes in individuals with multiple partners and non-heterosexual couples has not been established. Safer sex practices should be used with suppressive therapy (see current Centers for Disease Control and Prevention [CDC] Sexually Transmitted Diseases Treatment Guidelines).

Herpes Zoster: Valacyclovir tablets, USP are indicated for the treatment of herpes zoster (shingles) in immunocompetent adults. The efficacy of valacyclovir tablets, USP when initiated more than 72 hours after the onset of rash and the efficacy and safety of valacyclovir tablets, USP for treatment of disseminated herpes zoster have not been established.

1.2 Pediatric Patients

Cold Sores (Herpes Labialis): Valacyclovir tablets, USP are indicated for the treatment of cold sores (herpes labialis) in pediatric patients ≥ 12 years of age. The efficacy of

valacyclovir tablets, USP initiated after the development of clinical signs of a cold sore (e.g., papule, vesicle, or ulcer) has not been established.

Chickenpox: Valacyclovir tablets, USP are indicated for the treatment of chickenpox in immunocompetent pediatric patients 2 to <18 years of age. Based on efficacy data from clinical studies with oral acyclovir, treatment with valacyclovir tablets, USP should be initiated within 24 hours after the onset of rash [see CLINICAL STUDIES (14.4)].

1.3 Limitations of Use

The efficacy and safety of valacyclovir tablets, USP have not been established in:

Immunocompromised patients other than for the suppression of genital herpes in HIV-infected patients with a CD4+ cell count ≥ 100 cells/mm³.

Patients <12 years of age with cold sores (herpes labialis).

Patients <2 years of age or ≥ 18 years of age with chickenpox.

Patients <18 years of age with genital herpes.

Patients <18 years of age with herpes zoster.

Neonates and infants as suppressive therapy following neonatal herpes simplex virus (HSV) infection.

Valacyclovir tablets may be given without regard to meals.

Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from valacyclovir tablets 500 mg for use in pediatric patients for whom a solid dosage form is not appropriate [see DOSAGE AND ADMINISTRATION (2.3)].

2.1 Adult Dosing Recommendations

Cold Sores (Herpes Labialis): The recommended dosage of valacyclovir tablets for treatment of cold sores is 2 grams twice daily for 1 day taken 12 hours apart. Therapy should be initiated at the earliest symptom of a cold sore (e.g., tingling, itching, or burning).

Genital Herpes: Initial Episode: The recommended dosage of valacyclovir tablets for treatment of initial genital herpes is 1 gram twice daily for 10 days. Therapy was most effective when administered within 48 hours of the onset of signs and symptoms.

Recurrent Episodes: The recommended dosage of valacyclovir tablets for treatment of recurrent genital herpes is 500 mg twice daily for 3 days. Initiate treatment at the first sign or symptom of an episode.

Suppressive Therapy: The recommended dosage of valacyclovir tablets 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.

In HIV-infected patients with a CD4+ cell count ≥ 100 cells/mm³, the recommended dosage of valacyclovir tablets for chronic suppressive therapy of recurrent genital herpes is 500 mg twice daily.

Reduction of Transmission: The recommended dosage of valacyclovir tablets 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.

Herpes Zoster: The recommended dosage of valacyclovir tablets for treatment of herpes zoster is 1 gram 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 rash.

2.2 Pediatric Dosing Recommendations

Cold Sores (Herpes Labialis): The recommended dosage of valacyclovir tablets for the treatment of cold sores in pediatric patients ≥ 12 years of age is 2 grams twice daily for 1 day taken 12 hours apart. Therapy should be initiated at the earliest symptom of a cold sore (e.g., tingling, itching, or burning).

Chickenpox: The recommended dosage of valacyclovir tablets for treatment of chickenpox in immunocompetent pediatric patients 2 to <18 years of age is 20 mg/kg administered 3 times daily for 5 days. The total dose should not exceed 1 gram 3 times daily. Therapy should be initiated at the earliest sign or symptom [see USE IN SPECIFIC POPULATIONS (8.4), CLINICAL PHARMACOLOGY (12.3), CLINICAL STUDIES (14.4)].

2.3 Extemporaneous Preparation of Oral Suspension

Ingredients and Preparation per USP-NF: Valacyclovir tablets 500 mg, cherry flavor, and Suspension Structured Vehicle USP-NF (SSV). Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) should be prepared in lots of 100 mL.

Prepare Suspension at Time of Dispensing as Follows:

Prepare SSV according to the USP-NF.

Using a pestle and mortar, grind the required number of valacyclovir 500 mg tablets until a fine powder is produced (5 valacyclovir tablets for 25 mg/mL suspension; 10 valacyclovir tablets for 50 mg/mL suspension).

Gradually add approximately 5 mL aliquots of SSV to the mortar and triturate the powder until a paste has been produced. Ensure that the powder has been adequately wetted.

Continue to add approximately 5 mL aliquots of SSV to the mortar, mixing thoroughly between additions, until a concentrated suspension is produced, to a minimum total quantity of 20 mL SSV and a maximum total quantity of 40 mL SSV for both the 25 mg/mL and 50 mg/mL suspensions.

Transfer the mixture to a suitable 100 mL measuring flask.

Transfer the cherry flavor* to the mortar and dissolve in approximately 5 mL of SSV. Once dissolved, add to the measuring flask.

Rinse the mortar at least 3 times with approximately 5 mL aliquots of SSV, transferring the rinsing to the measuring flask between additions.

Make the suspension to volume (100 mL) with SSV and shake thoroughly to mix.

Transfer the suspension to an amber glass medicine bottle with a child-resistant closure.

The prepared suspension should be labeled with the following information "Shake well

before using. Store suspension between 2°C to 8°C (36°F to 46°F) in a refrigerator. Discard after 28 days.”

*The amount of cherry flavor added is as instructed by the suppliers of the cherry flavor.

2.4 Patients With Renal Impairment

Dosage recommendations for adult patients with reduced renal function are provided in Table 1 [see USE IN SPECIFIC POPULATIONS (8.5, 8.6), CLINICAL PHARMACOLOGY (12.3)]. Data are not available for the use of valacyclovir tablets in pediatric patients with a creatinine clearance <50 mL/min/1.73 m².

Table 1. Valacyclovir Tablets Dosage Recommendations for Adults With Renal Impairment

Indications

Normal Dosage Regimen
(Creatinine Clearance ≥ 50 mL/min)

Creatinine Clearance (mL/min)

30-49

10-29

<10

Cold sores (Herpes labialis)

Do not exceed 1 day of treatment.

Two 2 gram doses taken 12 hours apart

Two 1 gram doses taken 12 hours apart

Two 500 mg doses taken 12 hours apart

500 mg single dose

Genital herpes:

Initial episode

1 gram every 12 hours

no reduction

1 gram every 24 hours

500 mg every 24 hours

Genital herpes:

Recurrent episode

500 mg every 12 hours

no reduction

500 mg every 24 hours

500 mg every 24 hours

Genital herpes:

Suppressive therapy

Immunocompetent patients

1 gram every 24 hours

no reduction

500 mg every 24 hours

500 mg every 24 hours

Alternate dose for immunocompetent patients with ≤ 9 recurrences/year

500 mg every 24 hours

no reduction

500 mg every 48 hours

500 mg every 48 hours

HIV-infected patients

500 mg every 12 hours

no reduction

500 mg every 24 hours

500 mg every 24 hours

Herpes zoster

1 gram every 8 hours

1 gram every 12 hours

1 gram every 24 hours

500 mg every 24 hours

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

Peritoneal Dialysis: There is no information specific to administration of valacyclovir tablets 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 end-stage renal disease (ESRD) not receiving hemodialysis. Therefore, supplemental doses of valacyclovir tablets should not be required following CAPD or CAVHD.

Valacyclovir Tablets, USP:

500 mg: blue colored, capsule shaped, film coated tablets debossed with "C324 500" on one side and plain on the other side.

1 gram: blue colored, capsule shaped, film coated tablets with partial score bar on both sides and debossed with "C325 1000" on one side and plain on the other side.

Valacyclovir hydrochloride is contraindicated in patients who have had a demonstrated clinically significant hypersensitivity reaction (e.g., anaphylaxis) to valacyclovir, acyclovir, or any component of the formulation [see ADVERSE REACTIONS (6.3)].

5.1 Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS)

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 valacyclovir hydrochloride at doses of 8 grams per day. Treatment with valacyclovir hydrochloride should be stopped immediately if clinical signs, symptoms, and laboratory abnormalities consistent with TTP/HUS occur.

5.2 Acute Renal Failure

Cases of acute renal failure have been reported in:

Elderly patients with or without reduced renal function. Caution should be exercised when administering valacyclovir hydrochloride to geriatric patients, and dosage reduction is recommended for those with impaired renal function [see DOSAGE AND ADMINISTRATION (2.4), USE IN SPECIFIC POPULATIONS (8.5)].

Patients with underlying renal disease who received higher than recommended doses of valacyclovir hydrochloride for their level of renal function. Dosage reduction is recommended when administering valacyclovir hydrochloride to patients with renal impairment [see DOSAGE AND ADMINISTRATION (2.4), USE IN SPECIFIC POPULATIONS (8.6)].

Patients receiving other nephrotoxic drugs. Caution should be exercised when administering valacyclovir hydrochloride to patients receiving potentially nephrotoxic drugs.

Patients without adequate hydration. 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 for all patients.

In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored [see DOSAGE AND ADMINISTRATION (2.4), ADVERSE REACTIONS (6.3)].

5.3 Central Nervous System Effects

Central nervous system adverse reactions, including agitation, hallucinations, confusion, delirium, seizures, and encephalopathy, have been reported in both adult and pediatric patients with or without reduced renal function and in patients with underlying renal disease who received higher than recommended doses of valacyclovir hydrochloride for their level of renal function. Elderly patients are more likely to have central nervous system adverse reactions. Valacyclovir hydrochloride should be discontinued if central nervous system adverse reactions occur [see ADVERSE REACTIONS (6.3), USE IN SPECIFIC POPULATIONS (8.5, 8.6)].

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome [see WARNINGS AND PRECAUTIONS (5.1)].

Acute Renal Failure [see WARNINGS AND PRECAUTIONS (5.2)].

Central Nervous System Effects [see WARNINGS AND PRECAUTIONS (5.3)].

The most common adverse reactions reported in at least 1 indication by >10% of adult patients treated with valacyclovir hydrochloride and observed more frequently with valacyclovir hydrochloride compared to placebo are headache, nausea, and abdominal pain. The only adverse reaction reported in >10% of pediatric patients <18 years of age was headache.

6.1 Clinical Trials Experience in Adult Patients

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

Genital Herpes: Initial Episode: In a clinical study for the treatment of initial episodes of genital herpes, the adverse reactions reported by $\geq 5\%$ of patients receiving valacyclovir hydrochloride 1 gram twice daily for 10 days (n = 318) or oral acyclovir 200 mg 5 times daily for 10 days (n = 318), respectively, included headache (13%, 10%) and nausea (6%, 6%). For the incidence of laboratory abnormalities see Table 2.

Recurrent Episodes: In 3 clinical studies for the episodic treatment of recurrent genital herpes, the adverse reactions reported by $\geq 5\%$ of patients receiving valacyclovir hydrochloride 500 mg twice daily for 3 days (n = 402), valacyclovir hydrochloride 500 mg twice daily for 5 days (n = 1,136) or placebo (n = 259), respectively, included headache (16%, 11%, 14%) and nausea (5%, 4%, 5%). For the incidence of laboratory abnormalities see Table 2.

Suppressive Therapy: Suppression of Recurrent Genital Herpes in Immunocompetent Adults: In a clinical study for the suppression of recurrent genital herpes infections, the adverse reactions reported by patients receiving valacyclovir hydrochloride 1 gram once daily (n = 269), valacyclovir hydrochloride 500 mg once daily (n = 266), or placebo (n = 134), respectively, included headache (35%, 38%, 34%), nausea (11%, 11%, 8%), abdominal pain (11%, 9%, 6%), dysmenorrhea (8%, 5%, 4%), depression (7%, 5%, 5%), arthralgia (6%, 5%, 4%), vomiting (3%, 3%, 2%), and dizziness (4%, 2%, 1%). For the incidence of laboratory abnormalities see Table 2.

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

Reduction of Transmission: In a clinical study for the reduction of transmission of genital herpes, the adverse reactions reported by patients receiving valacyclovir hydrochloride 500 mg once daily (n = 743) or placebo once daily (n = 741), respectively, included headache (29%, 26%), nasopharyngitis (16%, 15%), and upper respiratory tract infection (9%, 10%).

Herpes Zoster: In 2 clinical studies for the treatment of herpes zoster, the adverse reactions reported by patients receiving valacyclovir hydrochloride 1 gram 3 times daily for 7 to 14 days (n = 967) or placebo (n = 195), respectively, included nausea (15%, 8%), headache (14%, 12%), vomiting (6%, 3%), dizziness (3%, 2%), and abdominal pain (3%, 2%). For the incidence of laboratory abnormalities see TABLE 2.

Table 2. Incidence (%) of Laboratory Abnormalities in Herpes Zoster and Genital Herpes Study Populations

Laboratory Abnormality

Herpes Zoster

Genital Herpes Treatment

Genital Herpes Suppression

Valacyclovir Hydrochloride 1 gram
3 times daily(n = 967)

Placebo(n = 195)

Valacyclovir Hydrochloride 1 gram
twice daily
(n = 1,194)

Valacyclovir Hydrochloride 500 mg
twice daily(n = 1,159)

Placebo(n = 439)

Valacyclovir Hydrochloride 1 gram
once daily (n = 269)

Valacyclovir Hydrochloride 500 mg
once daily (n = 266)

Placebo
(n = 134)

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/mm³)

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.

6.2 Clinical Trials Experience in Pediatric Patients

The safety profile of valacyclovir hydrochloride has been studied in 177 pediatric patients 1 month to <18 years of age. Sixty-five of these pediatric patients, 12 to <18 years of age, received oral tablets for 1 to 2 days for treatment of cold sores. The remaining 112 pediatric patients, 1 month to <12 years of age, participated in 3 pharmacokinetic and safety studies and received valacyclovir oral suspension. Fifty-one of these 112 pediatric patients received oral suspension for 3 to 6 days. The frequency, intensity, and nature of clinical adverse reactions and laboratory abnormalities were similar to those seen in adults.

Pediatric Patients 12 to <18 Years of Age (Cold Sores): In clinical studies for the treatment of cold sores, the adverse reactions reported by adolescent patients receiving valacyclovir hydrochloride 2 grams twice daily for 1 day, or valacyclovir hydrochloride 2 grams twice daily for 1 day followed by 1 gram twice daily for 1 day (n = 65, across both dosing groups), or placebo (n = 30), respectively, included headache (17%, 3%) and nausea (8%, 0%).

Pediatric Patients 1 Month to <12 Years of Age: Adverse events reported in more than 1 subject across the 3 pharmacokinetic and safety studies in children 1 month to <12 years of age were diarrhea (5%), pyrexia (4%), dehydration (2%), herpes simplex (2%), and rhinorrhea (2%). No clinically meaningful changes in laboratory values were observed.

6.3 Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of valacyclovir hydrochloride. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to valacyclovir hydrochloride.

General: Facial edema, hypertension, tachycardia.

Allergic: Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritus, rash, and urticaria [see CONTRAINDICATIONS (4)].

CNS Symptoms: Aggressive behavior; agitation; ataxia; coma; confusion; decreased consciousness; dysarthria; encephalopathy; mania; and psychosis, including auditory and visual hallucinations, seizures, tremors [see WARNINGS AND PRECAUTIONS (5.3), USE IN SPECIFIC POPULATIONS (8.5), (8.6)].

Eye: Visual abnormalities.

Gastrointestinal: Diarrhea.

Hepatobiliary Tract and Pancreas: Liver enzyme abnormalities, hepatitis.

Renal: Renal failure, renal pain (may be associated with renal failure) [see WARNINGS AND PRECAUTIONS (5.2), USE IN SPECIFIC POPULATIONS (8.5), (8.6)].

Hematologic: Thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis, TTP/HUS [see WARNINGS AND PRECAUTIONS (5.1)].

Skin: Erythema multiforme, rashes including photosensitivity, alopecia.

No clinically significant drug-drug or drug-food interactions with valacyclovir hydrochloride are known [see CLINICAL PHARMACOLOGY (12.3)].

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of valacyclovir hydrochloride or acyclovir in pregnant women. Based on prospective pregnancy registry data on 749 pregnancies, the overall rate of birth defects in infants exposed to acyclovir in-utero appears similar to the rate for infants in the general population. Valacyclovir hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

Animal reproduction studies performed at oral doses that provided up to 10 and 7 times the human plasma levels during the period of major organogenesis in rats and rabbits, respectively, revealed no evidence of teratogenicity.

8.3 Nursing Mothers

Following oral administration of a 500 mg dose of valacyclovir hydrochloride 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 valacyclovir hydrochloride 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. Caution should be exercised when valacyclovir hydrochloride is administered to a nursing woman.

8.4 Pediatric Use

Valacyclovir hydrochloride is indicated for treatment of cold sores in pediatric patients ≥ 12 years of age and for treatment of chickenpox in pediatric patients 2 to < 18 years of age [see INDICATIONS AND USAGE (1.2), DOSAGE AND ADMINISTRATION (2.2)].

The use of valacyclovir hydrochloride for treatment of cold sores is based on 2 double-blind, placebo-controlled clinical trials in healthy adults and adolescents (≥ 12 years of age) with a history of recurrent cold sores [see CLINICAL STUDIES (14.1)].

The use of valacyclovir hydrochloride for treatment of chickenpox in pediatric patients 2 to < 18 years of age is based on single-dose pharmacokinetic and multiple-dose safety data from an open-label trial with valacyclovir and supported by efficacy and safety data from 3 randomized, double-blind, placebo-controlled trials evaluating oral acyclovir in pediatric patients with chickenpox [see DOSAGE AND ADMINISTRATION (2.2), ADVERSE REACTIONS (6.2), CLINICAL PHARMACOLOGY (12.3), CLINICAL STUDIES (14.4)].

The efficacy and safety of valacyclovir have not been established in pediatric patients:

- < 12 years of age with cold sores
- < 18 years of age with genital herpes
- < 18 years of age with herpes zoster
- < 2 years of age with chickenpox

for suppressive therapy following neonatal HSV infection.

The pharmacokinetic profile and safety of valacyclovir oral suspension in children < 12 years of age were studied in 3 open-label studies. No efficacy evaluations were conducted in any of the 3 studies.

Study 1 was a single-dose pharmacokinetic, multiple-dose safety study in 27 pediatric patients 1 to < 12 years of age with clinically suspected varicella-zoster virus (VZV) infection [see DOSAGE AND ADMINISTRATION (2.2), ADVERSE REACTIONS (6.2), CLINICAL PHARMACOLOGY (12.3), CLINICAL STUDIES (14.4)].

Study 2 was a single-dose pharmacokinetic and safety study in pediatric patients 1 month to < 6 years of age who had an active herpes virus infection or who were at risk for herpes virus infection. Fifty-seven subjects were enrolled and received a single dose of 25 mg/kg valacyclovir oral suspension. In infants and children 3 months to < 6 years of age, this dose provided comparable systemic acyclovir exposures to that from a 1 gram dose of valacyclovir in adults (historical data). In infants 1 month to < 3 months of age, mean acyclovir exposures resulting from a 25 mg/kg dose were higher (C_{max} : $\uparrow 30\%$, AUC: $\uparrow 60\%$) than acyclovir exposures following a 1 gram dose of valacyclovir in adults. Acyclovir is not approved for suppressive therapy in infants and children following neonatal HSV infections; therefore valacyclovir is not recommended for this indication because efficacy cannot be extrapolated from acyclovir.

Study 3 was a single-dose pharmacokinetic, multiple-dose safety study in 28 pediatric

patients 1 to <12 years of age with clinically suspected HSV infection. None of the children enrolled in this study had genital herpes. Each subject was dosed with valacyclovir oral suspension, 10 mg/kg twice daily for 3 to 5 days. Acyclovir systemic exposures in pediatric patients following valacyclovir oral suspension were compared with historical acyclovir systemic exposures in immunocompetent adults receiving the solid oral dosage form of valacyclovir or acyclovir for the treatment of recurrent genital herpes. The mean projected daily acyclovir systemic exposures in pediatric patients across all age-groups (1 to <12 years of age) were lower (C_{max}: ↓20%, AUC: ↓33%) compared with the acyclovir systemic exposures in adults receiving valacyclovir 500 mg twice daily, but were higher (daily AUC: ↑16%) than systemic exposures in adults receiving acyclovir 200 mg 5 times daily. Insufficient data are available to support valacyclovir for the treatment of recurrent genital herpes in this age-group because clinical information on recurrent genital herpes in young children is limited; therefore, extrapolating efficacy data from adults to this population is not possible. Moreover, valacyclovir has not been studied in children 1 to <12 years of age with recurrent genital herpes.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of valacyclovir hydrochloride, 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 [see DOSAGE AND ADMINISTRATION (2.4), WARNINGS AND PRECAUTIONS (5.2, 5.3), CLINICAL PHARMACOLOGY (12.3)].

8.6 Renal Impairment

Dosage reduction is recommended when administering valacyclovir hydrochloride to patients with renal impairment [see DOSAGE AND ADMINISTRATION (2.4), WARNINGS AND PRECAUTIONS (5.2, 5.3)].

Caution should be exercised to prevent inadvertent overdose [see USE IN SPECIFIC POPULATIONS (8.5), (8.6)]. 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 (2.4)].

Valacyclovir hydrochloride, USP is the hydrochloride salt of the L-valyl ester of the antiviral drug acyclovir.

Valacyclovir tablets, USP are for oral administration. Each tablet contains valacyclovir hydrochloride, USP equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients crospovidone, FD&C Blue No. 2, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide.

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

[Structure]

Valacyclovir hydrochloride, USP is a white to off-white powder with the molecular formula C₁₃H₂₀N₆O₄•HCl and a molecular weight of 360.80. The maximum solubility in

water at 25°C is 174 mg/mL. The pKas for valacyclovir hydrochloride are 1.90, 7.47, and 9.43.

12.1 Mechanism of Action

Valacyclovir is an antiviral drug [see CLINICAL PHARMACOLOGY (12.4)].

12.3 Pharmacokinetics

The pharmacokinetics of valacyclovir and acyclovir after oral administration of valacyclovir hydrochloride have been investigated in 14 volunteer studies involving 283 adults and in 3 studies involving 112 pediatric subjects from 1 month to <12 years of age.

Pharmacokinetics in Adults: Absorption and Bioavailability: 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.

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

Acyclovir pharmacokinetic parameter estimates following administration of valacyclovir hydrochloride to healthy adult volunteers are presented in TABLE 3. There was a less than dose-proportional increase in acyclovir maximum concentration (C_{max}) and area under the acyclovir concentration-time curve (AUC) after single-dose and multiple-dose administration (4 times daily) of valacyclovir hydrochloride from doses between 250 mg to 1 gram.

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

Table 3. Mean (\pm SD) Plasma Acyclovir Pharmacokinetic Parameters Following Administration of Valacyclovir Hydrochloride to Healthy Adult Volunteers

Dose

Single-Dose Administration

(N = 8)

Multiple-Dose Administration*

(N = 24, 8 per treatment arm)

C_{max} (\pm SD)

(mcg/mL)

AUC (\pm SD)

(hr•mcg/mL)

C_{max} (\pm SD)

(mcg/mL)

AUC (\pm SD)

(hr•mcg/mL)

100 mg

0.83 (± 0.14)

2.28 (± 0.40)

ND

ND

250 mg

2.15 (± 0.50)

5.76 (± 0.60)

2.11 (± 0.33)

5.66 (± 1.09)

500 mg

3.28 (± 0.83)

11.59 (± 1.79)

3.69 (± 0.87)

9.88 (± 2.01)

750 mg

4.17 (± 1.14)

14.11 (± 3.54)

ND

ND

1,000 mg

5.65 (± 2.37)

19.52 (± 6.04)

4.96 (± 0.64)

15.70 (± 2.27)

*Administered 4 times daily for 11 days.

ND = not done.

Distribution: The binding of valacyclovir to human plasma proteins ranges from 13.5% to 17.9%. The binding of acyclovir to human plasma proteins ranges from 9% to 33%.

Metabolism: 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 valacyclovir hydrochloride, 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, 46% and 47% of administered radioactivity was recovered in urine and feces, respectively, over 96 hours. Acyclovir accounted for 89% of the radioactivity excreted in the urine. Renal clearance of acyclovir following the administration of a single 1 gram dose of valacyclovir hydrochloride to 12 healthy volunteers was approximately 255 ± 86 mL/min which represents 42% 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 valacyclovir hydrochloride in volunteers with normal renal function.

Specific Populations: Renal Impairment: Reduction in dosage is recommended in patients with renal impairment [see DOSAGE AND ADMINISTRATION (2.4), Use in SPECIFIC POPULATIONS (8.5), (8.6)].

Following administration of valacyclovir hydrochloride 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 with 679.16 ± 162.76 mL/min/1.73 m² in healthy volunteers.

Hepatic Impairment: Administration of valacyclovir hydrochloride 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/mm³ who received valacyclovir hydrochloride 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.

Geriatrics: After single-dose administration of 1 gram of valacyclovir hydrochloride in healthy geriatric volunteers, the half-life of acyclovir was 3.11 ± 0.51 hours, compared with 2.91 ± 0.63 hours in healthy younger adult volunteers. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of valacyclovir hydrochloride 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 DOSAGE AND ADMINISTRATION (2.4), USE IN SPECIFIC POPULATIONS (8.5), (8.6)].

Pediatrics: Acyclovir pharmacokinetics have been evaluated in a total of 98 pediatric patients (1 month to <12 years of age) following administration of the first dose of an extemporaneous oral suspension of valacyclovir [see ADVERSE REACTIONS (6.2), USE IN SPECIFIC POPULATIONS (8.4)]. Acyclovir pharmacokinetic parameter estimates following a 20 mg/kg dose are provided in TABLE 4.

Table 4. Mean (\pm SD) Plasma Acyclovir Pharmacokinetic Parameter Estimates Following First-Dose Administration of 20 mg/kg Valacyclovir Oral Suspension to Pediatric Patients vs. 1 Gram Single Dose of Valacyclovir Hydrochloride to Adults

Parameter

Pediatric Patients
(20 mg/kg Oral Suspension)

Adults 1 gram Solid
Dose of Valacyclovir Hydrochloride
(N = 15)

1-<2 yr
(N = 6)

2-<6 yr
(N = 12)

6-<12 yr
(N = 8)

AUC (mcg.hr/mL)
Cmax (mcg/mL)

14.4 (\pm 6.26)
4.03 (\pm 1.37)

10.1 (\pm 3.35)
3.75 (\pm 1.14)

13.1 (\pm 3.43)
4.71 (\pm 1.20)

17.2 (\pm 3.10)
4.72 (\pm 1.37)

a Historical estimates using pediatric pharmacokinetic sampling schedule.

Drug Interactions: When valacyclovir hydrochloride is coadministered with antacids, cimetidine and/or probenecid, digoxin, or thiazide diuretics in patients with normal renal function, the effects are not considered to be of clinical significance (see below). Therefore, when valacyclovir hydrochloride is coadministered with these drugs in patients with normal renal function, no dosage adjustment is recommended.

Antacids: The pharmacokinetics of acyclovir after a single dose of valacyclovir hydrochloride (1 gram) were unchanged by coadministration of a single dose of antacids (Al³⁺ or Mg⁺⁺).

Cimetidine: Acyclovir Cmax and AUC following a single dose of valacyclovir hydrochloride (1 gram) increased by 8% and 32%, respectively, after a single dose of cimetidine (800 mg).

Cimetidine Plus Probenecid: Acyclovir Cmax and AUC following a single dose of valacyclovir hydrochloride (1 gram) increased by 30% and 78%, respectively, after a combination of cimetidine and probenecid, primarily due to a reduction in renal clearance of acyclovir.

Digoxin: The pharmacokinetics of digoxin were not affected by coadministration of valacyclovir hydrochloride 1 gram 3 times daily, and the pharmacokinetics of acyclovir after a single dose of valacyclovir hydrochloride (1 gram) was unchanged by coadministration of digoxin (2 doses of 0.75 mg).

Probenecid: Acyclovir C_{max} and AUC following a single dose of valacyclovir hydrochloride (1 gram) increased by 22% and 49%, respectively, after probenecid (1 gram).

Thiazide Diuretics: The pharmacokinetics of acyclovir after a single dose of valacyclovir hydrochloride (1 gram) were unchanged by coadministration of multiple doses of thiazide diuretics.

12.4 Microbiology

Mechanism of Action: Valacyclovir is a nucleoside analogue DNA polymerase inhibitor. Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against HSV types 1 (HSV-1) and 2 (HSV-2) and VZV both in cell culture 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 biochemical assays, acyclovir triphosphate inhibits 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 cell culture susceptibility of herpes viruses 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 (EC₅₀), vary greatly depending upon a number of factors. Using plaque-reduction assays, the EC₅₀ values against herpes simplex virus isolates range from 0.09 to 60 μM (0.02 to 13.5 mcg/mL) for HSV-1 and from 0.04 to 44 μM (0.01 to 9.9 mcg/mL) for HSV-2. The EC₅₀ values for acyclovir against most laboratory strains and clinical isolates of VZV range from 0.53 to 48 μM (0.12 to 10.8 mcg/mL). Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean EC₅₀ of 6 μM (1.35 mcg/mL).

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.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The data presented below include references to the steady-state acyclovir AUC observed in humans treated with 1 gram valacyclovir hydrochloride 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 (12.3)].

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.

14.1 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 valacyclovir hydrochloride 2 grams twice daily on Day 1 followed by placebo on Day 2, valacyclovir hydrochloride 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 valacyclovir hydrochloride or placebo in the prevention of progression of cold sore lesions beyond the papular stage.

14.2 Genital Herpes Infections

Initial Episode: Six hundred 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 valacyclovir hydrochloride 1 gram twice daily ($n = 323$) or oral acyclovir 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 valacyclovir hydrochloride 500 mg twice daily (n = 360) or placebo (n = 259). The median time to lesion healing was 4 days in the group receiving valacyclovir hydrochloride 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 valacyclovir hydrochloride 500 mg versus 4 days in the placebo group. The median time to cessation of pain was 3 days in the group receiving valacyclovir hydrochloride 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 valacyclovir hydrochloride 500 mg twice daily for 5 days (n = 398) or valacyclovir hydrochloride 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 5.

Table 5. Recurrence Rates in Immunocompetent Adults at 6 and 12 Months

Outcome

6 Months

12 Months

Valacyclovir Hydrochloride
1 gram once daily (n = 269)

Oral acyclovir
400 mg
twice daily(n = 267)

Placebo(n = 134)

Valacyclovir Hydrochloride 1 gram once daily
(n = 269)

Oral acyclovir
400 mg
twice daily(n = 267)

Placebo(n = 134)

Recurrence free

55%

54%

7%
 34%
 34%
 4%
 Recurrences
 35%
 36%
 83%
 46%
 46%
 85%
 Unknown*
 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 valacyclovir hydrochloride 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 valacyclovir hydrochloride 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 log₁₀ copies/mL. Among patients who received valacyclovir hydrochloride, the prestudy median CD4+ cell count was 336 cells/mm³; 11% had <100 cells/mm³, 16% had 100 to 199 cells/mm³, 42% had 200 to 499 cells/mm³, and 31% had ≥500 cells/mm³. Outcomes for the overall study population are shown in TABLE 6.

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

Outcome

Valacyclovir Hydrochloride
 500 mg twice daily
 (n = 194)

Placebo
(n = 99)

Recurrence free

65%

26%

Recurrences

17%

57%

Unknown*

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 valacyclovir hydrochloride 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 7.

Table 7. Percentage of Susceptible Partners Who Acquired HSV-2 Defined by the Primary and Selected Secondary Endpoints

Endpoint

Valacyclovir Hydrochloride*
(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 valacyclovir hydrochloride versus placebo. Individual results may vary based on consistency of safer sex practices.

14.3 Herpes Zoster

Two randomized double-blind clinical trials in immunocompetent adults with localized herpes zoster were conducted. Valacyclovir hydrochloride was compared with placebo in patients less than 50 years of age, and with oral acyclovir 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 valacyclovir hydrochloride 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 valacyclovir hydrochloride or oral acyclovir. 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 valacyclovir hydrochloride 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 valacyclovir hydrochloride, 14-day valacyclovir hydrochloride, and 7-day oral acyclovir, respectively.

14.4 Chickenpox

The use of valacyclovir hydrochloride for treatment of chickenpox in pediatric patients 2 to <18 years of age is based on single-dose pharmacokinetic and multiple-dose safety data from an open-label trial with valacyclovir and supported by safety and extrapolated efficacy data from 3 randomized, double-blind, placebo-controlled trials evaluating oral acyclovir in pediatric patients.

The single-dose pharmacokinetic and multiple-dose safety study enrolled 27 pediatric patients 1 to <12 years of age with clinically suspected VZV infection. Each subject was dosed with valacyclovir oral suspension, 20 mg/kg 3 times daily for 5 days. Acyclovir systemic exposures in pediatric patients following valacyclovir oral suspension were compared with historical acyclovir systemic exposures in immunocompetent adults receiving the solid oral dosage form of valacyclovir or acyclovir for the treatment of herpes zoster. The mean projected daily acyclovir exposures in pediatric patients across all age-groups (1 to <12 years of age) were lower (C_{max}: ↓13%, AUC: ↓30%) than the mean daily historical exposures in adults receiving valacyclovir 1 gram 3 times daily, but were higher (daily AUC: ↑50%) than the mean daily historical exposures in adults receiving acyclovir 800 mg 5 times daily. The projected daily exposures in pediatric patients were greater (daily AUC approximately 100% greater) than the exposures seen in immunocompetent pediatric patients receiving acyclovir 20 mg/kg 4 times daily for the treatment of chickenpox. Based on the pharmacokinetic and safety data from this study and the safety and extrapolated efficacy data from the acyclovir studies, oral valacyclovir 20 mg/kg 3 times a day for 5 days (not to exceed 1 gram 3 times daily) is recommended for the treatment of chickenpox in pediatric patients 2 to <18 years of age. Because the efficacy and safety of acyclovir for the treatment of chickenpox in children <2 years of age have not been established, efficacy data cannot be

extrapolated to support valacyclovir treatment in children <2 years of age with chickenpox. Valacyclovir is also not recommended for the treatment of herpes zoster in children because safety data up to 7 days' duration are not available [see USE IN SPECIFIC POPULATIONS (8.4)].

Valacyclovir tablets, USP 500 mg (blue colored, capsule shaped, film coated tablets debossed with "C324 500" on one side and plain on the other side) containing valacyclovir hydrochloride equivalent to 500 mg valacyclovir.

Valacyclovir tablets, USP 1 gram (blue colored, capsule shaped, film coated tablets with partial score bar on both sides and debossed with "C325 1000" on one side and plain on the other) containing valacyclovir hydrochloride equivalent to 1 gram valacyclovir.

Storage:

Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature]. Dispense in a well-closed container as defined in the USP.

VALACYCLOVIR HYDROCHLORIDE

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed. Dosage: See package insert. Store between 68-77 degrees F. For RX ONLY. Keep out of reach of children.

D NDC 72189-037-21

VALACYCLOVIR

1 gm **21 Tabs**

Generic For: **VALTREX**
Each film-coated tablet contains: Valacyclovir Hydrochloride USP, equivalent to Valacyclovir 1 gram

Lot# 14N01903
Prod# 4341-001-21
Packaged and Distributed By: **DIRECT Rx**

Discard After: 3/31/22
72189-037-21
14N01903 Dawsonville, GA 30534
AZCPA

Mfg Lot: VL216042A
Mfg Lot: VL142019 3563193
Mfg Lot: VL216042A
Mfg Lot: VL142019 3563193
Mfg Lot: VL216042A
Mfg Lot: VL142019 3563193
Mfg Lot: VL216042A
Mfg Lot: VL142019 3563193

VALACYCLOVIR 1 gm
NDC 72189-037-21 21 Tabs
Lot 14N01903 Exp 3/31/22
Mfg NDC 59746-325-30

VALACYCLOVIR 1 gm
NDC 72189-037-21 21 Tabs
Lot 14N01903 Exp 3/31/22
Mfg NDC 59746-325-30

VALACYCLOVIR 1 gm
NDC 72189-037-21 21 Tabs
Lot 14N01903 Exp 3/31/22
Mfg NDC 59746-325-30

VALACYCLOVIR 1 gm
NDC 72189-037-21 21 Tabs
Lot 14N01903 Exp 3/31/22
Mfg NDC 59746-325-30

Mrk. By Jubilant Cadista Pharm. Int.
Salisbury, MD 21801, USA
Mfg Lot: VL216042A
Mfg Lot: VL142019 3563193

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed. Dosage: See package insert. Store between 68-77 degrees F. For RX ONLY. Keep out of reach of children.

D NDC 72189-051-30

VALACYCLOVIR

1gm* **30 Tabs**

Generic For: **VALTREX**
Each film-coated tablet contains: 1.112 gram of valacyclovir hydrochloride USP equivalent to 1 gram of valacyclovir

Lot# 150C1906
Prod# 4341-001-30
Packaged and Distributed By: **DIRECT Rx**

Discard After: 12/31/20
72189-051-30
150C1906 Dawsonville, GA 30534
AZRFP

Mfg Lot: VLC18099
Mfg Lot: BW 10/15/2019 T143336
Mfg Lot: VLC18099
Mfg Lot: BW 10/15/2019 T143336
Mfg Lot: VLC18099
Mfg Lot: BW 10/15/2019 T143336
Mfg Lot: VLC18099
Mfg Lot: BW 10/15/2019 T143336

VALACYCLOVIR 1gm*
NDC 72189-051-30 30 Tabs
Lot 150C1906 Exp 12/31/20
Mfg NDC 31722-705-30

VALACYCLOVIR 1gm*
NDC 72189-051-30 30 Tabs
Lot 150C1906 Exp 12/31/20
Mfg NDC 31722-705-30

VALACYCLOVIR 1gm*
NDC 72189-051-30 30 Tabs
Lot 150C1906 Exp 12/31/20
Mfg NDC 31722-705-30

VALACYCLOVIR 1gm*
NDC 72189-051-30 30 Tabs
Lot 150C1906 Exp 12/31/20
Mfg NDC 31722-705-30

Mfg For: Cambiar Pharmaceuticals, Inc.
Piscataway, NJ 08854
Mfg Lot: VLC18099
Mfg Lot: BW 10/15/2019 T143336

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed. See package insert. Store between 68-77 degrees F. For RX ONLY. Keep out of reach of children.

NDC 72189-037-60

VALACYCLOVIR

1gm*

60 Tabs

Generic For: **VALTREX**

Each film-coated tablet contains: Valacyclovir Hydrochloride USP, equivalent to Valacyclovir 1 gram

Lot# SAMPLE
Prod# 4341-001-60

Packaged and Distributed By: **DIRECT Rx**



Discard After: 3/31/22
72189-037-60
SAMPLE
3/31/22
AYJV8 Dawsonville, GA 30534

Mfg Lot: SAMPLE
NDC 72189-037-60 60 Tabs
Lot SAMPLE Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: SAMPLE
NDC 72189-037-60 60 Tabs
Lot SAMPLE Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: SAMPLE
NDC 72189-037-60 60 Tabs
Lot SAMPLE Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: SAMPLE
NDC 72189-037-60 60 Tabs
Lot SAMPLE Exp 3/31/22
Mfg NDC 59746-325-30

Mfr By: Jubilant Celltata Pharm. Inc.
Sellebury, MD 21801

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed. See package insert. Store between 68-77 degrees F. For RX ONLY. Keep out of reach of children.

NDC 72189-037-30

VALACYCLOVIR

1gm*

30 Tabs

Generic For: **VALTREX**

Each film-coated tablet contains: Valacyclovir Hydrochloride USP, equivalent to Valacyclovir 1 gram

Lot# 04SE1909
Prod# 4341-001-30

Packaged and Distributed By: **DIRECT Rx**



Discard After: 3/31/22
72189-037-30
04SE1909
3/31/22
AYJV3 Dawsonville, GA 30534

Mfg Lot: V1219035A
NDC 72189-037-30 30 Tabs
Lot 04SE1909 Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: V1219035A
NDC 72189-037-30 30 Tabs
Lot 04SE1909 Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: V1219035A
NDC 72189-037-30 30 Tabs
Lot 04SE1909 Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: V1219035A
NDC 72189-037-30 30 Tabs
Lot 04SE1909 Exp 3/31/22
Mfg NDC 59746-325-30

Mfr By: Jubilant Celltata Pharm. Inc.
Sellebury, MD 21801

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed. See package insert. Store between 68-77 degrees F. For RX ONLY. Keep out of reach of children.

NDC 72189-037-90

VALACYCLOVIR

1gm*

90 Tabs

Generic For: **VALTREX**

Each film-coated tablet contains: Valacyclovir Hydrochloride USP, equivalent to Valacyclovir 1 gram

Lot# SAMPLE
Prod# 4341-001-90

Packaged and Distributed By: **DIRECT Rx**



Discard After: 3/31/22
72189-037-90
SAMPLE
3/31/22
AYJWA Dawsonville, GA 30534

Mfg Lot: SAMPLE
NDC 72189-037-90 90 Tabs
Lot SAMPLE Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: SAMPLE
NDC 72189-037-90 90 Tabs
Lot SAMPLE Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: SAMPLE
NDC 72189-037-90 90 Tabs
Lot SAMPLE Exp 3/31/22
Mfg NDC 59746-325-30

Mfg Lot: SAMPLE
NDC 72189-037-90 90 Tabs
Lot SAMPLE Exp 3/31/22
Mfg NDC 59746-325-30

Mfr By: Jubilant Celltata Pharm. Inc.
Sellebury, MD 21801

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed. See package insert. Store between 68-77 degrees F. For RX ONLY. Keep out of reach of children.

NDC 72189-232-35

ACYCLOVIR

800mg

35 Tabs

Generic For: **ZOVIRAX**

Each tablet contains: Acyclovir USP, 800mg

Lot# 14JU2120
Prod# 4102-800-35

Packaged and Distributed By: **DIRECT Rx**



Discard After: 3/31/23
72189-232-35
14JU2120
3/31/23
BCJCH Dawsonville, GA 30534

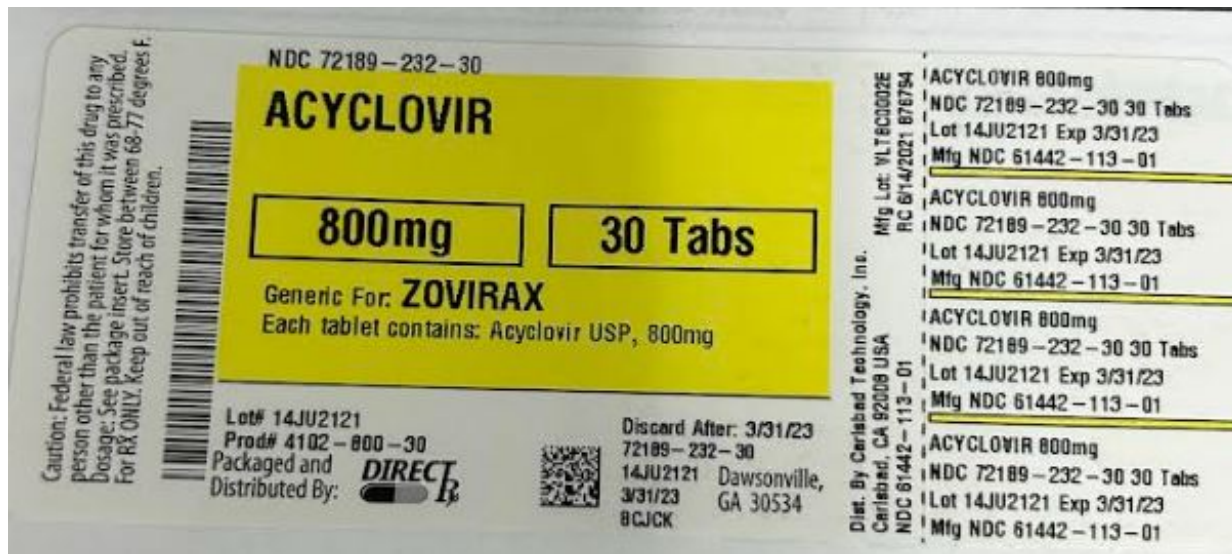
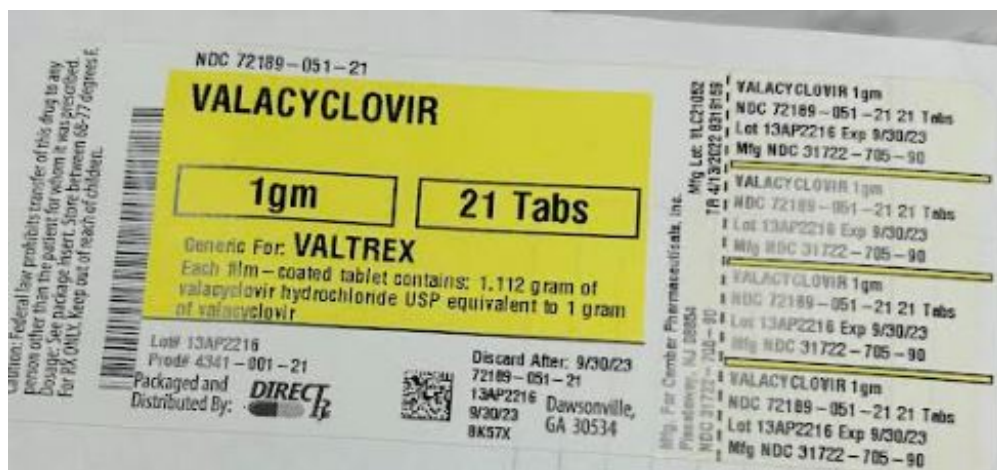
Mfg Lot: VLT8C0002E
NDC 72189-232-35 35 Tabs
Lot 14JU2120 Exp 3/31/23
Mfg NDC 61442-113-01

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Dist. By: Carisbad Technology, Inc.
Carisbad, CA 92008 USA



ACYCLOVIR

acyclovir tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72189-232(NDC:61442-113)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ACYCLOVIR (UNII: X4HES1O11F) (ACYCLOVIR - UNII:X4HES1O11F)	ACYCLOVIR	800 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6130)	

Product Characteristics

Color	white	Score	no score
Shape	OVAL	Size	19mm
Flavor		Imprint Code	CTI;113
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-232-35	35 in 1 BOTTLE; Type 0: Not a Combination Product	09/13/2021	
2	NDC:72189-232-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	09/13/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075382	09/13/2021	

VALACYCLOVIR HYDROCHLORIDE

valacyclovir hydrochloride tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72189-037(NDC:59746-325)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VALACYCLOVIR HYDROCHLORIDE (UNII: G447S0T1VC) (ACYCLOVIR - UNII:X4HES1O11F)	ACYCLOVIR	1 g

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
CROSPVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	

POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)

Product Characteristics

Color	blue	Score	2 pieces
Shape	CAPSULE	Size	23mm
Flavor		Imprint Code	C3251000
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-037-21	21 in 1 BOTTLE; Type 0: Not a Combination Product	11/18/2019	
2	NDC:72189-037-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/18/2019	
3	NDC:72189-037-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/18/2019	
4	NDC:72189-037-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	11/18/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201506	11/18/2019	

VALACYCLOVIR

valacyclovir tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72189-051(NDC:31722-705)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VALACYCLOVIR HYDROCHLORIDE (UNII: G447S0T1VC) (ACYCLOVIR - UNII:X4HES1O11F)	ACYCLOVIR	1 g

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

CROSPROVIDONE (15 MPAS AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I3O)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
POVIDONE (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	white	Score	2 pieces
Shape	CAPSULE	Size	23mm
Flavor		Imprint Code	I;87
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-051-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/17/2020	
2	NDC:72189-051-21	21 in 1 BOTTLE; Type 0: Not a Combination Product	06/17/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203047	06/17/2020	

Labeler - DIRECT RX (079254320)

Registrant - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(72189-037, 72189-051, 72189-232)