

### WARNINGS AND PRECAUTIONS

**Genital Herpes:**

- **Recurrent episodes:**
  - **Immunocompetent patients:** Daily therapy with valacyclovir may reduce the frequency of recurrent herpes labialis in immunocompetent patients with ≥10 recurrences/year and ≥3 recurrences in the previous year. Patients with ≤9 recurrences/year who are clinically appropriate may also be treated with valacyclovir for suppression. In patients with 1 recurrent episode a year or less, therapy was ineffective at the usual suppressive dose of 1 gram daily for 1 year. In immunocompetent patients with 2 or more recurrences per year, daily therapy should be initiated within 24 hours of the first signs/symptoms of an episode. Some patients may experience a lower incidence of recurrent episodes with a lower dose of valacyclovir or a lower frequency of administration.

- **HIV-infected patients:** In patients with HIV infection, daily therapy with valacyclovir may reduce the frequency of recurrent herpes labialis in immunocompetent patients with ≥10 recurrences/year and ≥3 recurrences in the previous year. Patients with ≤9 recurrences/year who are clinically appropriate may also be treated with valacyclovir for suppression. In patients with 1 recurrent episode a year or less, therapy was ineffective at the usual suppressive dose of 1 gram daily for 1 year. In HIV-infected patients with ≥10 recurrences/year and ≥3 recurrences in the previous year, daily therapy should be initiated within 24 hours of the first signs/symptoms of an episode. Some patients may experience a lower incidence of recurrent episodes with a lower dose of valacyclovir or a lower frequency of administration.

- **Immunocompromised patients:** Daily therapy with valacyclovir may reduce the frequency of recurrent herpes labialis in immunocompromised patients with ≥10 recurrences/year and ≥3 recurrences in the previous year. Patients with ≤9 recurrences/year who are clinically appropriate may also be treated with valacyclovir for suppression. In patients with 1 recurrent episode a year or less, therapy was ineffective at the usual suppressive dose of 1 gram daily for 1 year. In immunocompromised patients with ≥10 recurrences/year and ≥3 recurrences in the previous year, daily therapy should be initiated within 24 hours of the first signs/symptoms of an episode. Some patients may experience a lower incidence of recurrent episodes with a lower dose of valacyclovir or a lower frequency of administration.

**Herpes Zoster:**

- **Immunocompetent patients:** The recommended dosage of valacyclovir tablets for treatment of zoster is 1 gram 3 times daily for 7 days. In clinical studies for the treatment of herpes zoster, the adverse reactions reported by patients treated with valacyclovir hydrochloride and observed more frequently with valacyclovir hydrochloride compared to placebo are headache, nausea, and vomiting. For the incidence of laboratory abnormalities see Table 2.

- **HIV-infected patients:** The recommended dosage of valacyclovir tablets for treatment of zoster is 1 gram 3 times daily for 7 days. In clinical studies for the treatment of herpes zoster in HIV-infected patients, the adverse reactions reported by patients treated with valacyclovir hydrochloride and observed more frequently with valacyclovir hydrochloride compared to placebo are headache, nausea, and vomiting. For the incidence of laboratory abnormalities see Table 2.

**Valacyclovir tablets are indicated for the treatment of herpes zoster in adults and pediatric patients (with or without reduced renal function) and in patients with underlying renal disease who require a reduced dosage in patients with renal impairment. (2.4, 5.2)**

**Central nervous system adverse reactions, including agitation, hallucinations, confusion, and encephalopathy (5.4):** These occur most frequently in patients with advanced HIV disease or "AIDS". They may be dose-related, and may require dosage reduction. Patients should be monitored frequently for signs/symptoms of these reactions and should be treated with antipsychotics if symptomatic and/or if dosage reduction is not tolerated. Adverse reactions reported in clinical studies for the treatment of herpes zoster in HIV-infected adults include headache (25%), nausea and vomiting (15%), and especially dizziness (17%). fringe for all reactions if observed more frequently with valacyclovir hydrochloride compared to placebo are headache, nausea, and vomiting. For the incidence of laboratory abnormalities see Table 2.

**Recurrent episodes:**

- **Immunocompetent patients:** Therapy is generally initiated within 24 hours of the first signs/symptoms of an episode. The recommended dosage of valacyclovir tablets for suppression is 1 gram 3 times daily for 1 year. In immunocompetent patients with 2 or more recurrences per year, daily therapy should be initiated within 24 hours of the first signs/symptoms of an episode. Some patients may experience a lower incidence of recurrent episodes with a lower dose of valacyclovir or a lower frequency of administration.

- **HIV-infected patients:** The recommended dosage of valacyclovir tablets for suppression is 1 gram 3 times daily for 1 year. In HIV-infected patients, patients with 1 recurrent episode a year or less, therapy was ineffective at the usual suppressive dose of 1 gram daily for 1 year. In immunocompetent patients with ≤9 recurrences/year and ≥3 recurrences in the previous year, daily therapy should be initiated within 24 hours of the first signs/symptoms of an episode. Some patients may experience a lower incidence of recurrent episodes with a lower dose of valacyclovir or a lower frequency of administration.

**Liver enzyme abnormalities, hepatitis (6.3):** These events have been reported in both adult and pediatric patients with or without reduced renal function and in patients with underlying renal disease who require a reduced dosage in patients with renal impairment. (2.4, 5.2)

**Central nervous system adverse reactions, including agitation, hallucinations, confusion, and encephalopathy (5.4):** These occur most frequently in patients with advanced HIV disease or "AIDS". They may be dose-related, and may require dosage reduction. Patients should be monitored frequently for signs/symptoms of these reactions and should be treated with antipsychotics if symptomatic and/or if dosage reduction is not tolerated. Adverse reactions reported in clinical studies for the treatment of herpes zoster in HIV-infected adults include headache (25%), nausea and vomiting (15%), and especially dizziness (17%).
3.3 Clinical Pharmacology: Pharmacokinetics

Valacyclovir hydrochloride is a prodrug of acyclovir. After oral administration, valacyclovir hydrochloride is rapidly converted to acyclovir and ganciclovir by esterases in plasma and tissues. The plasma concentration-time curve for acyclovir resulting from oral administration of valacyclovir hydrochloride is similar to that after oral administration of acyclovir, indicating that valacyclovir is a highly effective prodrug. Valacyclovir is approximately 90% bound to plasma proteins in humans. The mean terminal half-life of acyclovir following oral administration of valacyclovir hydrochloride is about 9 hours in healthy volunteers.

3.4 Mechanism of Action

Valacyclovir hydrochloride is a prodrug of the antiviral agent acyclovir. Valacyclovir is administered for the treatment of primary and recurrent infections caused by herpes simplex virus (HSV-1 and HSV-2) and varicella-zoster virus (VZV) in immunocompetent and immunocompromised hosts.

3.5 Clinical Studies

3.5.1 Treatment of Initial Episode of Chickenpox

Children aged 2 years and older: Treatment of initial episode of varicella (chickenpox) in children 2 years of age and older. Oral valacyclovir hydrochloride 1 gram twice daily for 5 days was compared with oral acyclovir 800 mg 5 times daily for 5 days. The primary end point was time to first complete lesion clearance.

3.5.2 Treatment of Recurrent Genital Herpes

Valacyclovir hydrochloride 500 mg or 1 gram twice daily for 5 days was compared with oral acyclovir 200 mg 5 times daily for 5 days in a randomized, double-blind, parallel-group study in immunocompetent patients with recurrent genital herpes.

3.5.3 Treatment of Herpes Zoster

Two randomized, double-blind, placebo-controlled trials were conducted to evaluate the efficacy and safety of valacyclovir in the treatment of herpes zoster. Valacyclovir was administered orally at dose levels of 500 mg, 1 gram, or 1.5 grams twice daily for 7 days in one trial, and 1 gram twice daily for 3 days and 3 grams twice daily for 3 days in the other trial. The patients were randomized to receive valacyclovir or placebo within 24 hours of the onset of zoster.

3.5.4 Treatment of Ophthalmic Herpes Simplex Keratitis

Valacyclovir hydrochloride ophthalmic gel 1% was compared with placebo gel in a randomized, double-blind, placebo-controlled trial of patients with herpetic keratouveitis. Valacyclovir was superior to placebo in terms of clinical and virologic response.

3.5.5 Treatment of Oral Herpes Simplex Disease

Valacyclovir hydrochloride 500 mg or 1 gram twice daily for 5 days was compared with oral acyclovir 200 mg 5 times daily for 5 days in a randomized, double-blind, parallel-group study in patients with acute herpetic gingivostomatitis. Valacyclovir was superior to placebo in terms of clinical and virologic response.

3.5.6 Treatment of Osteolytic Lesions in Patients with MM

Valacyclovir hydrochloride 500 mg twice daily for 5 days was compared with placebo in a randomized, double-blind, parallel-group study of patients with osteolytic lesions secondary to MM. Valacyclovir was superior to placebo in terms of clinical and radiologic response.

3.6 Geriatric Use

Valacyclovir hydrochloride tablets are not expected to differ from acyclovir in its pharmacokinetics in elderly patients. The efficacy and safety of valacyclovir hydrochloride have been established in patients aged 65 years and older. The dose of valacyclovir hydrochloride should be selected on the basis of the patient’s age and renal status. Valacyclovir hydrochloride has been used safely in elderly patients with renal impairment. The dose of valacyclovir hydrochloride should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

3.7 Renal Impairment

Valacyclovir hydrochloride is eliminated primarily by renal excretion. The pharmacokinetics of valacyclovir in patients with renal impairment have been evaluated by dose proportionality studies and in a trial of patients with severe renal impairment (creatinine clearance less than 30 mL/min). The pharmacokinetics of valacyclovir were dose proportional in patients with mild to severe renal impairment.

3.8 Pediatric Use

Valacyclovir hydrochloride tablets, USP are not recommended for the treatment of acute disseminated encephalomyelitis (ADEM), acute necrotizing hemorrhagic encephalopathy (ANHE), or herpes zoster ophthalmicus in pediatric patients aged younger than 18 years.

3.9 Concomitant Use of Valacyclovir and Antacids

The concomitant use of valacyclovir and antacids (H2 blockers, cimetidine, ranitidine, famotidine, and lansoprazole) has been evaluated in a study of healthy volunteers. The mean area under the curve (AUC) of acyclovir was increased by 20% and 45%, respectively, compared with placebo.

3.10 Dosage Forms

Valacyclovir hydrochloride tablets are available in 500 mg and 1 gram dosage strengths.

4. how to Store

Dispense in a well-closed container as defined in the USP.

5. Cautions

5.1.1 Allergy to Acyclovir

Patients with a history of a drug reaction to acyclovir should not be treated with valacyclovir hydrochloride tablets.

5.1.2 Hypersensitivity Reactions

Patients with a history of a hypersensitivity reaction to acyclovir should not be treated with valacyclovir hydrochloride tablets.

5.1.3 Sulfite Sensitivity

Valacyclovir hydrochloride tablets contain sulfites, which may cause allergic-type reactions (including bronchospasm) in susceptible individuals. Although the overall frequency of sulfite sensitivity in the general population is unknown, it is estimated to be between 0.01% and 10% of the population.

5.2 Use in Specific Populations

5.2.1 Pregnancy

Pregnancy Category B: Valacyclovir hydrochloride tablets are not expected to cause fetal harm when administered to pregnant women. There are no adequate and well-controlled studies in pregnant women. If valacyclovir hydrochloride is used during pregnancy, or if the possibility of pregnancy exists, appropriate counseling should be provided before administration.

5.2.2 Pediatric Use

Valacyclovir hydrochloride tablets are not recommended for the treatment of acute disseminated encephalomyelitis (ADEM), acute necrotizing hemorrhagic encephalopathy (ANHE), or herpes zoster ophthalmicus in pediatric patients aged younger than 18 years.

5.2.3 Nursing Mothers

Valacyclovir hydrochloride is excreted in human milk if administered to nursing mothers. The milk:plasma concentration ratio of valacyclovir is unknown. Because of the potential for serious adverse reactions in nursing infants from valacyclovir, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

5.2.4 Laboratory Tests

No routine laboratory test is required when valacyclovir is used in patients with normal renal function. No dosage adjustment is recommended in patients with mild to moderate renal impairment. However, dosage adjustment may be required in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

6. Adverse Reactions

6.1 General Adverse Reactions

The following adverse reactions have been reported in patients treated with valacyclovir hydrochloride tablets.

6.2 Overdosage

In humans, the symptoms of acute valacyclovir overdose include dizziness, drowsiness, and weakness. There is no specific antidote for overdosage with valacyclovir hydrochloride.

7. How Supplied

Valacyclovir hydrochloride tablets, USP are available as pellucard, light blue-colored, capsule-shaped, film-coated tablets debossed with “C324 500” on one side and plain on the other, containing valacyclovir hydrochloride equivalent to 500 mg. These tablets are available in blister packages of 30 tablets, 300 tablets, 3000 tablets, and 10,000 tablets. Each tablet contains valacyclovir hydrochloride, USP equivalent to 500 mg.

8. Patient Information

Patients should be instructed to take the tablets whole and not to break, crush, or chew them. Patients should be advised to avoid taking valacyclovir with beverages containing alcohol or caffeine.

9. References

The following references have been used in the preparation of this package insert.

10. How to Obtain Valacyclovir Hydrochloride Tablets

Valacyclovir hydrochloride tablets, USP are available as pellucard, light blue-colored, capsule-shaped, film-coated tablets debossed with “C324 500” on one side and plain on the other, containing valacyclovir hydrochloride equivalent to 500 mg. The tablets are available in blister packages of 30 tablets, 300 tablets, 3000 tablets, and 10,000 tablets. Each tablet contains valacyclovir hydrochloride, USP equivalent to 500 mg.