

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VALTREX safely and effectively. See full prescribing information for VALTREX.

VALTREX® (valacyclovir hydrochloride) Caplets

Initial U.S. Approval: 1995

RECENT MAJOR CHANGES

Indications and Usage, Pediatric Patients (1.2) 9/2008
Dosage and Administration, Pediatric Patients (2.2, 2.3) 9/2008

INDICATIONS AND USAGE

VALTREX is a nucleoside analogue DNA polymerase inhibitor indicated for:
Adult Patients (1.1)

- Cold Sores (Herpes Labialis)
- Genital Herpes
 - Treatment in immunocompetent patients (initial or recurrent episode)
 - Suppression in immunocompetent or HIV-infected patients
 - Reduction of transmission
- Herpes Zoster

Pediatric Patients (1.2)

- Cold Sores (Herpes Labialis)
- Chickenpox

Limitations of Use (1.3)

- The efficacy and safety of VALTREX have not been established in immunocompromised patients other than for the suppression of genital herpes in HIV-infected patients.

DOSAGE AND ADMINISTRATION

Adult Dosage (2.1)	
Cold Sores	2 grams every 12 hours for 1 day
Genital Herpes	
Initial episode	1 gram twice daily for 10 days
Recurrent episodes	500 mg twice daily for 3 days
Suppressive therapy	
Immunocompetent patients	1 gram once daily
Alternate dose in patients with ≤9 recurrences/yr	500 mg once daily
HIV-infected patients	500 mg twice daily
Reduction of transmission	500 mg once daily
Herpes Zoster	1 gram 3 times daily for 7 days
Pediatric Dosage (2.2)	
Cold Sores (≥12 years of age)	2 grams every 12 hours for 1 day
Chickenpox (2 to <18 years of age)	20 mg/kg 3 times daily for 5 days; not to exceed 1 gram 3 times daily

Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) can be prepared from the 500 mg VALTREX Caplets. (2.3)

DOSAGE FORMS AND STRENGTHS

Caplets: 500 mg (unscored), 1 gram (partially scored) (3)

CONTRAINDICATIONS

Hypersensitivity to valacyclovir (e.g., anaphylaxis), acyclovir, or any component of the formulation. (4)

WARNINGS AND PRECAUTIONS

- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS): Has occurred in patients with advanced HIV disease and in allogeneic bone marrow transplant and renal transplant patients receiving 8 grams per day of VALTREX in clinical trials. Discontinue treatment if clinical symptoms and laboratory findings consistent with TTP/HUS occur. (5.1)
- **Acute renal failure:** May occur in elderly patients (with or without reduced renal function), patients with underlying renal disease who receive higher than recommended doses of VALTREX for their level of renal function, patients who receive concomitant nephrotoxic drugs, or inadequately hydrated patients. Use with caution in elderly patients and reduce dosage in patients with renal impairment. (2.4, 5.2)
- **Central nervous system adverse reactions** (e.g., agitation, hallucinations, delirium, and encephalopathy): May occur in elderly patients (with or without reduced renal function) and in patients with underlying renal disease who receive higher than recommended doses of VALTREX for their level of renal function. Use with caution in elderly patients and reduce dosage in patients with renal impairment. (2.4, 5.3)

ADVERSE REACTIONS

- The most common adverse reactions reported in at least one indication in >10% of adult patients treated with VALTREX and more commonly than in patients treated with placebo are headache, nausea, and abdominal pain. (6.1)
- The only adverse reaction occurring in >10% of pediatric patients <18 years of age was headache. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2008
VTX:XPI

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*Sections or subsections omitted from the full prescribing information are not listed.

1

2 **FULL PRESCRIBING INFORMATION**

3 **1 INDICATIONS AND USAGE**

4 **1.1 Adult Patients**

5 Cold Sores (Herpes Labialis): VALTREX is indicated for treatment of cold sores
6 (herpes labialis). The efficacy of VALTREX initiated after the development of clinical signs of a
7 cold sore (e.g., papule, vesicle, or ulcer) has not been established.

8 Genital Herpes: Initial Episode: VALTREX is indicated for treatment of the initial
9 episode of genital herpes in immunocompetent adults. The efficacy of treatment with VALTREX
10 when initiated more than 72 hours after the onset of signs and symptoms has not been
11 established.

12 Recurrent Episodes: VALTREX is indicated for treatment of recurrent episodes of
13 genital herpes in immunocompetent adults. The efficacy of treatment with VALTREX when
14 initiated more than 24 hours after the onset of signs and symptoms has not been established.

15 Suppressive Therapy: VALTREX is indicated for chronic suppressive therapy of
16 recurrent episodes of genital herpes in immunocompetent and in HIV-infected adults. The
17 efficacy and safety of VALTREX for the suppression of genital herpes beyond 1 year in
18 immunocompetent patients and beyond 6 months in HIV-infected patients have not been
19 established.

20 Reduction of Transmission: VALTREX is indicated for the reduction of
21 transmission of genital herpes in immunocompetent adults. The efficacy of VALTREX for the
22 reduction of transmission of genital herpes beyond 8 months in discordant couples has not been
23 established. The efficacy of VALTREX for the reduction of transmission of genital herpes in
24 individuals with multiple partners and non-heterosexual couples has not been established. Safer
25 sex practices should be used with suppressive therapy (see current Centers for Disease Control
26 and Prevention [CDC] *Sexually Transmitted Diseases Treatment Guidelines*).

27 Herpes Zoster: VALTREX is indicated for the treatment of herpes zoster (shingles) in
28 immunocompetent adults. The efficacy of VALTREX when initiated more than 72 hours after
29 the onset of rash and the efficacy and safety of VALTREX for treatment of disseminated herpes
30 zoster have not been established.

31 **1.2 Pediatric Patients**

32 Cold Sores (Herpes Labialis): VALTREX is indicated for the treatment of cold sores
33 (herpes labialis) in pediatric patients ≥ 12 years of age. The efficacy of VALTREX initiated after
34 the development of clinical signs of a cold sore (e.g., papule, vesicle, or ulcer) has not been
35 established.

36 Chickenpox: VALTREX is indicated for the treatment of chickenpox in
37 immunocompetent pediatric patients 2 to <18 years of age. Based on efficacy data from clinical
38 studies with oral acyclovir, treatment with VALTREX should be initiated within 24 hours after

39 the onset of rash [see *Clinical Studies (14.4)*].

40 **1.3 Limitations of Use**

41 The efficacy and safety of VALTREX have not been established in:

- 42 • Immunocompromised patients other than for the suppression of genital herpes in
- 43 HIV-infected patients with a CD4+ cell count ≥ 100 cells/mm³.
- 44 • Patients <12 years of age with cold sores (herpes labialis).
- 45 • Patients <2 years of age or ≥ 18 years of age with chickenpox.
- 46 • Patients <18 years of age with genital herpes.
- 47 • Patients <18 years of age with herpes zoster.
- 48 • Neonates and infants as suppressive therapy following neonatal herpes simplex virus (HSV)
- 49 infection.

50 **2 DOSAGE AND ADMINISTRATION**

- 51 • VALTREX may be given without regard to meals.
- 52 • Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously
- 53 from 500 mg VALTREX Caplets for use in pediatric patients for whom a solid dosage form
- 54 is not appropriate [see *Dosage and Administration (2.3)*].

55 **2.1 Adult Dosing Recommendations**

56 Cold Sores (Herpes Labialis): The recommended dosage of VALTREX for treatment

57 of cold sores is 2 grams twice daily for 1 day taken 12 hours apart. Therapy should be initiated at

58 the earliest symptom of a cold sore (e.g., tingling, itching, or burning).

59 Genital Herpes: Initial Episode: The recommended dosage of VALTREX for treatment

60 of initial genital herpes is 1 gram twice daily for 10 days. Therapy was most effective when

61 administered within 48 hours of the onset of signs and symptoms.

62 Recurrent Episodes: The recommended dosage of VALTREX for treatment of

63 recurrent genital herpes is 500 mg twice daily for 3 days. Initiate treatment at the first sign or

64 symptom of an episode.

65 Suppressive Therapy: The recommended dosage of VALTREX for chronic

66 suppressive therapy of recurrent genital herpes is 1 gram once daily in patients with normal

67 immune function. In patients with a history of 9 or fewer recurrences per year, an alternative

68 dose is 500 mg once daily.

69 In HIV-infected patients with a CD4+ cell count ≥ 100 cells/mm³, the recommended

70 dosage of VALTREX for chronic suppressive therapy of recurrent genital herpes is 500 mg twice

71 daily.

72 Reduction of Transmission: The recommended dosage of VALTREX for reduction

73 of transmission of genital herpes in patients with a history of 9 or fewer recurrences per year is

74 500 mg once daily for the source partner.

75 Herpes Zoster: The recommended dosage of VALTREX for treatment of herpes zoster

76 is 1 gram 3 times daily for 7 days. Therapy should be initiated at the earliest sign or symptom of

77 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 VALTREX 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 VALTREX 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: VALTREX Caplets 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 VALTREX 500 mg Caplets until a fine powder is produced (5 VALTREX Caplets for 25 mg/mL suspension; 10 VALTREX Caplets 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° to 8°C (36° 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 VALTREX in pediatric patients with a creatinine clearance

118 <50 mL/min/1.73 m².

119

120 **Table 1. VALTREX 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

121

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

126 **Peritoneal Dialysis:** There is no information specific to administration of VALTREX in
127 patients receiving peritoneal dialysis. The effect of chronic ambulatory peritoneal dialysis
128 (CAPD) and continuous arteriovenous hemofiltration/dialysis (CAVHD) on acyclovir
129 pharmacokinetics has been studied. The removal of acyclovir after CAPD and CAVHD is less


130 pronounced than with hemodialysis, and the pharmacokinetic parameters closely resemble those
131 observed in patients with end-stage renal disease (ESRD) not receiving hemodialysis. Therefore,
132 supplemental doses of VALTREX should not be required following CAPD or CAVHD.

133 **3 DOSAGE FORMS AND STRENGTHS**

134 Caplets:

- 135 • 500 mg: blue, film-coated, capsule-shaped tablets printed with "VALTREX 500 mg."
- 136 • 1 gram: blue, film-coated, capsule-shaped tablets, with a partial scorebar on both sides,
137 printed with "VALTREX 1 gram."

138 **4 CONTRAINDICATIONS**


139  VALTREX is contraindicated in patients who have had a demonstrated clinically
140 significant hypersensitivity reaction (e.g., anaphylaxis) to valacyclovir, acyclovir, or any
141 component of the formulation [see Adverse Reactions (6.3)].

142 **5 WARNINGS AND PRECAUTIONS**

143 **5.1 Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome** 144 **(TTP/HUS)**

145 TTP/HUS, in some cases resulting in death, has occurred in patients with advanced HIV
146 disease and also in allogeneic bone marrow transplant and renal transplant recipients
147 participating in clinical trials of VALTREX at doses of 8 grams per day. Treatment with
148 VALTREX should be stopped immediately if clinical signs, symptoms, and laboratory
149 abnormalities consistent with TTP/HUS occur.

150 **5.2 Acute Renal Failure**

151  Cases of acute renal failure have been reported in:


- 152 • **Elderly patients with or without reduced renal function.** Caution should be exercised when
153 administering VALTREX to geriatric patients, and dosage reduction is recommended for
154 those with impaired renal function [see Dosage and Administration (2.4), Use in Specific
155 Populations (8.5)].
- 156 • **Patients with underlying renal disease** who received higher than recommended doses of
157 VALTREX for their level of renal function. Dosage reduction is recommended when
158 administering VALTREX to patients with renal impairment [see Dosage and Administration
159 (2.4), Use in Specific Populations (8.6)].
- 160 • **Patients receiving other nephrotoxic drugs.** Caution should be exercised when administering
161 VALTREX to patients receiving potentially nephrotoxic drugs.
- 162 • **Patients without adequate hydration.** Precipitation of acyclovir in renal tubules may occur
163 when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Adequate hydration
164 should be maintained for all patients.

165 In the event of acute renal failure and anuria, the patient may benefit from hemodialysis
166 until renal function is restored [see Dosage and Administration (2.4), Adverse Reactions (6.3)].

167 **5.3 Central Nervous System Effects**

168 Central nervous system adverse reactions, including agitation, hallucinations, confusion,
169 delirium, seizures, and encephalopathy, have been reported in elderly patients with or without
170 reduced renal function and in patients with underlying renal disease who received higher than
171 recommended doses of VALTREX for their level of renal function. VALTREX should be
172 discontinued if central nervous system adverse reactions occur [see Adverse Reactions (6.3), Use
173 in Specific Populations (8.5, 8.6)].


174 6 ADVERSE REACTIONS

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

- 177 • Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome [see Warnings and
178 Precautions (5.1)].
- 179 • Acute Renal Failure [see Warnings and Precautions (5.2)].
- 180 • Central Nervous System Effects [see Warnings and Precautions (5.3)].

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

185 6.1 Clinical Trials Experience in Adult Patients

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

189 **Cold Sores (Herpes Labialis):** In clinical studies for the treatment of cold sores, the
190 adverse reactions reported by patients receiving VALTREX 2 grams twice daily (n = 609) or
191 placebo (n = 609) for 1 day, respectively, included headache (14%, 10%) and dizziness (2%,
192 1%). The frequencies of abnormal ALT (>2 x ULN) were 1.8% for patients receiving
193 VALTREX compared with 0.8% for placebo. Other laboratory abnormalities (hemoglobin, white
194 blood cells, alkaline phosphatase, and serum creatinine) occurred with similar frequencies in the
195 2 groups.


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

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

206 **Suppressive Therapy: Suppression of Recurrent Genital Herpes in**

207 **Immunocompetent Adults:** In a clinical study for the suppression of recurrent genital herpes
208 infections, the adverse reactions reported by patients receiving VALTREX 1 gram once daily
209 (n = 269), VALTREX 500 mg once daily (n = 266), or placebo (n = 134), respectively, included
210 headache (35%, 38%; 34%), nausea (11%, 11%, 8%), abdominal pain (11%, 9%, 6%),
211 dysmenorrhea (8%, 5%, 4%), depression (7%, 5%, 5%), arthralgia (6%, 5%, 4%), vomiting (3%,
212 3%, 2%), and dizziness (4%, 2%, 1%). For the incidence of laboratory abnormalities see Table 2.

213 **Suppression of Recurrent Genital Herpes in HIV-Infected Patients:** In
214 HIV-infected patients, frequently reported adverse reactions for VALTREX (500 mg twice daily;
215 n = 194, median days on therapy = 172) and placebo (n = 99, median days on therapy = 59),
216 respectively, included headache (13%, 8%), fatigue (8%, 5%), and rash (8%, 1%).

217 Post-randomization laboratory abnormalities that were reported more frequently in valacyclovir
218 jects versus placebo included elevated alkaline phosphatase (4%, 2%), elevated ALT (14%,
219 10%), elevated AST (16%, 11%), decreased neutrophil counts (18%, 10%), and decreased
220 platelet counts (3%, 0%), respectively.

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

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

230

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

Laboratory Abnormality	Herpes Zoster		Genital Herpes Treatment			Genital Herpes Suppression		
	VALTREX ¹ 1 gram 3 times daily (n = 967)	Placebo (n = 195)	VALTREX 1 gram twice daily (n = 1,194)	VALTREX 500 mg twice daily (n = 1,159)	Placebo (n = 439)	VALTREX 1 gram once daily (n = 269)	VALTREX 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/mm ³)	1.0%	1.2%	0.3%	0.1%	0.7%	0.4%	1.1%	1.5%
AST (SGOT) (>2 x ULN)	1.0%	0%	1.0%	*	0.5%	4.1%	3.8%	3.0%
Serum creatinine (>1.5 x ULN)	0.2%	0%	0.7%	0%	0%	0%	0%	0%

233 *Data were not collected prospectively.

234 LLN = Lower limit of normal.

235 ULN = Upper limit of normal.

236

237 **6.2 Clinical Trials Experience in Pediatric Patients**

238 The safety profile of VALTREX has been studied in 177 pediatric patients
 239 1 month to <18 years of age. Sixty-five of these pediatric patients, 12 to <18 years of
 240 age, received oral caplets for 1 to 2 days for treatment of cold sores. The remaining
 241 112 pediatric patients, 1 month to <12 years of age, participated in 3 pharmacokinetic
 242 and safety studies and received valacyclovir oral suspension. Fifty-one of these
 243 112 pediatric patients received oral suspension for 3 to 6 days. The frequency,
 244 intensity, and nature of clinical adverse reactions and laboratory abnormalities were
 245 similar to those seen in adults.

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

251 **Pediatric Patients 1 Month to <12 Years of Age:** Adverse events reported in more
 252 than 1 subject across the 3 pharmacokinetic and safety studies in children 1 month to <12 years
 253 of age were diarrhea (5%), pyrexia (4%), dehydration (2%), herpes simplex (2%), and rhinorrhea
 254 (2%). No clinically meaningful changes in laboratory values were observed.

255 **6.3  Postmarketing Experience**

256 In addition to adverse events reported from clinical trials, the following events have been
257 identified during postmarketing use of VALTREX. Because they are reported voluntarily from a
258 population of unknown size, estimates of frequency cannot be made. These events have been
259 chosen for inclusion due to a combination of their seriousness, frequency of reporting, or
260 potential causal connection to VALTREX.

261 General: Facial edema, hypertension, tachycardia.

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

264 CNS Symptoms: Aggressive behavior; agitation; ataxia; coma; confusion; decreased
265 consciousness; dysarthria; encephalopathy; mania; and psychosis, including auditory and visual
266 hallucinations, seizures, tremors [see *Warnings and Precautions (5.3), Use in Specific*
267 *Populations (8.5), (8.6)*].

268 Eye: Visual abnormalities.

269 Gastrointestinal: Diarrhea.

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

271 Renal: Renal failure, renal pain (may be associated with renal failure) [see *Warnings and*
272 *Precautions (5.2), Use in Specific Populations (8.5), (8.6)*].

273 Hematologic: Thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis, TTP/HUS
274 [see *Warnings and Precautions (5.1)*].

275 Skin: Erythema multiforme, rashes including photosensitivity, alopecia.

276 **7 DRUG INTERACTIONS**

277 No clinically significant drug-drug or drug-food interactions with VALTREX are known
278 [see *Clinical Pharmacology (12.3)*].

279 **8 USE IN SPECIFIC POPULATIONS**

280 **8.1 Pregnancy**

281 Pregnancy Category B. There are no adequate and well-controlled studies of VALTREX
282 or acyclovir in pregnant women. Based on prospective pregnancy registry data on
283 749 pregnancies, the overall rate of birth defects in infants exposed to acyclovir in-utero appears
284 similar to the rate for infants in the general population. VALTREX should be used during
285 pregnancy only if the potential benefit justifies the potential risk to the fetus.

286 A prospective epidemiologic registry of acyclovir use during pregnancy was established
287 in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed
288 to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The
289 occurrence rate of birth defects approximates that found in the general population. However, the
290 small size of the registry is insufficient to evaluate the risk for less common defects or to permit
291 reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their
292 developing fetuses.

293 Animal reproduction studies performed at oral doses that provided up to 10 and 7 times
294 the human plasma levels during the period of major organogenesis in rats and rabbits,

295 respectively, revealed no evidence of teratogenicity.

296 **8.3 Nursing Mothers**

297 Following oral administration of a 500 mg dose of VALTREX to 5 nursing mothers, peak
298 acyclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 times (median 1.4) the
299 corresponding maternal acyclovir serum concentrations. The acyclovir breast milk AUC ranged
300 from 1.4 to 2.6 times (median 2.2) maternal serum AUC. A 500 mg maternal dosage of
301 VALTREX twice daily would provide a nursing infant with an oral acyclovir dosage of
302 approximately 0.6 mg/kg/day. This would result in less than 2% of the exposure obtained after
303 administration of a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir to the
304 nursing infant. Unchanged valacyclovir was not detected in maternal serum, breast milk, or
305 infant urine. Caution should be exercised when VALTREX is administered to a nursing woman.

306 **8.4 Pediatric Use**

307 VALTREX is indicated for treatment of cold sores in pediatric patients ≥ 12 years of age
308 and for treatment of chickenpox in pediatric patients 2 to < 18 years of age [*see Indications and*
309 *Usage (1.2), Dosage and Administration (2.2)*].

310 The use of VALTREX for treatment of cold sores is based on 2 double-blind,
311 placebo-controlled clinical trials in healthy adults and adolescents (≥ 12 years of age) with a
312 history of recurrent cold sores [*see Clinical Studies (14.1)*].

313 The use of VALTREX for treatment of chickenpox in pediatric patients 2 to < 18 years of
314 age is based on single-dose pharmacokinetic and multiple-dose safety data from an open-label
315 trial with valacyclovir and supported by efficacy and safety data from 3 randomized,
316 double-blind, placebo-controlled trials evaluating oral acyclovir in pediatric patients with
317 chickenpox [*see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical*
318 *Pharmacology (12.3), Clinical Studies (14.4)*].

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

- 320 • < 12 years of age with cold sores
- 321 • < 18 years of age with genital herpes
- 322 • < 18 years of age with herpes zoster
- 323 • < 2 years of age with chickenpox
- 324 • for suppressive therapy following neonatal HSV infection.

325 The pharmacokinetic profile and safety of valacyclovir oral suspension in children
326 < 12 years of age were studied in 3 open-label studies. No efficacy evaluations were conducted in
327 any of the 3 studies.

328 Study 1 was a single-dose pharmacokinetic, multiple-dose safety study in 27 pediatric
329 patients 1 to < 12 years of age with clinically suspected varicella-zoster virus (VZV) infection
330 [*see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3),*
331 *Clinical Studies (14.4)*].

332 Study 2 was a single-dose pharmacokinetic and safety study in pediatric patients 1 month
333 to < 6 years of age who had an active herpes virus infection or who were at risk for herpes virus
334 infection. Fifty-seven subjects were enrolled and received a single dose of 25 mg/kg valacyclovir

335 oral suspension. In infants and children 3 months to <6 years of age, this dose provided
336 comparable systemic acyclovir exposures to that from a 1 gram dose of valacyclovir in adults
337 (historical data). In infants 1 month to <3 months of age, mean acyclovir exposures resulting
338 from a 25 mg/kg dose were higher (C_{max} : ↑30%, AUC: ↑60%) than acyclovir exposures
339 following a 1 gram dose of valacyclovir in adults. Acyclovir is not approved for suppressive
340 therapy in infants and children following neonatal HSV infections; therefore valacyclovir is not
341 recommended for this indication because efficacy cannot be extrapolated from acyclovir.

342 Study 3 was a single-dose pharmacokinetic, multiple-dose safety study in 28 pediatric
343 patients 1 to <12 years of age with clinically suspected HSV infection. None of the children
344 enrolled in this study had genital herpes. Each subject was dosed with valacyclovir oral
345 suspension, 10 mg/kg twice daily for 3 to 5 days. Acyclovir systemic exposures in pediatric
346 patients following valacyclovir oral suspension were compared with historical acyclovir systemic
347 exposures in immunocompetent adults receiving the solid oral dosage form of valacyclovir or
348 acyclovir for the treatment of recurrent genital herpes. The mean projected daily acyclovir
349 systemic exposures in pediatric patients across all age-groups (1 to <12 years of age) were lower
350 (C_{max} : ↓20%, AUC: ↓33%) compared with the acyclovir systemic exposures in adults receiving
351 valacyclovir 500 mg twice daily, but were higher (daily AUC: ↑16%) than systemic exposures in
352 adults receiving acyclovir 200 mg 5 times daily. Insufficient data are available to support
353 valacyclovir for the treatment of recurrent genital herpes in this age-group because clinical
354 information on recurrent genital herpes in young children is limited; therefore, extrapolating
355 efficacy data from adults to this population is not possible. Moreover, valacyclovir has not been
356 studied in children 1 to <12 years of age with recurrent genital herpes.

357 **8.5 Geriatric Use**

358 Of the total number of subjects in clinical studies of VALTREX, 906 were 65 and over,
359 and 352 were 75 and over. In a clinical study of herpes zoster, the duration of pain after healing
360 (post-herpetic neuralgia) was longer in patients 65 and older compared with younger adults.
361 Elderly patients are more likely to have reduced renal function and require dose reduction.
362 Elderly patients are also more likely to have renal or CNS adverse events [*see Dosage and*
363 *Administration (2.4), Warnings and Precautions (5.2, 5.3), Clinical Pharmacology (12.3)]].*

364 **8.6 Renal Impairment**

365 Dosage reduction is recommended when administering VALTREX to patients with renal
366 impairment [*see Dosage and Administration (2.4), Warnings and Precautions (5.2, 5.3)]].*

367 **10 OVERDOSAGE**

368 Caution should be exercised to prevent inadvertent overdose [*see Use in Specific*
369 *Populations (8.5), (8.6)]]. Precipitation of acyclovir in renal tubules may occur when the*
370 *solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure*
371 *and anuria, the patient may benefit from hemodialysis until renal function is restored [see*
372 *Dosage and Administration (2.4)]].*

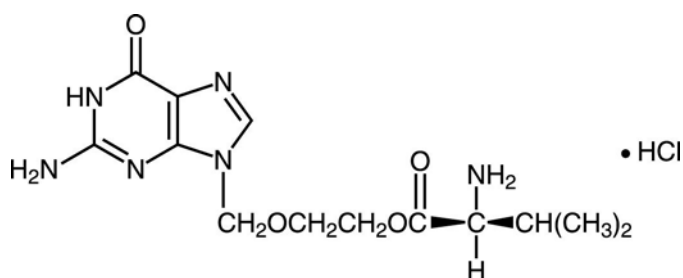
373 **11 DESCRIPTION**

374 VALTRESX (valacyclovir hydrochloride) is the hydrochloride salt of the *L*-valyl ester of
375 the antiviral drug acyclovir.

376 VALTRESX Caplets are for oral administration. Each caplet contains valacyclovir
377 hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba
378 wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium
379 stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium
380 dioxide. The blue, film-coated caplets are printed with edible white ink.

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

384



387 Valacyclovir hydrochloride is a white to off-white powder with the molecular formula
388 $C_{13}H_{20}N_6O_4 \cdot HCl$ and a molecular weight of 360.80. The maximum solubility in water at 25°C is
389 174 mg/mL. The $pK_{a,s}$ for valacyclovir hydrochloride are 1.90, 7.47, and 9.43.

390 **12 CLINICAL PHARMACOLOGY**

391 **12.1 Mechanism of Action**

392 Valacyclovir is an antiviral drug [see *Clinical Pharmacology (12.4)*].

393 **12.3 Pharmacokinetics**

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

397 Pharmacokinetics in Adults: Absorption and Bioavailability: After oral
398 administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract and
399 nearly completely converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic
400 metabolism.

401 The absolute bioavailability of acyclovir after administration of VALTRESX is
402 54.5% ± 9.1% as determined following a 1 gram oral dose of VALTRESX and a 350 mg
403 intravenous acyclovir dose to 12 healthy volunteers. Acyclovir bioavailability from the
404 administration of VALTRESX is not altered by administration with food (30 minutes after an
405 873 Kcal breakfast, which included 51 grams of fat).

406 Acyclovir pharmacokinetic parameter estimates following administration of VALTRESX

407 to healthy adult volunteers are presented in Table 3. There was a less than dose-proportional
 408 increase in acyclovir maximum concentration (C_{max}) and area under the acyclovir
 409 concentration-time curve (AUC) after single-dose and multiple-dose administration (4 times
 410 daily) of VALTREX from doses between 250 mg to 1 gram.

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

413

414 **Table 3. Mean (\pm SD) Plasma Acyclovir Pharmacokinetic Parameters Following**
 415 **Administration of VALTREX 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 (\pm 0.14)	2.28 (\pm 0.40)	ND	ND
250 mg	2.15 (\pm 0.50)	5.76 (\pm 0.60)	2.11 (\pm 0.33)	5.66 (\pm 1.09)
500 mg	3.28 (\pm 0.83)	11.59 (\pm 1.79)	3.69 (\pm 0.87)	9.88 (\pm 2.01)
750 mg	4.17 (\pm 1.14)	14.11 (\pm 3.54)	ND	ND
1,000 mg	5.65 (\pm 2.37)	19.52 (\pm 6.04)	4.96 (\pm 0.64)	15.70 (\pm 2.27)

416 *Administered 4 times daily for 11 days.

417 ND = not done.

418

419 *Distribution:* The binding of valacyclovir to human plasma proteins ranges from
 420 13.5% to 17.9%. The binding of acyclovir to human plasma proteins ranges from 9% to 33%.

421 *Metabolism:* Valacyclovir is converted to acyclovir and L-valine by first-pass
 422 intestinal and/or hepatic metabolism. Acyclovir is converted to a small extent to inactive
 423 metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither
 424 valacyclovir nor acyclovir is metabolized by cytochrome P450 enzymes. Plasma concentrations
 425 of unconverted valacyclovir are low and transient, generally becoming non-quantifiable by
 426 3 hours after administration. Peak plasma valacyclovir concentrations are generally less than
 427 0.5 mcg/mL at all doses. After single-dose administration of 1 gram of VALTREX, average
 428 plasma valacyclovir concentrations observed were 0.5, 0.4, and 0.8 mcg/mL in patients with
 429 hepatic dysfunction, renal insufficiency, and in healthy volunteers who received concomitant
 430 cimetidine and probenecid, respectively.

431 **Elimination:** The pharmacokinetic disposition of acyclovir delivered by valacyclovir
 432 is consistent with previous experience from intravenous and oral acyclovir. Following the oral
 433 administration of a single 1 gram dose of radiolabeled valacyclovir to 4 healthy subjects, 46%
 434 and 47% of administered radioactivity was recovered in urine and feces, respectively, over
 435 96 hours. Acyclovir accounted for 89% of the radioactivity excreted in the urine. Renal clearance
 436 of acyclovir following the administration of a single 1 gram dose of VALTREX to 12 healthy
 437 volunteers was approximately 255 ± 86 mL/min which represents 42% of total acyclovir

438 apparent plasma clearance.

439 The plasma elimination half-life of acyclovir typically averaged 2.5 to 3.3 hours in all
440 studies of VALTREX in volunteers with normal renal function.

441 **Specific Populations: Renal Impairment:** Reduction in dosage is recommended in
442 patients with renal impairment [see Dosage and Administration (2.4), Use in Specific
443 Populations (8.5), (8.6)].

444 Following administration of VALTREX to volunteers with ESRD, the average acyclovir
445 half-life is approximately 14 hours. During hemodialysis, the acyclovir half-life is approximately
446 4 hours. Approximately one third of acyclovir in the body is removed by dialysis during a 4-hour
447 hemodialysis session. Apparent plasma clearance of acyclovir in dialysis patients was
448 86.3 ± 21.3 mL/min/1.73 m² compared with 679.16 ± 162.76 mL/min/1.73 m² in healthy
449 volunteers.

450 **Hepatic Impairment:** Administration of VALTREX to patients with moderate
451 (biopsy-proven cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver
452 disease indicated that the rate but not the extent of conversion of valacyclovir to acyclovir is
453 reduced, and the acyclovir half-life is not affected. Dosage modification is not recommended for
454 patients with cirrhosis.

455 **HIV Disease:** In 9 patients with HIV disease and CD4+ cell counts <150 cells/mm³
456 who received VALTREX at a dosage of 1 gram 4 times daily for 30 days, the pharmacokinetics
457 of valacyclovir and acyclovir were not different from that observed in healthy volunteers.

458 **Geriatrics:** After single-dose administration of 1 gram of VALTREX in healthy
459 geriatric volunteers, the half-life of acyclovir was 3.11 ± 0.51 hours, compared with
460 2.91 ± 0.63 hours in healthy younger adult volunteers. The pharmacokinetics of acyclovir
461 following single- and multiple-dose oral administration of VALTREX in geriatric volunteers
462 varied with renal function. Dose reduction may be required in geriatric patients, depending on
463 the underlying renal status of the patient [see Dosage and Administration (2.4), Use in Specific
464 Populations (8.5), (8.6)].

465 **Pediatrics:** Acyclovir pharmacokinetics have been evaluated in a total of 98 pediatric
466 patients (1 month to <12 years of age) following administration of the first dose of an
467 extemporaneous oral suspension of valacyclovir [see Adverse Reactions (6.2), Use in Specific
468 Populations (8.4)]. Acyclovir pharmacokinetic parameter estimates following a 20 mg/kg dose
469 are provided in Table 4.

470

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

Parameter	Pediatric Patients (20 mg/kg Oral Suspension)			Adults 1 gram Solid Dose of VALTREX* (N = 15)
	1 - <2 yr (N = 6)	2 - <6 yr (N = 12)	6 - <12 yr (N = 8)	
AUC (mcg•hr/mL)	14.4 (\pm 6.26)	10.1 (\pm 3.35)	13.1 (\pm 3.43)	17.2 (\pm 3.10)
C _{max} (mcg/mL)	4.03 (\pm 1.37)	3.75 (\pm 1.14)	4.71 (\pm 1.20)	4.72 (\pm 1.37)

474 *Historical estimates using pediatric pharmacokinetic sampling schedule.

475
 476 **Drug Interactions:** When VALTREX is coadministered with antacids, cimetidine and/or
 477 probenecid, digoxin, or thiazide diuretics in patients with normal renal function, the effects are
 478 not considered to be of clinical significance (see below). Therefore, when VALTREX is
 479 coadministered with these drugs in patients with normal renal function, no dosage adjustment is
 480 recommended.

481 **Antacids:** The pharmacokinetics of acyclovir after a single dose of VALTREX
 482 (1 gram) were unchanged by coadministration of a single dose of antacids (Al³⁺ or Mg⁺⁺).

483 **Cimetidine:** Acyclovir C_{max} and AUC following a single dose of VALTREX (1 gram)
 484 increased by 8% and 32%, respectively, after a single dose of cimetidine (800 mg).

485 **Cimetidine Plus Probenecid:** Acyclovir C_{max} and AUC following a single dose of
 486 VALTREX (1 gram) increased by 30% and 78%, respectively, after a combination of cimetidine
 487 and probenecid, primarily due to a reduction in renal clearance of acyclovir.

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

491 **Probenecid:** Acyclovir C_{max} and AUC following a single dose of VALTREX
 492 (1 gram) increased by 22% and 49%, respectively, after probenecid (1 gram).

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


495 **12.4 Microbiology**

496 **Mechanism of Action:** Valacyclovir is a nucleoside analogue DNA polymerase
 497 inhibitor. Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated
 498 antiviral activity against HSV types 1 (HSV-1) and 2 (HSV-2) and VZV both in cell culture and
 499 in vivo.

500 The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme
 501 thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into
 502 acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into
 503 diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.
 504 In biochemical assays, acyclovir triphosphate inhibits replication of herpes viral DNA. This is
 505 accomplished in 3 ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation

506 and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA
507 polymerase. The greater antiviral activity of acyclovir against HSV compared with VZV is due
508 to its more efficient phosphorylation by the viral TK.

509 **Antiviral Activities:** The quantitative relationship between the cell culture susceptibility
510 of herpesviruses to antivirals and the clinical response to therapy has not been established in
511 humans, and virus sensitivity testing has not been standardized. Sensitivity testing results,
512 expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell
513 culture (EC₅₀), vary greatly depending upon a number of factors. Using plaque-reduction assays,
514 the EC₅₀ values against herpes simplex virus isolates range from 0.09 to 60 μM (0.02 to
515 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
516 values for acyclovir against most laboratory strains and clinical isolates of VZV range from 0.53
517 to 48 μM (0.12 to 10.8 mcg/mL). Acyclovir also demonstrates activity against the Oka vaccine
518 strain of VZV with a mean EC₅₀ of 6 μM (1.35 mcg/mL).

519  **Resistance:** Resistance of HSV and VZV to acyclovir can result from qualitative and
520 quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of VZV with
521 reduced susceptibility to acyclovir have been recovered from patients with AIDS. In these cases,
522 TK-deficient mutants of VZV have been recovered.

523 Resistance of HSV and VZV to acyclovir occurs by the same mechanisms. While most of
524 the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been
525 found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK
526 altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe
527 disease in immunocompromised patients. The possibility of viral resistance to valacyclovir (and
528 therefore, to acyclovir) should be considered in patients who show poor clinical response during
529 therapy.

530 **13 NONCLINICAL TOXICOLOGY**

531 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

532 The data presented below include references to the steady-state acyclovir AUC observed
533 in humans treated with 1 gram VALTREX given orally 3 times a day to treat herpes zoster.
534 Plasma drug concentrations in animal studies are expressed as multiples of human exposure to
535 acyclovir [see *Clinical Pharmacology (12.3)*].

536 Valacyclovir was noncarcinogenic in lifetime carcinogenicity bioassays at single daily
537 doses (gavage) of valacyclovir giving plasma acyclovir concentrations equivalent to human
538 levels in the mouse bioassay and 1.4 to 2.3 times human levels in the rat bioassay. There was no
539 significant difference in the incidence of tumors between treated and control animals, nor did
540 valacyclovir shorten the latency of tumors.

541 Valacyclovir was tested in 5 genetic toxicity assays. An Ames assay was negative in the
542 absence or presence of metabolic activation. Also negative were an in vitro cytogenetic study
543 with human lymphocytes and a rat cytogenetic study.

544 In the mouse lymphoma assay, valacyclovir was not mutagenic in the absence of

545 metabolic activation. In the presence of metabolic activation (76% to 88% conversion to
546 acyclovir), valacyclovir was mutagenic.
547 Valacyclovir was mutagenic in a mouse micronucleus assay.
548 Valacyclovir did not impair fertility or reproduction in rats at 6 times human plasma
549 levels.

550 **14** **NICAL STUDIES**

551 **14.1 Cold Sores (Herpes Labialis)**

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

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

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

563 **14.2 Genital Herpes Infections**

564 Initial Episode: Six hundred and forty-three immunocompetent adults with first-episode
565 genital herpes who presented within 72 hours of symptom onset were randomized in a
566 double-blind trial to receive 10 days of VALTREX 1 gram twice daily ($n = 323$) or oral
567 acyclovir 200 mg 5 times a day ($n = 320$). For both treatment groups: the median time to lesion
568 healing was 9 days, the median time to cessation of pain was 5 days, the median time to
569 cessation of viral shedding was 3 days.

570 Recurrent Episodes: Three double-blind trials (2 of them placebo-controlled) in
571 immunocompetent adults with recurrent genital herpes were conducted. Patients self-initiated
572 therapy within 24 hours of the first sign or symptom of a recurrent genital herpes episode.

573 In 1 study, patients were randomized to receive 5 days of treatment with either
574 VALTREX 500 mg twice daily ($n = 360$) or placebo ($n = 259$). The median time to lesion
575 healing was 4 days in the group receiving VALTREX 500 mg versus 6 days in the placebo
576 group, and the median time to cessation of viral shedding in patients with at least 1 positive
577 culture (42% of the overall study population) was 2 days in the group receiving VALTREX
578 500 mg versus 4 days in the placebo group. The median time to cessation of pain was 3 days in
579 the group receiving VALTREX 500 mg versus 4 days in the placebo group. Results supporting
580 efficacy were replicated in a second trial.

581 In a third study, patients were randomized to receive VALTREX 500 mg twice daily for
582 5 days ($n = 398$) or VALTREX 500 mg twice daily for 3 days (and matching placebo twice daily
583 for 2 additional days) ($n = 402$). The median time to lesion healing was about 4½ days in both

584 treatment groups. The median time to cessation of pain was about 3 days in both treatment
 585 groups.

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

588 A double-blind, 12-month, placebo- and active-controlled study enrolled
 589 immunocompetent adults with a history of 6 or more recurrences per year. Outcomes for the
 590 overall study population are shown in Table 5.

591

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

Outcome	6 Months			12 Months		
	VALTREX 1 gram once daily (n = 269)	Oral acyclovir 400 mg twice daily (n = 267)	Placebo (n = 134)	VALTREX 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%

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

594

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

597 In a second study, 293 HIV-infected adults on stable antiretroviral therapy with a history
 598 of 4 or more recurrences of ano-genital herpes per year were randomized to receive either
 599 VALTREX 500 mg twice daily (n = 194) or matching placebo (n = 99) for 6 months. The
 600 median duration of recurrent genital herpes in enrolled subjects was 8 years, and the median
 601 number of recurrences in the year prior to enrollment was 5. Overall, the median prestudy HIV-1
 602 RNA was 2.6 log₁₀ copies/mL. Among patients who received VALTREX, the prestudy median
 603 CD4+ cell count was 336 cells/mm³; 11% had <100 cells/mm³, 16% had 100 to 199 cells/mm³,
 604 42% had 200 to 499 cells/mm³, and 31% had ≥500 cells/mm³. Outcomes for the overall study
 605 population are shown in Table 6.

606

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

Outcome	VALTREX 500 mg twice daily (n = 194)	Placebo (n = 99)
Recurrence free	65%	26%
Recurrences	17%	57%
Unknown*	18%	17%

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

609
 610 **Reduction of Transmission of Genital Herpes:** A double-blind, placebo-controlled
 611 study to assess transmission of genital herpes was conducted in 1,484 monogamous,
 612 heterosexual, immunocompetent adult couples. The couples were discordant for HSV-2
 613 infection. The source partner had a history of 9 or fewer genital herpes episodes per year. Both
 614 partners were counseled on safer sex practices and were advised to use condoms throughout the
 615 study period. Source partners were randomized to treatment with either VALTREX 500 mg once
 616 daily or placebo once daily for 8 months. The primary efficacy endpoint was symptomatic
 617 acquisition of HSV-2 in susceptible partners. Overall HSV-2 acquisition was defined as
 618 symptomatic HSV-2 acquisition and/or HSV-2 seroconversion in susceptible partners. The
 619 efficacy results are summarized in Table 7.

620
 621 **Table 7. Percentage of Susceptible Partners Who Acquired HSV-2 Defined by the Primary**
 622 **and Selected Secondary Endpoints**

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

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

626
 627 **14.3 Herpes Zoster**

628 Two randomized double-blind clinical trials in immunocompetent adults with localized
 629 herpes zoster were conducted. VALTREX was compared with placebo in patients less than
 630 50 years of age, and with oral acyclovir in patients greater than 50 years of age. All patients were
 631 treated within 72 hours of appearance of zoster rash. In patients less than 50 years of age, the
 632 median time to cessation of new lesion formation was 2 days for those treated with VALTREX
 633 compared with 3 days for those treated with placebo. In patients greater than 50 years of age, the
 634 median time to cessation of new lesions was 3 days in patients treated with either VALTREX or
 635 oral acyclovir. In patients less than 50 years of age, no difference was found with respect to the
 636 duration of pain after healing (post-herpetic neuralgia) between the recipients of VALTREX and
 637 placebo. In patients greater than 50 years of age, among the 83% who reported pain after healing
 638 (post-herpetic neuralgia), the median duration of pain after healing [95% confidence interval] in
 639 days was: 40 [31, 51], 43 [36, 55], and 59 [41, 77] for 7-day VALTREX, 14-day VALTREX,
 640 and 7-day oral acyclovir, respectively.

641 **14.4 Chickenpox**

642 The use of VALTREX for treatment of chickenpox in pediatric patients 2 to <18 years of
 643 age is based on single-dose pharmacokinetic and multiple-dose safety data from an open-label

644 trial with valacyclovir and supported by safety and extrapolated efficacy data from
645 3 randomized, double-blind, placebo-controlled trials evaluating oral acyclovir in pediatric
646 patients.

647 The single-dose pharmacokinetic and multiple-dose safety study enrolled 27 pediatric
648 patients 1 to <12 years of age with clinically suspected VZV infection. Each subject was dosed
649 with valacyclovir oral suspension, 20 mg/kg 3 times daily for 5 days. Acyclovir systemic
650 exposures in pediatric patients following valacyclovir oral suspension were compared with
651 historical acyclovir systemic exposures in immunocompetent adults receiving the solid oral
652 dosage form of valacyclovir or acyclovir for the treatment of herpes zoster. The mean projected
653 daily acyclovir exposures in pediatric patients across all age-groups (1 to <12 years of age) were
654 lower (C_{max} : ↓13%, AUC: ↓30%) than the mean daily historical exposures in adults receiving
655 valacyclovir 1 gram 3 times daily, but were higher (daily AUC: ↑50%) than the mean daily
656 historical exposures in adults receiving acyclovir 800 mg 5 times daily. The projected daily
657 exposures in pediatric patients were greater (daily AUC approximately 100% greater) than the
658 exposures seen in immunocompetent pediatric patients receiving acyclovir 20 mg/kg 4 times
659 daily for the treatment of chickenpox. Based on the pharmacokinetic and safety data from this
660 study and the safety and extrapolated efficacy data from the acyclovir studies, oral valacyclovir
661 20 mg/kg 3 times a day for 5 days (not to exceed 1 gram 3 times daily) is recommended for the
662 treatment of chickenpox in pediatric patients 2 to <18 years of age. Because the efficacy and
663 safety of acyclovir for the treatment of chickenpox in children <2 years of age have not been
664 established, efficacy data cannot be extrapolated to support valacyclovir treatment in children
665 <2 years of age with chickenpox. Valacyclovir is also not recommended for the treatment of
666 herpes zoster in children because safety data up to 7 days' duration are not available [*see Use in*
667 *Specific Populations (8.4)*].

668 **16 HOW SUPPLIED/STORAGE AND HANDLING**

669 VALTREX Caplets (blue, film-coated, capsule-shaped tablets) containing valacyclovir
670 hydrochloride equivalent to 500 mg valacyclovir and printed with "VALTREX 500 mg."

671 Bottle of 30 (NDC 0173-0933-08).

672 Bottle of 90 (NDC 0173-0933-10).

673 Unit dose pack of 100 (NDC 0173-0933-56).

674 VALTREX Caplets (blue, film-coated, capsule-shaped tablets, with a partial scorebar on
675 both sides) containing valacyclovir hydrochloride equivalent to 1 gram valacyclovir and printed
676 with "VALTREX 1 gram."


677 Bottle of 30 (NDC 0173-0565-04).

678 Bottle of 90 (NDC 0173-0565-10).

679 **Storage:**

680 Store at 15° to 25°C (59° to 77°F). Dispense in a well-closed container as defined in the
681 USP.

682 **17 PATIENT COUNSELING INFORMATION**

683  See FDA-Approved Patient Labeling (17.6).

684 **17.1 Importance of Adequate Hydration**

685 Patients should be advised to maintain adequate hydration.

686 **17.2 Cold Sores (Herpes Labialis)**

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

693 **17.3 Genital Herpes**

694 Patients should be informed that VALTREX is not a cure for genital herpes. Because
695 genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or
696 intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes
697 is frequently transmitted in the absence of symptoms through asymptomatic viral shedding.
698 Therefore, patients should be counseled to use safer sex practices in combination with
699 suppressive therapy with VALTREX. Sex partners of infected persons should be advised that
700 they might be infected even if they have no symptoms. Type-specific serologic testing of
701 asymptomatic partners of persons with genital herpes can determine whether risk for HSV-2
702 acquisition exists.

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

705 If medical management of a genital herpes recurrence is indicated, patients should be
706 advised to initiate therapy at the first sign or symptom of an episode.

707 There are no data on the effectiveness of treatment initiated more than 72 hours after the
708 onset of signs and symptoms of a first episode of genital herpes or more than 24 hours after the
709 onset of signs and symptoms of a recurrent episode.

710 There are no data on the safety or effectiveness of chronic suppressive therapy of more
711 than 1 year's duration in otherwise healthy patients. There are no data on the safety or
712 effectiveness of chronic suppressive therapy of more than 6 months' duration in HIV-infected
713 patients.

714 **17.4 Herpes Zoster**

715 There are no data on treatment initiated more than 72 hours after onset of the zoster rash.
716 Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes
717 zoster.

718 **17.5 Chickenpox**

719 Patients should be advised to initiate treatment at the earliest sign or symptom of
720 chickenpox.

721 **17.6 FDA-Approved Patient Labeling**



722 Patient labeling is provided as a tear-off leaflet at the end of this full prescribing
723 information.
724
725

726
727 Distributed by
728 GlaxoSmithKline
729 Research Triangle Park, NC 27709
730

731 Manufactured by:
732 GlaxoSmithKline
733 Research Triangle Park, NC 27709
734 or
735 DSM Pharmaceuticals, Inc.
736 Greenville, NC 27834
737

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739

740 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT
741



742 **PATIENT INFORMATION**

743 **VALTREX[®] (VAL-trex)**
744 **(valacyclovir hydrochloride) Caplets**
745

746 Read the Patient Information that comes with VALTREX before you start using it and each time
747 you get a refill. There may be new information. This information does not take the place of
748 talking to your healthcare provider about your medical condition or treatment. Ask your
749 healthcare provider or pharmacist if you have questions.
750

751 **What is VALTREX?**

752 VALTREX is a prescription antiviral medicine. VALTREX lowers the ability of herpes viruses
753 to multiply in your body.
754

755 VALTREX is used in adults:

- 756 • to treat cold sores (also called fever blisters or herpes labialis)
- 757 • to treat shingles (also called herpes zoster)
- 758 • to treat or control genital herpes outbreaks in adults with normal immune systems

- 759 • to control genital herpes outbreaks in adults infected with the human immunodeficiency virus
760 (HIV) with CD4+ cell count greater than 100 cells/mm³
761 • with safer sex practices to lower the chances of spreading genital herpes to others. Even with
762 safer sex practices, it is still possible to spread genital herpes.

763
764 VALTREX used daily with the following safer sex practices can lower the chances of passing
765 genital herpes to your partner.

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

769

770 VALTREX is used in children:

- 771 • to treat cold sores (for children ≥12 years of age)
772 • to treat chickenpox (for children 2 to <18 years of age).

773

774 **VALTREX does not cure herpes infections** (cold sores, chickenpox, shingles, or genital
775 herpes).

776

777 The efficacy of VALTREX has not been studied in children who have not reached puberty.

778

779 **What are cold sores, chickenpox, shingles, and genital herpes?**

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

783

784 **Chickenpox** is caused by a herpes virus. It causes an itchy rash of multiple small, red bumps that
785 look like pimples or insect bites usually appearing first on the abdomen or back and face. It can
786 spread to almost everywhere else on the body and may be accompanied by flu-like symptoms.

787

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

793

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

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

799

800 • Do not have sexual contact with your partner when you have any symptom or outbreak of
801 genital herpes.

802 • Use a condom made of latex or polyurethane whenever you have sexual contact.

803

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

805

806 **Who should not take VALTREX?**

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

810

811 **Before taking VALTREX, tell your healthcare provider:**

812 **About all your medical conditions, including:**

813 • **if you have had a bone marrow transplant or kidney transplant, or if you have**
814 **advanced HIV disease or "AIDS"**. Patients with these conditions may have a higher chance
815 for getting a blood disorder called thrombotic thrombocytopenic purpura/hemolytic uremic
816 syndrome (TTP/HUS). TTP/HUS can result in death.

817 • **if you have kidney problems**. Patients with kidney problems may have a higher chance for
818 getting side effects or more kidney problems with VALTREX. Your healthcare provider may
819 give you a lower dose of VALTREX.

820 • **if you are 65 years of age or older**. Elderly patients have a higher chance of certain side
821 effects. Also, elderly patients are more likely to have kidney problems. Your healthcare
822 provider may give you a lower dose of VALTREX.

823 • **if you are pregnant or planning to become pregnant**. Talk with your healthcare provider
824 about the risks and benefits of taking prescription drugs (including VALTREX) during
825 pregnancy.

826 • **if you are breastfeeding**. VALTREX may pass into your milk and it may harm your baby.
827 Talk with your healthcare provider about the best way to feed your baby if you are taking
828 VALTREX.


829 • **about all the medicines you take**, including prescription and non-prescription medicines,
830 vitamins, and herbal supplements. VALTREX may affect other medicines, and other
831 medicines may affect VALTREX. It is a good idea to keep a complete list of all the
832 medicines you take. Show this list to your healthcare provider and pharmacist any time you
833 get a new medicine.

834

835 **How should I take VALTREX?**

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

- 839 • Do not stop VALTREX or change your treatment without talking to your healthcare
840 provider.
- 841 • VALTREX can be taken with or without food.
- 842 • If you are taking VALTREX to treat cold sores, chickenpox, shingles, or genital herpes, you
843 should start treatment as soon as possible after your symptoms start. VALTREX may not
844 help you if you start treatment too late.
- 845 • If you miss a dose of VALTREX, take it as soon as you remember and then take your next
846 dose at its regular time. However, if it is almost time for your next dose, do not take the
847 missed dose. Wait and take the next dose at the regular time.
- 848 • Do not take more than the prescribed number of VALTREX Caplets each day. Call your
849 healthcare provider right away if you take too much VALTREX.
- 850


851  **What are the possible side effects of VALTREX?**

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

860

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

864

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

868

869 The most common side effect seen in children <18 years of age was headache.

870

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

872

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

875

876 **How should I store VALTREX?**

- 877 • Store VALTREX Caplets at room temperature, 59° to 77°F (15° to 25°C).

- 878 • Store VALTREX suspension between 2° to 8°C (36° to 46°F) in a refrigerator. Discard after
879 28 days.
- 880 • Keep VALTREX in a tightly closed container.
- 881 • Do not keep medicine that is out of date or that you no longer need.
- 882 • Keep VALTREX and all medicines out of the reach of children.

883

884 **General information about VALTREX**

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

888

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

893

894 **What are the ingredients in VALTREX?**

895 **Active Ingredient:** valacyclovir hydrochloride

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

899

900

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904

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908

909 or
910 DSM Pharmaceuticals, Inc.
911 Greenville, NC 27834

912

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914

915 Date of Issue
VTX:XPIL

**As you can see, after many thousands
being tested and around 20 million
having taken Valtrex worldwide...
there is still no known potential
damage whatsoever to the liver from
taking Valtrex.**

**For more accurate information on
Antivirals, HSV & HPV, see:**

www.ProjectAccept.org