

## PRESCRIBING INFORMATION

# VALTRESX<sup>®</sup>

### (valacyclovir hydrochloride)

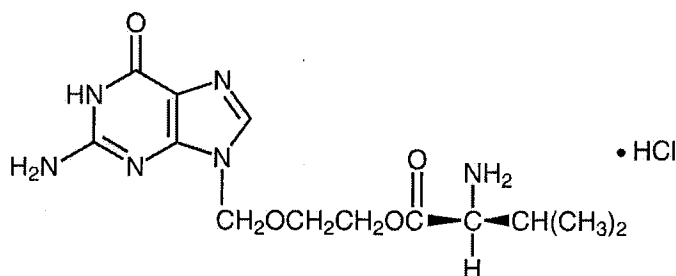
#### Caplets

#### DESCRIPTION

VALTRESX (valacyclovir hydrochloride) is the hydrochloride salt of *L*-valyl ester of the antiviral drug acyclovir (ZOVIRAX<sup>®</sup> Brand, GlaxoSmithKline).

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

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



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

#### MICROBIOLOGY

**Mechanism of Antiviral Action:** Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) both in vitro and in vivo.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared with VZV is due to its more efficient phosphorylation by the viral TK.

34 **Antiviral Activities:** The quantitative relationship between the in vitro susceptibility of  
35 herpesviruses to antivirals and the clinical response to therapy has not been established in  
36 humans, and virus sensitivity testing has not been standardized. Sensitivity testing results,  
37 expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell  
38 culture (IC<sub>50</sub>), vary greatly depending upon a number of factors. Using plaque-reduction assays,  
39 the IC<sub>50</sub> against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and  
40 from 0.01 to 9.9 mcg/mL for HSV-2. The IC<sub>50</sub> for acyclovir against most laboratory strains and  
41 clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity  
42 against the Oka vaccine strain of VZV with a mean IC<sub>50</sub> of 1.35 mcg/mL.

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

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

## 54 **CLINICAL PHARMACOLOGY**

55 After oral administration, valacyclovir hydrochloride is rapidly absorbed from the  
56 gastrointestinal tract and nearly completely converted to acyclovir and *L*-valine by first-pass  
57 intestinal and/or hepatic metabolism.

58 **Pharmacokinetics:** The pharmacokinetics of valacyclovir and acyclovir after oral  
59 administration of VALTREX have been investigated in 14 volunteer studies involving  
60 283 adults.

61 **Absorption and Bioavailability:** The absolute bioavailability of acyclovir after  
62 administration of VALTREX is 54.5% ± 9.1% as determined following a 1-gram oral dose of  
63 VALTREX and a 350-mg intravenous acyclovir dose to 12 healthy volunteers. Acyclovir  
64 bioavailability from the administration of VALTREX is not altered by administration with food  
65 (30 minutes after an 873 Kcal breakfast, which included 51 grams of fat).

66 There was a lack of dose proportionality in acyclovir maximum concentration (C<sub>max</sub>) and area  
67 under the acyclovir concentration-time curve (AUC) after single-dose administration of 100 mg,  
68 250 mg, 500 mg, 750 mg, and 1 gram of VALTREX to 8 healthy volunteers. The mean C<sub>max</sub>  
69 (± SD) was 0.83 (± 0.14), 2.15 (± 0.50), 3.28 (± 0.83), 4.17 (± 1.14), and 5.65 (± 2.37) mcg/mL,  
70 respectively; and the mean AUC (± SD) was 2.28 (± 0.40), 5.76 (± 0.60), 11.59 (± 1.79), 14.11  
71 (± 3.54), and 19.52 (± 6.04) hr•mcg/mL, respectively.

72 There was also a lack of dose proportionality in acyclovir  $C_{max}$  and AUC after the  
73 multiple-dose administration of 250 mg, 500 mg, and 1 gram of VALTREX administered 4 times  
74 daily for 11 days in parallel groups of 8 healthy volunteers. The mean  $C_{max}$  ( $\pm$  SD) was 2.11  
75 ( $\pm$  0.33), 3.69 ( $\pm$  0.87), and 4.96 ( $\pm$  0.64) mcg/mL, respectively, and the mean AUC ( $\pm$  SD) was  
76 5.66 ( $\pm$  1.09), 9.88 ( $\pm$  2.01), and 15.70 ( $\pm$  2.27) hr•mcg/mL, respectively.

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

79 **Distribution:** The binding of valacyclovir to human plasma proteins ranged from 13.5% to  
80 17.9%.

81 **Metabolism:** After oral administration, valacyclovir hydrochloride is rapidly absorbed from  
82 the gastrointestinal tract. Valacyclovir is converted to acyclovir and *L*-valine by first-pass  
83 intestinal and/or hepatic metabolism. Acyclovir is converted to a small extent to inactive  
84 metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither  
85 valacyclovir nor acyclovir is metabolized by cytochrome P450 enzymes. Plasma concentrations  
86 of unconverted valacyclovir are low and transient, generally becoming non-quantifiable by  
87 3 hours after administration. Peak plasma valacyclovir concentrations are generally less than  
88 0.5 mcg/mL at all doses. After single-dose administration of 1 gram of VALTREX, average  
89 plasma valacyclovir concentrations observed were 0.5, 0.4, and 0.8 mcg/mL in patients with  
90 hepatic dysfunction, renal insufficiency, and in healthy volunteers who received concomitant  
91 cimetidine and probenecid, respectively.

92 **Elimination:** The pharmacokinetic disposition of acyclovir delivered by valacyclovir is  
93 consistent with previous experience from intravenous and oral acyclovir. Following the oral  
94 administration of a single 1-gram dose of radiolabeled valacyclovir to 4 healthy subjects, 45.60%  
95 and 47.12% of administered radioactivity was recovered in urine and feces over 96 hours,  
96 respectively. Acyclovir accounted for 88.60% of the radioactivity excreted in the urine. Renal  
97 clearance of acyclovir following the administration of a single 1-gram dose of VALTREX to  
98 12 healthy volunteers was approximately  $255 \pm 86$  mL/min which represents 41.9% of total  
99 acyclovir apparent plasma clearance.

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

102 **End-Stage Renal Disease (ESRD):** Following administration of VALTREX to  
103 volunteers with ESRD, the average acyclovir half-life is approximately 14 hours. During  
104 hemodialysis, the acyclovir half-life is approximately 4 hours. Approximately one third of  
105 acyclovir in the body is removed by dialysis during a 4-hour hemodialysis session. Apparent  
106 plasma clearance of acyclovir in dialysis patients was  $86.3 \pm 21.3$  mL/min/1.73 m<sup>2</sup>, compared  
107 with  $679.16 \pm 162.76$  mL/min/1.73 m<sup>2</sup> in healthy volunteers.

108 Reduction in dosage is recommended in patients with renal impairment (see DOSAGE AND  
109 ADMINISTRATION).

110 **Geriatrics:** After single-dose administration of 1 gram of VALTREX in healthy geriatric  
111 volunteers, the half-life of acyclovir was  $3.11 \pm 0.51$  hours, compared with  $2.91 \pm 0.63$  hours in

112 healthy volunteers. The pharmacokinetics of acyclovir following single- and multiple-dose oral  
113 administration of VALTREX in geriatric volunteers varied with renal function. Dose reduction  
114 may be required in geriatric patients, depending on the underlying renal status of the patient (see  
115 PRECAUTIONS and DOSAGE AND ADMINISTRATION).

116 **Pediatrics:** Valacyclovir pharmacokinetics have not been evaluated in pediatric patients.

117 **Liver Disease:** Administration of VALTREX to patients with moderate (biopsy-proven  
118 cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver disease indicated  
119 that the rate but not the extent of conversion of valacyclovir to acyclovir is reduced, and the  
120 acyclovir half-life is not affected. Dosage modification is not recommended for patients with  
121 cirrhosis.

122 **HIV Disease:** In 9 patients with HIV disease and CD4 cell counts  $<150$  cells/mm<sup>3</sup> who  
123 received VALTREX at a dosage of 1 gram 4 times daily for 30 days, the pharmacokinetics of  
124 valacyclovir and acyclovir were not different from that observed in healthy volunteers (see  
125 WARNINGS).

126 **Drug Interactions:** The pharmacokinetics of digoxin was not affected by coadministration  
127 of VALTREX 1 gram 3 times daily, and the pharmacokinetics of acyclovir after a single dose of  
128 VALTREX (1 gram) was unchanged by coadministration of digoxin (2 doses of 0.75 mg), single  
129 doses of antacids (Al<sup>3+</sup> or Mg<sup>++</sup>), or multiple doses of thiazide diuretics. Acyclovir C<sub>max</sub> and  
130 AUC following a single dose of VALTREX (1 gram) increased by 8% and 32%, respectively,  
131 after a single dose of cimetidine (800 mg), or by 22% and 49%, respectively, after probenecid  
132 (1 gram), or by 30% and 78%, respectively, after a combination of cimetidine and probenecid,  
133 primarily due to a reduction in renal clearance of acyclovir. These effects are not considered to  
134 be of clinical significance in subjects with normal renal function. Therefore, no dosage  
135 adjustment is recommended when VALTREX is coadministered with digoxin, antacids, thiazide  
136 diuretics, cimetidine, or probenecid in subjects with normal renal function.

## 137 CLINICAL TRIALS

138 **Herpes Zoster:** Two randomized double-blind clinical trials in immunocompetent adults with  
139 localized herpes zoster were conducted. VALTREX was compared with placebo in patients less  
140 than 50 years of age, and to ZOVIRAX in patients greater than 50 years of age. All patients were  
141 treated within 72 hours of appearance of zoster rash. In patients less than 50 years of age, the  
142 median time to cessation of new lesion formation was 2 days for those treated with VALTREX  
143 compared with 3 days for those treated with placebo. In patients greater than 50 years of age, the  
144 median time to cessation of new lesions was 3 days in patients treated with either VALTREX or  
145 ZOVIRAX. In patients less than 50 years of age, no difference was found with respect to the  
146 duration of pain after healing (post-herpetic neuralgia) between the recipients of VALTREX and  
147 placebo. In patients greater than 50 years of age, among the 83% who reported pain after healing  
148 (post-herpetic neuralgia), the median duration of pain after healing [95% confidence interval] in  
149 days was: 40 [31, 51], 43 [36, 55], and 59 [41, 77] for 7-day VALTREX, 14-day VALTREX,  
150 and 7-day ZOVIRAX, respectively.

151 **Genital Herpes Infections: Initial Episode:** Six hundred and forty-three immunocompetent  
 152 adults with first episode genital herpes who presented within 72 hours of symptom onset were  
 153 randomized in a double-blind trial to receive 10 days of VALTREX 1 gram twice daily (n = 323)  
 154 or ZOVIRAX 200 mg 5 times a day (n = 320). For both treatment groups: the median time to  
 155 lesion healing was 9 days, the median time to cessation of pain was 5 days, the median time to  
 156 cessation of viral shedding was 3 days.

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

160 In 1 study, patients were randomized to receive 5 days of treatment with either VALTREX  
 161 500 mg twice daily (n = 360) or placebo (n = 259). The median time to lesion healing was 4 days  
 162 in the group receiving VALTREX 500 mg versus 6 days in the placebo group, and the median  
 163 time to cessation of viral shedding in patients with at least 1 positive culture (42% of the overall  
 164 study population) was 2 days in the group receiving VALTREX 500 mg versus 4 days in the  
 165 placebo group. The median time to cessation of pain was 3 days in the group receiving  
 166 VALTREX 500 mg versus 4 days in the placebo group. Results supporting efficacy were  
 167 replicated in a second trial.

168 In a third study, patients were randomized to receive VALTREX 500 mg twice daily for  
 169 5 days (n = 398) or VALTREX 500 mg twice daily for 3 days (and matching placebo twice daily  
 170 for 2 additional days) (n = 402). The median time to lesion healing was about 4½ days in both  
 171 treatment groups. The median time to cessation of pain was about 3 days in both treatment  
 172 groups.

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

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

178  
 179 **Table 1. Recurrence Rates in Immunocompetent Adults at 6 and 12 Months**

| Treatment Arm   | 6 Months                            |                                       |                      | 12 Months                           |                                       |                      |
|-----------------|-------------------------------------|---------------------------------------|----------------------|-------------------------------------|---------------------------------------|----------------------|
|                 | VALTREX<br>1 gram q.d.<br>(n = 269) | ZOVIRAX<br>400 mg b.i.d.<br>(n = 267) | Placebo<br>(n = 134) | VALTREX<br>1 gram q.d.<br>(n = 269) | ZOVIRAX<br>400 mg b.i.d.<br>(n = 267) | Placebo<br>(n = 134) |
| Recurrence free | 55%                                 | 54%                                   | 7%                   | 34%                                 | 34%                                   | 4%                   |
| Recurrences     | 35%                                 | 36%                                   | 83%                  | 46%                                 | 46%                                   | 85%                  |
| Unknowns*       | 10%                                 | 10%                                   | 10%                  | 19%                                 | 19%                                   | 10%                  |

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

181

182 Subjects with 9 or fewer recurrences per year showed comparable results with VALTREX  
183 500 mg once daily.

184 In a second study, 293 HIV-infected adults on stable antiretroviral therapy with a history of 4  
185 or more recurrences of ano-genital herpes per year were randomized to receive either VALTREX  
186 500 mg twice daily (n = 194) or matching placebo (n = 99) for 6 months. The median duration of  
187 recurrent genital herpes in enrolled subjects was 8 years, and the median number of recurrences  
188 in the year prior to enrollment was 5. Overall, the median prestudy HIV-1 RNA was  
189 2.6 log<sub>10</sub> copies/mL. Among patients who received VALTREX, the prestudy median CD4 cell  
190 count was 336 cells/mm<sup>3</sup>; 11% had <100 cells/mm<sup>3</sup>, 16% had 100 to 199 cells/mm<sup>3</sup>, 42% had  
191 200 to 499 cells/mm<sup>3</sup>, and 31% had ≥500 cells/mm<sup>3</sup>. Outcomes for the overall study population  
192 are shown in Table 2.

193

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

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

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

196

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

207

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

|                               | VALTREX*<br>(n = 743) | Placebo<br>(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%)            |

210 \* Results show reductions in risk of 75% (symptomatic HSV-2 acquisition), 50% (HSV-2  
 211 seroconversion), and 48% (overall HSV-2 acquisition) with VALTREX versus placebo.  
 212 Individual results may vary based on consistency of safer sex practices.  
 213

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

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

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

## 226 INDICATIONS AND USAGE

227 **Herpes Zoster:** VALTREX is indicated for the treatment of herpes zoster (shingles).

228 **Genital Herpes:** VALTREX is indicated for the treatment or suppression of genital herpes in  
 229 immunocompetent individuals and for the suppression of recurrent genital herpes in  
 230 HIV-infected individuals.

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

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

## 237 CONTRAINDICATIONS

238 VALTREX is contraindicated in patients with a known hypersensitivity or intolerance to  
 239 valacyclovir, acyclovir, or any component of the formulation.

240 **WARNINGS**

241 **Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), in**  
242 **some cases resulting in death, has occurred in patients with advanced HIV disease and also**  
243 **in allogeneic bone marrow transplant and renal transplant recipients participating in**  
244 **clinical trials of VALTREX at doses of 8 grams per day.**

245 **PRECAUTIONS**

246 **Dosage reduction is recommended when administering VALTREX to patients with renal**  
247 **impairment (see DOSAGE AND ADMINISTRATION).** Acute renal failure and central  
248 nervous system symptoms have been reported in patients with underlying renal disease who have  
249 received inappropriately high doses of VALTREX for their level of renal function. Similar  
250 caution should be exercised when administering VALTREX to geriatric patients (see Geriatric  
251 Use) and patients receiving potentially nephrotoxic agents.

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

257 Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is  
258 exceeded in the intratubular fluid. Adequate hydration should be maintained. In the event of  
259 acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is  
260 restored (see DOSAGE AND ADMINISTRATION).

261 The safety and efficacy of VALTREX have not been established in immunocompromised  
262 patients other than for the suppression of genital herpes in HIV-infected patients. The safety and  
263 efficacy of VALTREX for suppression of recurrent genital herpes in patients with advanced HIV  
264 disease (CD4 cell count  $<100$  cells/mm<sup>3</sup>) have not been established. The efficacy of VALTREX  
265 for the treatment of genital herpes in HIV-infected patients has not been established. The safety  
266 and efficacy of VALTREX have not been established for the treatment of disseminated herpes  
267 zoster.

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

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

271 **Herpes Zoster:** There are no data on treatment initiated more than 72 hours after onset of  
272 the zoster rash. Patients should be advised to initiate treatment as soon as possible after a  
273 diagnosis of herpes zoster.

274 **Genital Herpes:** Patients should be informed that VALTREX is not a cure for genital  
275 herpes. Because genital herpes is a sexually transmitted disease, patients should avoid contact  
276 with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners.  
277 Genital herpes is frequently transmitted in the absence of symptoms through asymptomatic viral  
278 shedding. Therefore, patients should be counseled to use safer sex practices in combination with



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

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

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

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

290 There are no data on the safety or effectiveness of chronic suppressive therapy of more than  
291 1 year's duration in otherwise healthy patients. There are no data on the safety or effectiveness of  
292 chronic suppressive therapy of more than 6 months' duration in HIV-infected patients.

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

299 **Drug Interactions:** See CLINICAL PHARMACOLOGY: Pharmacokinetics.

300 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** The data presented below  
301 include references to the steady-state acyclovir AUC observed in humans treated with 1 gram  
302 VALTREX given orally 3 times a day to treat herpes zoster. Plasma drug concentrations in  
303 animal studies are expressed as multiples of human exposure to acyclovir (see CLINICAL  
304 PHARMACOLOGY: Pharmacokinetics).

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

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

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

316 Valacyclovir was mutagenic in a mouse micronucleus assay.

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

318 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Valacyclovir was not teratogenic  
319 in rats or rabbits at 10 and 7 times human plasma levels, respectively, during the period of major  
320 organogenesis.

321 There are no adequate and well-controlled studies of VALTREX or ZOVIRAX in pregnant  
322 women. A prospective epidemiologic registry of acyclovir use during pregnancy was established  
323 in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed  
324 to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The  
325 occurrence rate of birth defects approximates that found in the general population. However, the  
326 small size of the registry is insufficient to evaluate the risk for less common defects or to permit  
327 reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their  
328 developing fetuses. VALTREX should be used during pregnancy only if the potential benefit  
329 justifies the potential risk to the fetus.

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

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

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

## 351 **ADVERSE REACTIONS**

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

354

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

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

356  
357 **Table 5. Incidence (%) of Adverse Events in Genital Herpes Study Populations**

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

358  
359 Laboratory abnormalities reported in clinical trials of VALTREX in otherwise healthy  
360 patients are listed in Table 6.

361  
362  
363

**Table 6. Incidence (%) of Laboratory Abnormalities in Herpes Zoster and Genital Herpes Study Populations**

| Laboratory Abnormality                        | Herpes Zoster               |              | Genital Herpes Treatment    |                             |              | Genital Herpes Suppression |                           |              |
|---|-----------------------------|--------------|-----------------------------|-----------------------------|--------------|----------------------------|---------------------------|--------------|
|   | VALTREX<br>1 gram<br>t.i.d. | Place-<br>bo | VALTREX<br>1 gram<br>b.i.d. | VALTREX<br>500 mg<br>b.i.d. | Place-<br>bo | VALTREX<br>1 gram q.d.     | VALTREX<br>500 mg<br>q.d. | Place-<br>bo |
| Hemoglobin<br>(<0.8 x LLN)                    | 0.8%                        | 0%           | 0.3%                        | 0.2%                        | 0%           | 0%                         | 0.8%                      | 0.8%         |
| White blood cells<br>(<0.75 x LLN)            | 1.3%                        | 0.6%         | 0.7%                        | 0.6%                        | 0.2%         | 0.7%                       | 0.8%                      | 1.5%         |
| Platelet count<br>(<100,000/mm <sup>3</sup> ) | 1.0%                        | 1.2%         | 0.3%                        | 0.1%                        | 0.7%         | 0.4%                       | 1.1%                      | 1.5%         |
| AST (SGOT)<br>(>2 x ULN)                      | 1.0%                        | 0%           | 1.0%                        | *                           | 0.5%         | 4.1%                       | 3.8%                      | 3.0%         |
| Serum creatinine<br>(>1.5 x ULN)              | 0.2%                        | 0%           | 0.7%                        | 0%                          | 0%           | 0%                         | 0%                        | 0%           |

364 \*Data were not collected prospectively.

365 LLN = Lower limit of normal.

366 ULN = Upper limit of normal.

367

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

376 **Reduction of Transmission:** In a clinical study for the reduction of transmission of  
377 genital herpes, the adverse events reported by patients receiving VALTREX 500 mg  
378 once daily (n = 743) or placebo once daily (n = 741) included headache (VALTREX  
379 29%, placebo 26%), nasopharyngitis (VALTREX 16%, placebo 15%), and upper  
380 respiratory tract infection (VALTREX 9%, placebo 10%). In this 8-month study, there  
381 were no clinically significant changes from baseline laboratory parameters in subjects  
382 receiving VALTREX compared with placebo.

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

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

389 **Observed During Clinical Practice:** The following events have been identified during post-  
390 approval use of VALTREX in clinical practice. Because they are reported voluntarily from a  
391 population of unknown size, estimates of frequency cannot be made. These events have been  
392 chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to  
393 VALTREX, or a combination of these factors.

394 **General:** Facial edema, hypertension, tachycardia.

395 **Allergic:** Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea,  
396 pruritus, rash, and urticaria.

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

400 **Eye:** Visual abnormalities.

401 **Gastrointestinal:** Diarrhea.

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

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

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

405 **Skin:** Erythema multiforme, rashes including photosensitivity, alopecia.

406 **Renal Impairment:** Renal failure and CNS symptoms have been reported in patients with renal  
407 impairment who received VALTREX or acyclovir at greater than the recommended dose. **Dose**  
408 **reduction is recommended in this patient population (see DOSAGE AND**  
409 **ADMINISTRATION).**

## 410 OVERDOSAGE

411 Caution should be exercised to prevent inadvertent overdose (see PRECAUTIONS).  
412 Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is  
413 exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may  
414 benefit from hemodialysis until renal function is restored (see DOSAGE AND  
415 ADMINISTRATION).

## 416 DOSAGE AND ADMINISTRATION

417 VALTREX Caplets may be given without regard to meals.

418 **Herpes Zoster:** The recommended dosage of VALTREX for the treatment of herpes zoster is  
419 1 gram orally 3 times daily for 7 days. Therapy should be initiated at the earliest sign or  
420 symptom of herpes zoster and is most effective when started within 48 hours of the onset of  
421 zoster rash. No data are available on efficacy of treatment started greater than 72 hours after rash  
422 onset.

423 **Genital Herpes: Initial Episodes:** The recommended dosage of VALTREX for treatment of  
424 initial genital herpes is 1 gram twice daily for 10 days.

425 There are no data on the effectiveness of treatment with VALTREX when initiated more than  
426 72 hours after the onset of signs and symptoms. Therapy was most effective when administered  
427 within 48 hours of the onset of signs and symptoms.

428 **Recurrent Episodes:** The recommended dosage of VALTREX for the treatment of  
429 recurrent genital herpes is 500 mg twice daily for 3 days.

430 If medical management of a genital herpes recurrence is indicated, patients should be advised  
431 to initiate therapy at the first sign or symptom of an episode. There are no data on the  
432 effectiveness of treatment with VALTREX when initiated more than 24 hours after the onset of  
433 signs or symptoms.

434 **Suppressive Therapy:** The recommended dosage of VALTREX for chronic suppressive  
435 therapy of recurrent genital herpes is 1 gram once daily in patients with normal immune function.  
436 In patients with a history of 9 or fewer recurrences per year, an alternative dose is 500 mg once  
437 daily. The safety and efficacy of therapy with VALTREX beyond 1 year have not been  
438 established.

439 In HIV-infected patients with CD4 cell count  $\geq 100$  cells/mm<sup>3</sup>, the recommended dosage of  
440 VALTREX for chronic suppressive therapy of recurrent genital herpes is 500 mg twice daily.  
441 The safety and efficacy of therapy with VALTREX beyond 6 months in patients with HIV  
442 infection have not been established.

443 **Reduction of Transmission:** The recommended dosage of VALTREX for reduction of  
444 transmission of genital herpes in patients with a history of 9 or fewer recurrences per year is  
445 500 mg once daily for the source partner. Patients should be counseled to use safer sex practices  
446 in combination with suppressive therapy with VALTREX. The efficacy of reducing transmission  
447 beyond 8 months in discordant couples has not been established.

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

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

455  
456

**Table 7. Dosages for Patients with Renal Impairment**

| Indications   | Normal Dosage Regimen (Creatinine Clearance ≥50) | Creatinine Clearance (mL/min)               |   |                       |
|---|--|---|---|-----------------------|
|   |  | 30-49                                       | 10-29                                       | <10                   |
| <b>Herpes zoster</b>  | 1 gram every 8 hours                             | 1 gram every 12 hours                       | 1 gram every 24 hours                       | 500 mg every 24 hours |
| <b>Genital herpes</b><br>Initial treatment                            | 1 gram every 12 hours                            | no reduction                                | 1 gram every 24 hours                       | 500 mg every 24 hours |
| <b>Genital herpes</b><br>Recurrent episodes                           | 500 mg every 12 hours                            | no reduction                                | 500 mg every 24 hours                       | 500 mg every 24 hours |
| <b>Genital herpes</b><br>Suppressive therapy                          | 1 gram every 24 hours                            | no reduction                                | 500 mg every 24 hours                       | 500 mg every 24 hours |
|   | 500 mg every 24 hours                            | no reduction                                | 500 mg every 48 hours                       | 500 mg every 48 hours |
| <b>Genital herpes</b><br>Suppressive therapy in HIV-infected patients | 500 mg every 12 hours                            | no reduction                                | 500 mg every 24 hours                       | 500 mg every 24 hours |
| <b>Herpes labialis (cold sores)</b>                                   | Two 2-gram doses taken about 12 hours apart      | Two 1-gram doses taken about 12 hours apart | Two 500-mg doses taken about 12 hours apart | 500-mg single dose    |
| <b>Do not exceed 1 day of treatment.</b>                              |  |   |   |                       |

457

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

462 **Peritoneal Dialysis:** There is no information specific to administration of VALTREX in  
463 patients receiving peritoneal dialysis. The effect of chronic ambulatory peritoneal dialysis  
464 (CAPD) and continuous arteriovenous hemofiltration/dialysis (CAVHD) on acyclovir  
465 pharmacokinetics has been studied. The removal of acyclovir after CAPD and CAVHD is less  
466 pronounced than with hemodialysis, and the pharmacokinetic parameters closely resemble those  
467 observed in patients with ESRD not receiving hemodialysis. Therefore, supplemental doses of  
468 VALTREX should not be required following CAPD or CAVHD.

469 **HOW SUPPLIED**

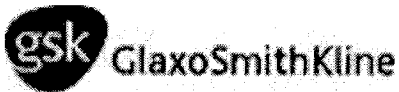
470 VALTREX Caplets (blue, film-coated, capsule-shaped tablets) containing valacyclovir  
471 hydrochloride equivalent to 500 mg valacyclovir and printed with "VALTREX 500 mg."

472 Bottle of 30 (NDC 0173-0933-08).  
473 Bottle of 90 (NDC 0173-0933-10).  
474 Unit dose pack of 100 (NDC 0173-0933-56).  
475 VALTREX Caplets (blue, film-coated, capsule-shaped tablets, with a partial scorebar on both  
476 sides) containing valacyclovir hydrochloride equivalent to 1 gram valacyclovir and printed with  
477 "VALTREX 1 gram."

478 Bottle of 30 (NDC 0173-0565-04).  
479 Bottle of 90 (NDC 0173-0565-10).

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

482  
483 VALTREX and ZOVIRAX are registered trademarks of GlaxoSmithKline.  
484  
485



486  
487 Distributed by:  
488 GlaxoSmithKline  
489 Research Triangle Park, NC 27709  
490

491 Manufactured by:  
492 GlaxoSmithKline  
493 Research Triangle Park, NC 27709  
494 or  
495 DSM Pharmaceuticals, Inc.  
496 Greenville, NC 27834  
497

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499

500 October 2007

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501  
502 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT  
503

-----  
504 **PATIENT INFORMATION**  
505 **VALTREX® (VAL-trex)**  
506 **(valacyclovir hydrochloride) Caplets**  
507

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



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

512

513 **What is VALTREX?**

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

516

517 VALTREX is used:

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

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

525

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

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

531

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

533

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

535

536 **What are cold sores, shingles, and genital herpes?**

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

540

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

546

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

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

552

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

556

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

558

### 559 **Who should not take VALTREX?**

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

563

### 564 **Before taking VALTREX, tell your healthcare provider:**

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

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

588

### 589 **How should I take VALTREX?**

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

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

604

#### 605 **What are the possible side effects of VALTREX?**

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

614

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

618

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

621

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

623

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

626

#### 627 **How should I store VALTREX?**

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

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

632

633 **General information about VALTREX**

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

637

638 This leaflet summarizes the most important information about VALTREX. If you would like  
639 more information, talk with your healthcare provider. You can ask your healthcare provider or  
640 pharmacist for information about VALTREX that is written for health professionals. More  
641 information is available at [www.VALTREX.com](http://www.VALTREX.com).

642

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

644 **Active Ingredient:** valacyclovir hydrochloride

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

648

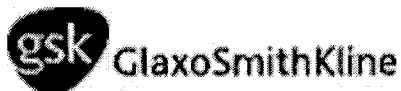
649 **Rx Only**

650

651 VALTREX is a registered trademark of GlaxoSmithKline.

652

653



654

655 Distributed by:

656 GlaxoSmithKline

657 Research Triangle Park, NC 27709

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659 Manufactured by:

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662 or

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