

VALTRES® (valacyclovir hydrochloride) Capslets

BRIEF SUMMARY



The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS: VALTRES is contraindicated in patients with a known hypersensitivity or intolerance to valacyclovir, acyclovir, or any component of the formulation.

WARNINGS: Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV disease and also in allogeneic bone marrow transplant and renal transplant recipients participating in clinical trials of VALTRES at doses of 8 grams per day. **PRECAUTIONS:** The efficacy of VALTRES has not been established for the treatment of disseminated herpes zoster, or suppression of recurrent genital herpes, or in immunocompromised patients.

Dosage adjustment is recommended when administering VALTRES to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Caution should also be exercised when administering VALTRES to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

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

Genital Herpes: Patients should be informed that VALTRES is not a cure for genital herpes. There are no data evaluating whether VALTRES will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

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

Drug Interactions: An additive increase in acyclovir AUC and C_{max} was observed when VALTRES was administered to healthy volunteers who were taking cimetidine, probenecid, or a combination of both cimetidine and probenecid (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

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

Valacyclovir was noncarcinogenic in lifetime carcinogenicity bioassays at single daily doses (gavage) of up to 120 mg/kg/day for mice and 100 mg/kg/day for rats. There was no significant difference in the incidence of tumors between treated and control animals, nor did valacyclovir shorten the latency of tumors. Plasma concentrations of acyclovir were equivalent to human levels in the mouse bioassay and 1.4 to 2.3 times human levels in the rat bioassay.

Valacyclovir was tested in five genetic toxicity assays. An Ames assay was negative in the absence or presence of metabolic activation. Also negative were an in vitro cytogenetic study with human lymphocytes and a rat cytogenetic study at a single oral dose of 3000 mg/kg (8 to 9 times human plasma levels).

In the mouse lymphoma assay, valacyclovir was negative in the absence of metabolic activation. In the presence of metabolic activation (76% to 88% conversion to acyclovir), valacyclovir was weakly mutagenic.

A mouse micronucleus assay was negative at 250 mg/kg but weakly positive at 500 mg/kg (acyclovir concentrations 26 to 51 times human plasma levels).



ZOVIRAX® (acyclovir) Capsules ZOVIRAX® (acyclovir) Tablets ZOVIRAX® (acyclovir) Suspension

BRIEF SUMMARY

The following is a brief summary only; see full prescribing information for complete product information, including references.

CONTRAINDICATIONS: ZOVIRAX Capsules, Tablets, and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS: ZOVIRAX Capsules, Tablets, and Suspension are intended for oral ingestion only.

PRECAUTIONS:

General: ZOVIRAX has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION section of full prescribing information).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir in vitro can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the in vitro sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY: Microbiology section of full prescribing information).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering ZOVIRAX to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered ZOVIRAX, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. ZOVIRAX Capsules, Tablets, and Suspension are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. ZOVIRAX does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of ZOVIRAX per day for 6 months in humans did not show similar findings. Chromosomal breaks were seen in vitro after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of ZOVIRAX per day for 1 year in humans did not show any abnormalities in structure or number of chromosomes.

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with ZOVIRAX showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that treatment of chickenpox with ZOVIRAX would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous ZOVIRAX is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced. The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics section of full prescribing information).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two in vitro cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weaning mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells in vitro. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically

Valacyclovir did not impair fertility or reproduction in rats at 200 mg/kg/day (6 times human plasma levels).

Pregnancy: Teratogenic Effects: Pregnancy Category B. Valacyclovir was not teratogenic in rats or rabbits given 400 mg/kg (which results in exposures of 10 and 7 times human plasma levels, respectively) during the period of major organogenesis. There are no adequate and well-controlled studies of VALTRES or ZOVIRAX in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy has been ongoing since 1984. As of December 1994, outcomes of live births have been documented in 380 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. VALTRES should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to VALTRES, Glaxo Wellcome Inc. maintains a Valacyclovir in Pregnancy Registry. Physicians are encouraged to register their patients by calling (800) 722-9292, ext. 39437.

Nursing Mothers: There is no experience with VALTRES. However, acyclovir concentrations have been documented in breast milk in two women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. VALTRES should be administered to a nursing mother with caution and only when indicated.

Pediatric Use: Safety and effectiveness of VALTRES in pediatric patients have not been established.

Geriatric Use: Of the total number of patients included in clinical studies of VALTRES, 810 were age 65 or older, and 339 were age 75 or older. A total of 34 volunteers age 65 or older completed a pharmacokinetic trial of VALTRES. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of VALTRES in geriatric volunteers varied with renal function. Dosage reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: The adverse events reported by greater than 2% of a given treatment group in clinical trials of VALTRES are listed in Table 1.

Table 1
Incidence (%) of Adverse Events in Herpes Zoster and Genital Herpes Study Populations

Adverse Event	Herpes Zoster			Genital Herpes			
	VALTRES 1 gram t.i.d. (n=967)	ZOVIRAX 800 mg 5x daily (n=376)	Placebo (n=195)	VALTRES 1 gram b.i.d. (n=1,194)	VALTRES 500 mg b.i.d. (n=359)	ZOVIRAX 200 mg 5x daily (n=822)	Placebo (n=439)
Nausea	15	19	8	6	6	7	8
Headache	14	13	12	16	17	12	14
Vomiting	6	8	3	1	1	2	<1
Diarrhea	5	7	6	4	5	3	6
Constipation	4	5	3	<1	1	1	1
Asthenia	4	5	4	2	1	2	4
Dizziness	3	6	2	3	2	2	3
Abdominal Pain	3	3	2	2	3	2	3
Anorexia	2	3	2	<1	<1	<1	<1

OVERDOSAGE: There have been no reports of overdosage from the administration of VALTRES. However, it is known that precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

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significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F₁ generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 month, respectively, caused testicular atrophy. Plasma levels were not measured in the 1-month study and were 24 to 48 times human levels in the 6-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for 1 month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for 1 year (6 to 12 times human levels).

Pregnancy: Teratogenic Effects: Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity. In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to systemic acyclovir, Glaxo Wellcome Inc. maintains an Acyclovir in Pregnancy Registry. Physicians are encouraged to register patients by calling (800) 722-9292, ext. 58465.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when ZOVIRAX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS:

Herpes Simplex: Short-Term Administration: The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered ZOVIRAX were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered ZOVIRAX (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with ZOVIRAX were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with ZOVIRAX for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%), and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year included asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster: The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral ZOVIRAX 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%), and constipation (2.4%).

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral ZOVIRAX in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral ZOVIRAX in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE: Patients have ingested intentional overdoses of up to 100 capsules (20 g) of ZOVIRAX, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION section of full prescribing information).

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