ZOVIRAX® (ACYCLOVIR) OINTMENT 5%

05/10/2006

ZOVIRAX® (acyclovir) Ointment 5%, For the management of initial herpes genitalis

Treat Early. Speed Healing.

The power of acyclovir in an ointment formulation

Ask your healthcare professional if a prescription for ZOVIRAX® Ointment is right for you

Clinical Trials

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Successful treatment of initial genital herpes

In 2 double-blinded, placebo-controlled studies, treatment of initial primary genital herpes with ZOVIRAX® Ointment resulted in shorter duration of viral shedding from lesions:*

- 2.3 days vs 5.6 days with placebo ($p<0.001$)[1]†
- 4.1 days vs 7.0 days with placebo[2]‡

Time to complete healing was also shortened:§

- 11.2 days vs 15.8 days with placebo ($p<0.05$)[1]†
- 7.1 days vs 10.5 days with placebo[2]‡

ZOVIRAX® Ointment is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous herpes simplex virus infection in immunocompromised patients.

Mild pain (including transient burning, stinging, and itching) has been reported with no significant difference between ZOVIRAX® Ointment and placebo. ZOVIRAX® Ointment does not prevent transmission of HSV infections.

Proven 20-year record of safety and tolerability

No significant difference reported between ZOVIRAX® Ointment and placebo in all studies for:[3]

- Rate or type of adverse event**
- Abnormal clinical laboratory findings

Minimal systemic absorption[3]

ZOVIRAX® Ointment works where it should and spares healthy cells by:[3]

- Selectively converting into the active form when in contact with HSV-infected cells
- Remaining inert when in contact with healthy cells

No interactions reported with concomitantly administered topical or systemic drugs[3]

Early intervention promotes best possible clinical results[4]

Patients should be instructed to initiate ZOVIRAX® Ointment therapy as early as possible following onset of prodromal signs (eg, tingling) and symptoms.[3]

ZOVIRAX® Ointment 5% is contraindicated for patients who develop hypersensitivity or chemical intolerance to the components of the formulation.

Help your patients remember: Treat early. Speed healing.

Remind them that HSV is a recurrent infection.

Instruct patients that, once a condition triggers the first signs and symptoms of an infection, immediately begin treatment with ZOVIRAX® Ointment.

1 Corey L, Benedetti JK, Critchlow CW, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. *Am J Med.* 1982;73:326-334.

2 Corey L, Nahmias AJ, Guinan ME, et al. A trial of topical acyclovir in genital herpes simplex infections. *N Engl J Med.* 1982.306:1313-1319.

3 ZOVIRAX® Ointment 5%. Prescribing Information. GlaxoSmithKline. 2004.

4 Wagstaff AJ, Faulds D, Goa KL. Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs.* 1994;47:153-205.

* Patients experienced initial infections for up to 6 days before beginning therapy. They applied ZOVIRAX® Ointment 4 times daily for 7 days; the recommended treatment course is 6 times daily for 7 days.

** In controlled clinical trials, there was no significant difference in patients reporting mild pain (including transient burning and stinging) between ZOVIRAX® Ointment 5% (30%) and placebo; treatment was discontinued in 2 of these patients. Other local reactions among acyclovir-treated patients included pruritus (4%)2.

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† Virus no longer present is a measure of the antiviral effect of ZOVIRAX® Ointment and means that the replication and shedding of the virus have ceased at the sites cultured.

‡ For the best clinical response, ZOVIRAX® Ointment should be initiated as early as possible following the onset of signs and symptoms.

§ Antiviral and complete healing results based on ZOVIRAX® Ointment applied 4 to 6 times a day for 7 days; the recommended treatment course is 6 times a day for 7 days.

ZOVIRAX® (acyclovir) Ointment 5%

En Español

- WHAT CAN I DO TO TREAT IT?
  - How Does ZOVIRAX® Ointment Work?
  - Tips on Speaking With Your Doctor
  - FAQs
- HEALTHCARE PROFESSIONALS
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What Can I Do To Treat It?

Join our free program today to receive valuable tips on how to live with genital herpes, delivered straight to you via e-mail!

Sign up for your $10 ZOVIRAX® Ointment rebate

Genital herpes is caused by a virus that can be spread to others, so it's important to treat it with an antiviral medication. ZOVIRAX® (acyclovir) Ointment 5% is a prescription topical medication applied at the site of outbreak. ZOVIRAX® Ointment:

- Soothes at the site with its targeted treatment[1]
- Attacks the herpes virus and stops it from copying itself[1,2]
- Has no known drug interactions with other topical or systemic drugs[2]
- Reduces viral shedding, which means it can reduce chances of spreading the virus to others
- Has been clinically proven to:
  - Shorten the duration of itching and pain*[1]
  - Shorten the duration of the lesion when compared to placebo*[1]

ZOVIRAX® Ointment 5% is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients.

Mild pain (including transient burning, stinging, and itching) has been reported with no significant difference between ZOVIRAX® Ointment and placebo. ZOVIRAX® Ointment does not prevent transmission of HSV infections.

** Duration of itching: ZOVIRAX® Ointment (3.6 days) vs placebo (8.0 days) at primary first episode of genital herpes (P<0.01).*
Duration of pain: ZOVIRAX® Ointment (5.2 days) vs placebo (7.0 days) at primary first episode of genital herpes (P<0.05).
Duration of lesion: ZOVIRAX® Ointment (11.2 days) vs placebo (15.8 days) at primary first episode of genital herpes (P<0.05).

Reference:

1. Corey L, Benedetti JK, Critchlow CW, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. Am J Med. 1982;73:326-334.
2. Zovirax (acyclovir) ointment 5% [prescribing information]. Bridgewater, NJ: Biovail Pharmaceuticals Inc; 2004.

Proud Supporter of STD Awareness Month

APRIL 2006

Did You Know?

Up to 90% of people with genital herpes are unaware that they have the virus.[1]

Speak with your doctor or nurse for more information.

For more information, visit www.zoviraxointment4.com.

BIOVAIL

Reference: 1. American Social Health Association Web site. Learn about herpes: questions & answers. Available at: http://www.ashastd.org/herpes/herpes_learn_questions.cfm. Accessed November 30, 2005.

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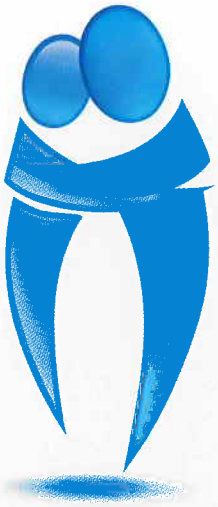

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ZOVIRAX®
(acyclovir)
Ointment 5%

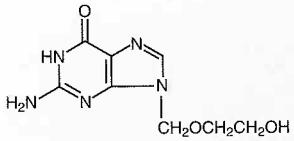
PRESCRIBING INFORMATION

DESCRIPTION

ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analogue active against herpes viruses. ZOVIRAX Ointment 5% is a formulation for topical administration. Each gram of ZOVIRAX Ointment 5% contains 50 mg of acyclovir in a polyethylene glycol (PEG) base.

Acyclovir is a white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/mL. The pka's of acyclovir are 2.27 and 9.25.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one; it has the following structural formula:



VIROLOGY

Mechanism of Antiviral Action: Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV).

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 into 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 to VZV is due to its more efficient phosphorylation by the viral TK.

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

Drug Resistance: Resistance of HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY

Two clinical pharmacology studies were performed with ZOVIRAX Ointment 5% in immunocompromised adults at risk of developing mucocutaneous Herpes simplex virus infections or with localized varicella-zoster infections. These studies were designed to evaluate the dermal tolerance, systemic toxicity, and percutaneous absorption of acyclovir.

In 1 of these studies, which included 16 inpatients, the complete ointment or its vehicle were randomly administered in a dose of 1-cm strips (25 mg acyclovir) 4 times a day for 7 days to an intact skin surface area of 4.5 square inches. No local intolerance, systemic toxicity, or contact dermatitis were observed. In addition, no drug was detected in blood and urine by radioimmunoassay (sensitivity, 0.01 mcg/mL).

The other study included 11 patients with localized varicella-zoster infections. In this uncontrolled study, acyclovir was detected in the blood of 9 patients and in the urine of all patients tested. Acyclovir levels in plasma ranged from <0.01 to 0.28 mcg/mL in 8 patients with normal renal function, and from <0.01 to 0.78 mcg/mL in 1 patient with impaired renal function. Acyclovir excreted in the urine ranged from <0.02% to 9.4% of the daily dose. Therefore, systemic absorption of acyclovir after topical application is minimal.

CLINICAL TRIALS

In clinical trials of initial genital herpes infections, ZOVIRAX Ointment 5% has shown a decrease in healing time and, in some cases, a decrease in duration of viral shedding and duration of pain. In studies in immunocompromised patients mainly with herpes labialis, there was a decrease in duration of viral shedding and a slight decrease in duration of pain.

In studies of recurrent genital herpes and of herpes labialis in nonimmunocompromised patients, there was no evidence of clinical benefit; there was some decrease in duration of viral shedding.

INDICATIONS AND USAGE

ZOVIRAX (acyclovir) Ointment 5% is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients.

CONTRAINDICATIONS

ZOVIRAX Ointment 5% is contraindicated in patients who develop hypersensitivity to the components of the formulation.

WARNINGS

ZOVIRAX Ointment 5% is intended for cutaneous use only and should not be used in the eye.

PRECAUTIONS

General: The recommended dosage, frequency of applications, and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION). There are no data to support the use of ZOVIRAX Ointment 5% to prevent transmission of infection to other persons or prevent recurrent infections when applied in the absence of signs and symptoms. ZOVIRAX Ointment 5% should not be used for the prevention of recurrent HSV infections. Although clinically significant viral resistance associated with the use of ZOVIRAX Ointment 5% has not been observed, this possibility exists.

Drug Interactions: Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with ZOVIRAX Ointment 5%.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Systemic exposure following topical administration of acyclovir is minimal. Dermal carcinogenicity studies were not conducted. Results from the studies of carcinogenesis, mutagenesis, and fertility are not included in the full prescribing information for ZOVIRAX Ointment 5% due to the minimal exposures of acyclovir that result from dermal application. Information on these studies is available in the full prescribing information for ZOVIRAX Capsules, Tablets, and Suspension and ZOVIRAX for Injection.
Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Acyclovir was not teratogenic in the mouse, rabbit, or rat at exposures greatly in excess of human exposure. There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Systemic acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: It is not known whether topically applied acyclovir is excreted in breast milk. Systemic exposure following topical administration is minimal. After oral administration of ZOVIRAX, acyclovir concentrations have been documented in breast milk in 2 women and ranged from 0.6 to 4.1 times the corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg per day. Nursing mothers who have active herpetic lesions near or on the breast should avoid nursing.
Geriatric Use: Clinical studies of ZOVIRAX Ointment did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic absorption of acyclovir after topical administration is minimal (see CLINICAL PHARMACOLOGY).
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In the controlled clinical trials, mild pain (including transient burning and stinging) was reported by about 30% of patients in both the active and placebo arms; treatment was discontinued in 2 of these patients. Local pruritus occurred in 4% of these patients. In all studies, there was no significant difference between the drug and placebo group in the rate or type of reported adverse reactions nor were there any differences in abnormal clinical laboratory findings.
Observed During Clinical Practice: Based on clinical practice experience in patients treated with ZOVIRAX Ointment in the US, 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 that have been received since market introduction include:
General: Edema and/or pain at the application site.
Skin: Pruritus, rash.

OVERDOSAGE

Overdosage by topical application of ZOVIRAX Ointment 5% is unlikely because of limited transcutaneous absorption (see CLINICAL PHARMACOLOGY).

DOSAGE AND ADMINISTRATION

Apply sufficient quantity to adequately cover all lesions every 3 hours, 6 times per day for 7 days. The dose size per application will vary depending upon the total lesion area but should approximate a one-half inch ribbon of ointment per 4 square inches of surface area. A finger cot or rubber glove should be used when applying ZOVIRAX to prevent autoinoculation of other body sites and transmission of infection to other persons. **Therapy should be initiated as early as possible following onset of signs and symptoms.**

HOW SUPPLIED

Each gram of ZOVIRAX Ointment 5% contains 50 mg acyclovir in a polyethylene glycol base. It is supplied as follows:
15-g tubes (NDC 64455-993-94)
3-g tubes (NDC 64455-993-41).
Store at 15° to 25°C (59° to 77°F) in a dry place.

Manufactured by
GlaxoSmithKline
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Pharmaceuticals, Inc.
Bridgewater, NJ 08807

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