CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 018604/S014

Trade Name: ZOVIRAX OINTMENT 5%

Generic Name: ACYCLOVIR

Sponsor: GLAXOWELLCOME, INC

Approval Date: 01/08/97

Indication(s): TREATMENT OF HERPES ZOSTER AND CHICKENPOX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 018604/S014

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 018604/S014

APPROVAL LETTER

JAN 8 1997

NDA 18-604/S-014

Glaxo Wellcome Inc.
Attention: Robert Watson
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Watson:

We acknowledge your September 27, 1996 supplemental New Drug Application received on September 30, 1996 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZOVIRAX® (acyclovir) 5% Ointment.

This supplemental application provides for the addition of a Pediatric Use statement in the "Precautions" section in response to the December 13, 1994 final rule governing the "Pediatric Use" subsection of prescription drug labeling.

We have completed the review of this supplemental application and it is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact Mr. David Clinton Staten, Jr., Regulatory Health Manager at (301) 827-2335.

Sincerely yours,

/S/ 1-8-97

Donna J. Freeman, M.D.
Acting Director
Division of Anti-Viral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018604/S014

FINAL PRINTED LABELING

Final Printed Labeling
ZOVIRAX® (acyclovir) Tablets
Package Outsert

APPROVED

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

JAN 8 1997

Labeling:
NDA No:
Reviewed:

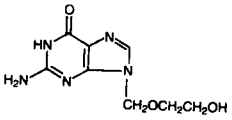
DESCRIPTION: ZOVIRAX is the brand name for acyclovir, an antiviral drug. ZOVIRAX Capsules, Tablets, and Suspension are formulations for oral administration. Each capsule of ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.

Each 800 mg tablet of ZOVIRAX contains 800 mg of acyclovir and the inactive ingredients FD&C Blue No. 2, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Each 400 mg tablet of ZOVIRAX contains 400 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Each teaspoonful (5 mL) of ZOVIRAX Suspension contains 200 mg of acyclovir and the inactive ingredients methylparaben 0.1% and propylparaben 0.02% (added as preservatives), carboxymethylcellulose sodium, flavor, glycerin, microcrystalline cellulose, and sorbitol.

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:



Acyclovir is a white, crystalline powder with a molecular weight of 225 daltons, and a maximum solubility in water of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY: Mechanism of Antiviral Effects: Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV, and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] 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.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. In vitro, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic in vitro for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus-infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir in vitro.

Microbiology: The quantitative relationship between the in vitro susceptibility of herpes simplex and varicella-zoster viruses to acyclovir 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 (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 μg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 μg/mL (plaque reduction in green monkey kidney (GMK) cells).[1] The ID_{50} against

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Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤0.9 μg/mL acyclovir and 50% of all isolates were sensitive to ≤0.2 μg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤2.2 μg/mL and 50% of all isolates were sensitive to ≤0.7 μg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 μg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 μg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 μg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 μg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 μg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 μg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, ZOVIRAX Capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 μg/mL (0.47 to 0.54 μg/mL) and 0.31 μg/mL (0.18 to 0.41 μg/mL), respectively, and following the final 800 mg dose were 2.8 μg/mL (2.3 to 3.1 μg/mL) and 1.8 μg/mL (1.3 to 2.5 μg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, ZOVIRAX Capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 μg/mL (0.66 to 1.8 μg/mL) and 0.55 μg/mL (0.14 to 1.1 μg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m^2 and 600 mg/m^2, in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

A single oral dose bioavailability study in 23 normal volunteers showed that ZOVIRAX Capsules 200 mg are bioequivalent to 200 mg acyclovir in aqueous solution; and in a separate study in 20 volunteers, it was shown that ZOVIRAX Suspension is bioequivalent to ZOVIRAX Capsules. In a different single-dose bioavailability/bioequivalence study in 24 volunteers, one ZOVIRAX 800 mg Tablet was demonstrated to be bioequivalent to four ZOVIRAX 200 mg Capsules.

In a multiple-dose crossover study where 23 volunteers received ZOVIRAX as one 200 mg capsule, one 400 mg tablet, and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 μg/mL, 1.21 and 0.63 μg/mL, and 1.61 and 0.83 μg/mL for the 200, 400, and 800 mg dosage regimens, respectively.

In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy)methyl]guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

INDICATIONS AND USAGE: ZOVIRAX Capsules, Tablets, and Suspension are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

ZOVIRAX Capsules, Tablets, and Suspension are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella).

Genital Herpes Infections:

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional, and psychosocial difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus, orally administered ZOVIRAX is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections–commonly known as initial genital herpes):

Double-blind, placebo-controlled studies[23,24,25] have demonstrated that orally administered ZOVIRAX significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system

some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention, or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous ZOVIRAX.

Recurrent Episodes: Double-blind, placebo-controlled studies[16,26-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered ZOVIRAX given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received ZOVIRAX 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with ZOVIRAX. Re-evaluation will usually require a trial off ZOVIRAX to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered ZOVIRAX should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of in vitro mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies[31,32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections:

In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to ZOVIRAX and 94 to placebo), ZOVIRAX (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33]

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to ZOVIRAX and 43 to placebo), ZOVIRAX (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).[34]

Chickenpox:

In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented **within 24 hours** of the onset of a typical chickenpox rash, ZOVIRAX was administered orally 4 times daily for 5 to 7 days at doses of 10, 15, or 20 mg/kg depending on the age group. Treatment with ZOVIRAX reduced the maximum number of lesions (336 vs. greater than 500; lesions beyond 500 were not counted). Treatment with ZOVIRAX also shortened the mean time to 50% healing (7.1 days vs. 8.7 days), reduced the number of vesicular lesions by the second day of treatment (49 vs. 113), and decreased the proportion of patients with fever (temperature greater than 100°F) by the second day (19% vs. 57%). Treatment with ZOVIRAX did not affect the antibody response to varicella-zoster virus measured 1 month and 1 year following the treatment.[35]

In two concurrent double-blind, placebo-controlled studies, a total of 883 normal patients, ages 2 to 18 years, were enrolled **within 24 hours** of the onset of a typical chickenpox rash, and ZOVIRAX was administered at 20 mg/kg orally up to 800 mg 4 times daily for 5 days. In the larger study of 815 children ages 2 to 12 years, treatment with ZOVIRAX reduced the median maximum number of lesions (277 vs. 386), reduced the median number of vesicular lesions by the second day of treatment (26 vs. 40), and reduced the proportion of patients with moderate to severe itching by the third day of treatment (15% vs. 34%).[36] In addition, in both studies (883 patients, ages 2 to 18 years), treatment with ZOVIRAX also decreased the proportion of patients with fever (temperature greater than 100°F), anorexia, and lethargy by the second day of treatment, and decreased the mean number of residual lesions on Day 28.[36,37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at 1 month following treatment in patients receiving ZOVIRAX compared to patients receiving placebo.[38]

Diagnosis:

Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. While cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39]

Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

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).

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).

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

[illegible] zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39]

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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.[40] 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.[28]

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.[41] 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 5 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 5 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 Pharmacokinetics).

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, weanling 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 postimplantation 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 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 months, 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.[42] 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.[43,44] 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 pediatric patients 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%).

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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).

DOSAGE AND ADMINISTRATION:

Treatment of Initial Genital Herpes: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg (two 200 mg capsules, one 400 mg tablet, or two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules, two 400 mg tablets, one 800 mg tablet, or four teaspoonfuls [20 mL] suspension) every 4 hours orally, 5 times daily for 7 to 10 days.

Treatment of Chickenpox: ***Children (2 years of age and older):*** 20 mg/kg **per dose** orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73 m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	> 10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	> 10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.[47,48]

HOW SUPPLIED: ZOVIRAX Capsules (blue, opaque cap and body) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200" – Bottle of 100 (NDC 0173-0991-55), and unit dose pack of 100 (NDC 0173-0991-56). Store at 15° to 25°C (59° to 77°F) and protect from moisture.

ZOVIRAX Tablets (light blue, oval) containing 800 mg acyclovir and engraved with "ZOVIRAX 800" – Bottle of 100 (NDC 0173-0945-55) and unit dose pack of 100 (NDC 0173-0945-56). Store at 15° to 25°C (59° to

Hemodialysis: For patients who [illegible] half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

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ZOVIRAX Tablets (white, shield-shaped) containing 400 mg acyclovir and engraved with "ZOVIRAX" on one side and a triangle on the other side – Bottle of 100 (NDC 0173-0949-55). Store at 15° to 25°C (59° to 77°F) and protect from moisture.

ZOVIRAX Suspension (off-white, banana-flavored) containing 200 mg acyclovir in each teaspoonful (5 mL) – Bottle of 1 pint (473 mL) (NDC 0173-0953-96). Store at 15° to 25°C (59° to 77°F).

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U.S. Patent No. 4,199,574

GlaxoWellcome

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May 1996 RL-316

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018604/S014

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: December 16, 1996

To: 18-604 (SLR-014)

From: Therese A. Cvetkovich, M.D. /S/ 12/16/96
Medical Officer, DAVDP

Subject: Approval of NDA 18-604 Supplement -014

Through: Rachel Behrman, M.D., M.P.H
Team Leader, DAVDP /S/

The revision in this Changes Being Effected supplement provides for the addition of a Pediatric Use statement in the "Precautions" section. This addition is found to be acceptable.

cc:
DIV file
original file
HFD-530/D.Staten
HFD-530/T.Cvetkovich

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CDER PEDIATRIC USE SUPPLEMENT

NDA / NUMBER:	SUPPLEMENT / NUMBER:	LETTER DATE:
18604	Draft SLR- 014	9-27-96

SUPPLEMENT SUBMITTED UNDER 21 CFR 201.57 (f) (9)
(See back of form for complete definitions.)

PLEASE CHECK ALL THAT APPLY:

- ☐ (ii)
- ☐ (iii)
- ☐ (iv)
- ☐ (v)
- ☒ (vi)
- ☐ (vii)
- ☐ (viii)

CLINICAL EFFICACY TRIALS:

- ☐ Raw data / Study Analyses
- ☐ Literature

HARMACOKINETICS AND / OR PHARMACODYNAMICS:

- ☐ Raw data / Study Analyses
- ☐ Literature

SAFETY / ADVERSE REACTIONS:

Clinical Efficacy Trials:

- ☐ Raw data / Study Analyses
- ☐ Literature

Anecdotal Reports:

- ☐ MedWatch / Form 3500
- ☐ Literature

OTHER:

PROJECT MANAGER: /S/ _____ DATE: 10/4/96

PLEASE COMPLETE THIS FORM AND RETURN TOP COPY TO THE DOCUMENT ROOM FOR DATA ENTRY.

FORM FDA 3437 (06/95) EF

15.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date OCT 10 1996

NDA No. 18-604

David M. Cocchetto, Ph.D.
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Attention: David M. Cocchetto, Ph.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Zovirax (acyclovir) Ointment 5%

NDA Number: 18-604

Supplement Number: S-014

Date of Supplement: September 27, 1996

Date of Receipt: September 30, 1996

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 254
5516 Nicholson Lane, HFD-530
Rockville, MD 20857

Sincerely yours,

/S/

Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products
Center for Drug Evaluation and Research

FORM FDA 3217e (3/94)

ORIGINAL

GlaxoWellcome

September 27, 1996

NDA NO. 18604 REF. NO. 2.0U

NDA SUPPL FOR Draft

Donna J. Freeman, M.D.
Acting Director
Division of Antiviral Drug Products
Food and Drug Administration, HFD-530
ATTN: DOCUMENT CONTROL ROOM
Fourth Floor
9201 Corporate Blvd.
Rockville, MD 20850

Noted
10/21/96
/S/

Re: NDA 18-604; ZOVIRAX® (acyclovir) Ointment 5%;
SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED;
Revision of Labeling on Pediatric Use

Dear Dr. Freeman:

Reference is made to NDA 18-604 as approved by the Food and Drug Administration on March 29, 1982. Please also refer to the final rule governing the "Pediatric Use" subsection of prescription drug labeling, as published in the Federal Register on December 13, 1994. The purpose of this letter is to inform you of our effort to assure compliance with this revised regulation.

Zovirax® Ointment 5% is indicated in the management of initial herpes genitalis and in limited nonlife-threatening mucocutaneous *Herpes simplex* virus infections in immunocompromised patients. Subsequent to the issuance of the final pediatric rule, we have reviewed the labeling for Zovirax® Ointment 5% and have found that the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for this drug product. Thus, in accordance with 21 CFR (f)(9)(vi), we have amended this labeling by the addition of a Pediatric Use statement in the "Precautions" section which reads: "Safety and effectiveness in pediatric patients have not been established.".

A copy of the draft revised labeling showing the above noted change is included in Attachment 1. A copy of the revised draft labeling is included in Attachment 2. This change is being implemented in advance of the December 13, 1996 deadline, and samples of the final printed labeling will be submitted in the Annual Report to this NDA.

Glaxo Wellcome Research and Development

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Research Triangle Park
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919 248 2100

A Division of
Glaxo Wellcome Inc.

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☒ N.A.L. ☐ MEMO

/S/ 10/22/96

CSO INITIALS DATE

In addition to these editorial changes in labeling, we wish to inform the Division of the following results of our review of this labeling:

- The currently approved labeling contains the identities of each excipient in the drug product.
- The CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the labeling are an accurate reflection of the safety profile of this drug product.
- The ongoing monitoring of postmarketing reports of adverse experiences and resultant periodic reports to this NDA (per 21 CFR 314.80) is our ongoing means of identifying and reporting any significant change in the type or frequency of adverse experiences with this drug product.

Based on these actions and the conclusions of our review, we believe that we are in compliance with the final rule on the Pediatric Use subsection.

This submission is provided in duplicate. Please contact me at (919)-483-5127 for any matters regarding this submission. Thank you.

Sincerely,

David M. Cocchetto

David M. Cocchetto, Ph.D.
Director, Regulatory Affairs

Attachments 1-2