CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-872

Name: Acyclovir Capsules, 200 mg

Sponsor: ESI Lederle, Inc.

Approval Date: April 22, 1997

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APPLICATION NUMBER:

ANDA 74-872

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APPLICATION NUMBER:

ANDA 74-872

APPROVAL LETTER

ANDA 74-872

ESI Lederle, Inc.
Attention: Nicholas C. Tantillo
401 North Middletown Road
Pearl River, NY 10965-1299

Dear Sir:

This is in reference to your abbreviated new drug application dated March 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Capsules, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Capsules, 200 mg of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gordon R Johnston for

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

4-22-97

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ON ORIGINAL

cc: ANDA 74-872
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HFD-610/JPhillips
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Endorsements:

HFD-645/RBrown/4/9/97 R Brown 4/10/97

HFD-613/JWhite/4/9/97 J. White 4/11/97

HFD-647/JSimmons/GSmith/4/9/97 4-11-97

HFD-671/TAmes/4/9/97 4/14/97

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F/T by pah/4/10/97

this is a Category II Acyclovir approval.
a TA letter was issued on 3/27/97. the
firm has not amended the application.
Recommend: approve on 4/22/97
Robert Rudolph
4/15/97

Acceptable
EES dated 3/27/97.
J. Phillips 4/18/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-872

TENTATIVE APPROVAL LETTER

ANDA 74-872

ESI Lederle, Inc.
Attention: Nicholas C. Tantillo
401 North Middletown Road
Pearl River, NY 10965-1299

Dear Mr. Tantillo:

This is in reference to your abbreviated new drug application dated March 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

Reference is also made to your amendments dated November 26, 1996, and February 12, and March 20, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly your application is **tentatively approved.** This determination is contingent upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug products) and is, therefore, subject to change on the basis of new information that may come to our attention. The reference listed drug product upon which you based your application is subject to a period of patent protection and, therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355 (j)(4)(B)(ii), until the period has expired, i.e., April 22, 1997.

Any significant change in the conditions outlined in this abbreviated application requires Agency approval before the change may be made effective.

Prior to the issuance of a final approval letter by the Agency your product is <u>not</u> to be deemed approved for marketing under 21 U.S.C. 355 and will not to be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list, published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to April 22, 1997, you should amend your application accordingly.

Should you have further questions, contact Mr. Timothy W. Ames, Project Manager, at (301) 594-0309.

The introduction or delivery for introduction into interstate commerce of the drug before the effective approval date is prohibited under 21 U.S.C. 311(d).

Sincerely yours,

Gordon R. Johnston for 3/27/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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Endorsements:

HFD-645/RBrown/3/5/97 3/11/97

HFD-613/JWhite/3/5/97 3/11/97 3/12/97

HFD-647/JSimmons/3/5/97 3/11/97

HFD-671/TAmes/ 3/12/97 3/24/97

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TYPE OF LETTER: TENTATIVE APPROVAL

3/27/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-872

APPROVED LABELING

Acyclovir Capsules
CI 4845

ESI LEDERLE™

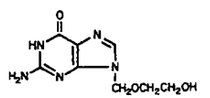
Acyclovir Capsules

DESCRIPTION

Acyclovir is an antiviral drug. Acyclovir capsules are formulated for oral administration.

Each capsule of acyclovir contains 200 mg of acyclovir and the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, and sodium starch glycolate. The capsule shells contain gelatin, titanium dioxide and black ink, which contains black iron oxide, blue #2 aluminum lake, red #40 aluminum lake, blue #1 aluminum lake and D&C yellow #10 aluminum lake.

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:



$C_8H_{11}N_5O_3$ M.W. 225.21

Acyclovir is a white to off-white, crystalline powder with a molecular weight of 225.21, 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.[5,5] 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 mcg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

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 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤ 0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤ 2.2 mcg/mL and 50% of all isolates were sensitive to ≤ 0.7 mcg/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.[11-15] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/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 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/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 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/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]

APR 22 1997

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, acyclovir 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 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.3 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir 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 mcg/mL (0.66 to 1.8 mcg/mL) and 0.55 mcg/mL (0.14 to 1.1 mcg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m², in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

In a reported single-dose bioavailability/bioequivalence study in 24 volunteers, one acyclovir 800 mg tablet was demonstrated to be bioequivalent to four acyclovir 200 mg capsules.

In a multiple-dose crossover study where 23 volunteers received acyclovir 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 mcg/mL, 1.21 and 0.63 mcg/mL, and 1.61 and 0.83 mcg/mL for the 200, 400, and 800 mg dosage regimens, respectively.

In another study, 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

Acyclovir capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir capsules 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 acyclovir 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 acyclovir 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 involvement, urinary retention, or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous acyclovir.

Recurrent Episodes:

Double-blind, placebo-controlled studies[6,26-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir 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 acyclovir 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 one year of therapy, the frequency and severity of the patient's genital herpes infection should be reevaluated to assess the need for continuation of acyclovir therapy. Reevaluation will usually require a trial off acyclovir 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 acyclovir 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 reevaluation.

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 acyclovir and 94 to placebo), acyclovir (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 acyclovir and 43 to placebo), acyclovir (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, acyclovir 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 acyclovir reduced the maximum number of lesions (336 vs. greater than 500; lesions beyond 500 were not counted). Treatment with acyclovir 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 acyclovir 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 acyclovir 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 acyclovir 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 acyclovir 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 one month following treatment in patients receiving acyclovir 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

Acyclovir capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS

Acyclovir capsules are intended for oral ingestion only.

PRECAUTIONS

General

Acyclovir 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 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 acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

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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 acyclovir, 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. Acyclovir capsules are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir 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 acyclovir per day for six 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 acyclovir per day for one 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 acyclovir 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 acyclovir would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions

Coadministration 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 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**).

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 one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one 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.

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Nursing Mothers

Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir 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 acyclovir 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 acyclovir 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 acyclovir (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 acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for one 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 acyclovir 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 acyclovir 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 acyclovir 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 acyclovir, 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) every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease

400 mg (two 200 mg capsules) 2 times daily for up to 12 months, followed by reevaluation. 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) 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) 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/1.73m²)	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

Acyclovir capsules for oral administration are supplied as follows:
200 mg—white, hard shell capsule imprinted "511" on the cap and "ACYCLOVIR" and "200 mg" on the body, available as:

NDC 59911-5831-1—Bottle of 100
NDC 59911-5831-3—Bottle of 100 with CRC
NDC 59911-5831-2—Bottle of 1000

Caution: Federal law prohibits dispensing without prescription.

DISPENSE IN A TIGHT, LIGHT-RESISTANT CONTAINER WITH A CHILD-RESISTANT CLOSURE. PROTECT FROM LIGHT AND MOISTURE.

STORE BETWEEN 15°-25°C (59°-77°F).

REFERENCES

1. O'Brien JJ, Campoli-Richards DM. Acyclovir—an updated review of its antiviral activity, pharmacokinetic properties, and therapeutic efficacy. *Drugs.* 1989;37:233-309.
2. Littler E, Zeuthen J, McBride AA, et al. Identification of an Epstein-Barr virus-coded thymidine kinase. *EMBO J.* 1986;5:1959-1966.
3. Miller WH, Miller RL. Phosphorylation of acyclovir (acycloguanosine) monophosphate by GMP kinase. *J Biol Chem.* 1980;255:7204-7207.
4. Furman PA, St Clair MH, Fyfe JA, et al. Inhibition of herpes simplex virus-induced DNA polymerase activity and viral DNA replication by 9-(2-hydroxyethoxymethyl)guanine and its triphosphate. *J Virol.* 1979;32:72-77.
5. Derse D, Cheng YC, Furman PA, et al. Inhibition of purified human and herpes simplex virus-induced DNA polymerases by 9-(2-hydroxyethoxymethyl)guanine triphosphate: effects on primer-template function. *J Biol Chem.* 1981;256:11447-11451.
6. McGuirt PV, Shaw JE, Elion GB, et al. Identification of small DNA fragments synthesized in herpes simplex virus-infected cells in the presence of acyclovir. *Antimicrob Agents Chemother.* 1984;25:507-509.
7. Barry DW, Blum MR. Antiviral drugs: acyclovir. In: Turner P, Shand DG, eds. *Recent Advances in Clinical Pharmacology,* ed 3. New York: Churchill Livingstone; 1983:chap 4.
8. DeClercq E. Comparative efficacy of antiherpes drugs in different cell lines. *Antimicrob Agents Chemother.* 1982;21:661-663.
9. McLaren C, Ellis MN, Hunter GA. A colorimetric assay for the measurement of the sensitivity of herpes simplex viruses to antiviral agents. *Antiviral Res.* 1983;3:223-234.
10. Barry DW, Nusinoff-Lehrman S. Viral resistance in clinical practice: summary of five years experience with acyclovir. In: Kono R, Nakajima A, eds. *Herpes Viruses and Virus Chemotherapy (Ex Med Int Congr Ser 667).* New York: *Excerpta Medica ;* 1985:269-270.
11. Dekker C, Ellis MN, McLaren C, et al. Virus resistance in clinical practice. *J Antimicrob Chemother.* 1983;12(suppl B):137-152.
12. Sibrack CD, Gutman LT, Wilfert CM, et al. Pathogenicity of acyclovir-resistant herpes simplex virus type 1 from an immunodeficient child. *J Infect Dis.* 1982;146:673-682.
13. Crumpacker CS, Schnipper LE, Marlowe SI, et al. Resistance to antiviral drugs of herpes simplex virus isolated from a patient treated with acyclovir. *N Engl J Med.* 1982;306:343-346.
14. Wade JC, Newton B, McLaren C, et al. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: a double-blind trial. *Ann Intern Med.* 1982;96:265-269.
15. Burns WH, Saral R, Santos GW, et al. Isolation and characterization of resistant herpes simplex virus after acyclovir therapy. *Lancet.* 1982;1:421-423.
16. Straus SE, Takiff HE, Seidlin M, et al. Suppression of frequently recurring genital herpes: a placebo-controlled double-blind trial of oral acyclovir. *N Engl J Med.* 1984;310:1545-1550.
17. Collins P. Viral sensitivity following the introduction of acyclovir. *Am J Med.* 1988;85:129-134.
18. Erlich KS, Mills J, Chatis P, et al. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. *N Engl J Med.* 1989;320:293-296.
19. Hill EL, Ellis MN, Barry DW. In: *28th Intersci Conf on Antimicrob Agents Chemother.* Los Angeles: 1988, Abst. No. 0840:260.
20. Ellis MN, Keller PM, Fyfe JA, et al. Clinical isolates of herpes simplex virus type 2 that induces thymidine kinase with alterated substrate specificity. *Antimicrob Agents Chemother.* 1987;31:1117-1125.
21. Collins P, Larder BA, Oliver NM, et al. Characterization of a DNA polymerase mutant of herpes simplex virus from a severely immunocompromised patient receiving acyclovir. *J Gen Virol.* 1989;70:375-382.
22. Field HJ, Darby G, Wildy P. Isolation and characterization of acyclovir-resistant mutants of herpes simplex virus. *J Gen Virol.* 1980;49:115-124.
23. Bryson YJ, Dillon M, Lovett M, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir: a randomized double-blind controlled trial in normal subjects. *N Engl J Med.* 1983;308:916-921.
24. Mertz GJ, Critchlow CW, Benedetti J, et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. *JAMA.* 1984;252:1147-1151.
25. Nilsen AE, Aasen T, Halsos AM, et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet.* 1982;2:571-573.
26. Douglas JM, Critchlow C, Benedetti J, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. *N Engl J Med.* 1984;310:1551-1556.
27. Mindel A, Weller IV, Faherty A, et al. Prophylactic oral acyclovir in recurrent genital herpes. *Lancet.* 1984;2:57-59.
28. Mattison HR, Reichman RC, Benedetti J, et al. Double-blind, placebo-controlled trial comparing long-term suppressive with short-term oral acyclovir therapy for management of recurrent genital herpes. *Am J Med.* 1988;85(suppl 2A):20-25.
29. Straus SE, Croen KD, Sawyer MH, et al. Acyclovir suppression of frequently recurring genital herpes. *JAMA.* 1988;260:2227-2230.
30. Mertz GJ, Eron L, Kaufman R, et al. The Acyclovir Study Group. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med.* 1988;85(suppl 2A):14-19.
31. Goldberg LH, Kaufman R, Conant MA, et al. Episodic twice daily treatment for recurrent genital herpes. *Am J Med.* 1988:85:10-13.
32. Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir: a controlled trial. *JAMA.* 1984;251:2103-2107.
33. Huff JC, Bean B, Balfour HH Jr, et al. Therapy of herpes zoster with oral acyclovir. *Am J Med.* 1988;85(suppl 2A): 85-89.
34. Morton P, Thompson AN. Oral acyclovir in the treatment of herpes zoster: a general practice. *NZ Med J.* 1989;102:93-95.
35. Balfour HH Jr, Kelly JM, Suarez CS, et al. Acyclovir treatment of varicella in otherwise healthy children. *J Pediatr.* 1990;116:633-639.
36. Dunkle LM, Arvin AM, Whitley RJ, et al. A controlled trial of acyclovir for chickenpox in normal children. *N Engl J Med.* 1991;325:1539-1544.
37. Balfour HH Jr, Rotbart HA, Feldman S, et al. Acyclovir treatment of varicella in otherwise healthy adolescents. *J Pediatr.* 1992;120:627-633.
38. Rotbart HA, Levin MJ, Hayward AR, Immune responses to varicella zoster virus infections in healthy children. *J Infect Dis.* 1993;167:195-199.
39. Naib ZM, Nahmias AJ, Josey WE, et al. Relation of cytohistopathology of genital herpesvirus infection to cervical anaplasia. *Cancer Res.* 1973;33:1452-1463.
40. Douglas JM, David LG, Remington ML, et al. A double-blind, placebo-controlled trial of the effect of chronically administered oral acyclovir on sperm production in man with frequently recurrent genital herpes. *J Infect Dis.* 1988;157:588-593.
41. Laskin OL, deMiranda P, King DH, et al. Effects of probenecid on the pharmacokinetics and elimination of acyclovir in humans. *Antimicrob Agents Chemother.* 1982;21:804-807.
42. Stahlmann R, Klug S, Lewandowski C, et al. Teratogenicity of acyclovir in rats. *Infection.* 1987;15:261-262.
43. Lau RJ, Emery MG, Galinsky RE, et al. Unexpected accumulation of acyclovir in breast milk with estimate of infant exposure. *Obstet Gynecol.* 1987;69:468-471.
44. Meyer LJ, deMiranda P, Sheth N, et al. Acyclovir in human breast milk. *Am J Obstet Gynecol.* 1988;158:586-588.
45. Laskin OL, Longstreth JA, Whelton A, et al. Effect of renal failure on the pharmacokinetics of acyclovir. *Am J Med.* 1982;73:197-201.
46. Krasny HC, Liao SH, deMiranda P, et al. Influence of hemodialysis on acyclovir pharmacokinetics in patients with chronic renal failure. *Am J Med.* 1982;73:202-204.
47. Boelart J, Schurgers M, Daneels R, et al. Multiple dose pharmacokinetics of intravenous acyclovir in patients on continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother.* 1987;20:69-76.
48. Shah GM, Winer RL, Krasny HC. Acyclovir pharmacokinetics in a patient on continuous ambulatory peritoneal dialysis. *Am J Kidney Dis.* 1986;7:507-510.

ESI Lederle Inc.
Philadelphia, PA 19101
CI 4845 Issued February 6, 1997 Printed in USA

NDA # 19-893

NDC 59911-5831-3

ESI LEDERLE

Acyclovir Capsules

200 mg

100 Capsules

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains acyclovir, USP 200 mg.

Usual Dosage: See package circular for full prescribing information.

Store between 15°-25° C (59°-77° F).

Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

ESI Lederle Inc.
Philadelphia, PA 19101
U5831-03

SAMPLE 90% MAGNIFICATION
N 3 00000-0000-0

Control No.

Exp. Date

APR 22 1997

NDC 59911-5831-1

ESI LEDERLE

Acyclovir Capsules

200 mg

100 Capsules

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains acyclovir, USP 200 mg.

Usual Dosage: See package circular for full prescribing information.

This is a bulk container not intended for household use.

Store between 15°-25° C (59°-77° F).

Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

ESI Lederle Inc.
Philadelphia, PA 19101 U5831-01

SAMPLE 90% MAGNIFICATION
N 3 00000-0000-0

Control No.

Exp. Date

APR 22 1997

NDC 59911-5831-2

ESI LEDERLE™

Acyclovir Capsules

200 mg

1000 Capsules

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains acyclovir, USP 200 mg.

Usual Dosage: See package circular for full prescribing information.

Store between 15°-25° C (59°-77° F).

Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

ESI Lederle Inc.
Philadelphia, PA 19101

U5831-02

APR 22 1997

Control No.

Exp. Date

SAMPLE 100% MAGNIFICATION
N 3 00000-0000-0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-872

LABELING REVIEWS

1.1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: August 15, 1996

Date of Submission: March 27, 1996

Primary Reviewer: Jacqueline White, Pharm.D.

ANDA Number: 74-872 Review Cycle: First

Applicant's Name [as seen on 356(h)]: ESI Lederle Inc.

Manufacturer's Name (If different than applicant):

Proprietary Name: None

Established Name: Acyclovir Capsules, 200 mg

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

[NOTE: These deficiencies can be located on the x-drive as detailed in notes from Ted Sherwood regarding the New X-Drive]

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER: 100s and 1000s

   a. Delete "[redacted]" from your storage recommendations.

   b. Revise the Usual Dosage statement to read:

      For indications, dosage, precautions, etc., see package insert.

2. INSERT:

   a. DESCRIPTION

      i. To be in accord with USP 23, make the following revisions in the last paragraph:

...a white to off-white crystalline powder with a molecular weight of 225.21, and ...

b. CLINICAL PHARMACOLOGY

i. Mechanism of Antiviral Effects

Delete the extra spaces in the last paragraph.

... phosphorylation in cytomegalovirus-infected cells ...

ii. Pharmacokinetics

If you do not plan to combine this insert to include the information for your proposed Acyclovir Tablets 200 mg, the subject of ANDA 74-834, delete the third paragraph ("A single oral dose"). However, since the package insert does make reference to a 200 mg dose (DOSAGE AND ADMINISTRATION), we encourage you to combine the insert for both the capules and the tablets, as does the reference listed drug, Zovirax.

c. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, Impairment of Fertility, paragraph 1 (last sentence) -

...lower dosing schedules (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

ii. Pediatric Use

...in pediatric patients less...

d. HOW SUPPLIED

Include a "Dispense in" statement, as seen on the container labels, (i.e., "Dispense in a tight, light-resistant container...").

Revise your container labels and package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling and final printed container labels. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert labeling only for tentative approval.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

NOTE TO THE CHEMIST

1. Inactive ingredients:

   Is the firm's list of inactive ingredients listed in the DESCRIPTION section consistent with their components statements?

   [The jackets/volumes containing this information have been signed out to the chemist reviewer].

2. Container/Closure:

   a. In the HOW SUPPLIED section the firm has indicated that they plan to supply their drug product as follows:
      100's - non child-resistant cap
      100's - child resistant
      1000's - non child resistant cap
      Do you concur?

   b. Does the firm's container protect this drug product from light?

   [The jackets/volumes containing this information are signed out to the chemist reviewer].

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			

Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.			
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [See NOTE TO THE CHEMIST]			
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	

Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients differ].	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? [See NOTE TO THE CHEMIST].			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. [See comment under DESCRIPTION].	x		

Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [pending]			
Insert labeling references a food effect or a no-effect? If so, was a food study done? [See FTR].			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. [See FTR].	x		
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. [See FTR].			

FOR THE RECORD:

1. Labeling review was based on the labeling of ZOVIRAX® (Burroughs Wellcome: Approved 9/7/95; Revised 5/95).

2. Dispensing recommendations:

   USP: Not USP [However, USP packaging and storage for acyclovir is "Preserve in tight containers].
   NDA: Tight, light resistant container
   ANDA:Tight, light resistant container with a child resistant closure.

   Storage recommendations:

   NDA: Store at 15° to 25°C (59° to 77°F) and protect from moisture.
   ANDA: Store at controlled room temperature 15° - 25°C (59° - 77°F). Protect from light and moisture. [See comment under CONTAINER].

3. Patents/Exclusivity

   RLD patent expires 4/22/97. [Approved drug products; 16 ed.] Lederle's patent and certification and exclusivity statement accurately acknowledge this patent.

4. The firm's capsule imprints described in the HOW SUPPLIED section is consistent with the firm's finished dosage form capsule description. [Vol. B1.4, p.2293]

5. Components/Composition

   The jackets/volumes containing this information are signed out to the chemist reviewer.
   [See NOTE TO THE CHEMSIT].

6. Container/Closure

The jackets/volumes containing this information are signed out to the chemist reviewer.
[See NOTE TO THE CHEMIST].

7. Zovirax® by Burroughs Wellcome, for oral use is available as:

200 mg capsule - 100s & unit dose 100s
200 mg caplet - 100s & unit dose 100s
400 mg tablet - 100s
800 mg tablets - 100s & unit dose 100s
200 mg/5 mL suspension - Bottle of 1 pint (473 mL)

This ANDA is for a 200 mg capsule packaged in 100s and 1000s.

[ ]

8. In the Pharmacokinetics subsection of CLINICAL PHARMACOLOGY the paragraph that compares the bioavailability of tablets and capsules to the suspension and/or solution has been deleted. This ANDA is for the capsule formulation only. The firm has appropriately left out other information concerning tablets and suspension. This is consistent with other ANDA's for acyclovir capsules insert labeling.

9. The following information is from a previous review/reveiwer FTR regarding this ANDA or acyclovir.

   a. The insert mentions no food effect -

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

      Previous reviews of other BE studies have shown that food increases the AUC and Cmax by as much as 40 to 60% for both generic and reference product. Both these parameters were increased after food for the studies submitted to this ANDA as well. The DAVDP has been made aware of the food effect findings and a recommendation to change the Zovirax® labeling has been made.

b. It was decided in a meeting between OGD and DAVDP that the issue of generic firms participation in the Pregnancy Exposure Registry should be based on BW's decision. This decision was forwarded to the Division of Antiviral Drug Products on 5/1/96 - that generic products not be allowed to refer to the pregnancy registry.

Reviewer 10/10/96
Date

Acting Team Leader,
Labeling Review Branch 10/10/96
Date

cc: ANDA 74-872
Division File
HFD-613/JWhite/AVezza (no cc)
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review

APPEARS THIS WAY
ON ORIGINAL