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Approval Package for:

APPLICATION NUMBER:

ANDA 74-872

Name: Acyclovir Capsules, 200 mg

Sponsor: ESI Lederle, Inc.

Approval Date: April 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 74-872
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HFD-610/JPhillips
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HFD-92

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

LEDERLE™

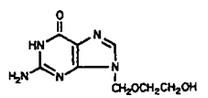
Acyclovir Capsules

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.[5,6] 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 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]

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[16,26-32] 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.

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 5 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 nonstandard 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.

CODE INSERTED HERE

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).

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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)
njg/9/23/96/x:\new\...Lederle\...\74872na1.l
review

APPEARS THIS WAY
ON ORIGINAL

TENTATIVE APPROVAL SUMMARY

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

ANDA Number: 74-872

Date of Submission: November 26, 1996

Applicant's Name: ESI Lederle Inc.

Established Name: Acyclovir Capsules, 200 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?
- insert is printers proof [note: the firm refers to their insert labeling as final print]
- ~9 copies in blue volume & the other copies in the red volume

Container Labels: Satisfactory in final print as of 11/26/96 submission 100s and 1000s.

Carton Labeling: n/a

Unit Dose Blister Label: n/a

Unit Dose Carton Label: n/a

Professional Package Insert Labeling: Satisfactory in printers proof as of 11/26/96

Patient Package Insert Labeling: n/a

Auxiliary Labeling: n/a

Revisions needed post-approval:
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 ...

ii. Include titanium dioxide and the dyes of the imprinting ink in the list of inactive ingredients.

b. CLINICAL PHARMACOLOGY (Pharmacokinetics)

i. Third paragraph -

A). Delete the first sentence, "[redacted] ...[redacted] ".

B). Revise the remaining sentence to read, "In a reported single-dose ...".

ii. Fifth paragraph -

Delete the text "[redacted]".

c. ADVERSE REACTIONS (Observed During Clinical Practice)

Nervous

... paresthesia, seizure, somnolence ...

[Add "seizure]

d. OVERDOSAGE

Revise the print of the section heading "OVERDOSAGE" to be consistent with your other section headings.

e. DOSAGE AND AMINISTRATION

In the first sentence of the first four subsections, include the number of capsules per dose in parenthesis following the recommended dose, as seen in the innovator's labeling.

[i.e., 200 mg (one 200 mg capsule) every 4 ...]

NOTE: The firm plans to combine their insert labeling for their capsule and tablet drug products post-approval.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Zovirax Capsules

NDA Number: 18828

NDA Drug Name: acyclovir capsules

NDA Firm: Glaxo Welcome Inc.

Date of Approval of NDA Insert and supplement #: Revised insert labeling for NDA 18828/S-019, approved 1/8/97 and revised 5/96.

Has this been verified by the MIS system for the NDA?
Yes
Was this approval based upon an OGD labeling guidance? No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: Acyclovir capsules
Basis of Approval for the Carton Labeling: n/a

Other Comments:

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 from RLD].	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 approval summary under future revisions & FTR]			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)	x		
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)			
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® (Glaxo Welcome Inc: Revised insert labeling for NDA 18828/S-019, approved 1/8/97 and revised 5/96.

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 between 15° - 25°C (59° - 77°F). Protect from light and moisture.

3. Patents/Exclusivity

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

4. The firm revised the capsule imprints described in the HOW SUPPLIED section and they are consistent with the firm's finished dosage form capsule description. [Vol. 1.1, 11/26/96 submission]

5. Components/Composition

The list of inactive ingredients in the DESCRIPTION section is consistent with the Components and Composition section. However, see future request under the approval summary. [Vol. B1.2, p.1636 & 1804]

6. Container/Closure
100s - CRC
100s - nonCRC
1000s- nonCRC
[Vol. B1.3, section XIV]

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 should be deleted; [to be consistent with other ANDA's for acyclovir capsules insert labeling]. This ANDA is for the capsule formulation only.
NOTE: The firm plans to combine their insert labeling for both thier capsule and tablet drug product post-approval.

9. Bioequivalence/Pharmacokinetic data

-Both fasting & fed studies were done. See Bio. review dated 10/3/96.
-Fasting study
    -ANDA & RLD C_{max} & t_{max} were comparable to each other. The C_{max} was comparable to one of the RLD studies found in the insert labeling. Steady state plasma levels were reported in the RLD insert, however neither t_{max} nor $t_{1/2}$ were listed. ANDA & RLD t_{max} & $t_{1/2}$ were comparable to each other.
-Food study
    -It was reported that food appears to increase t_{max} and decrease AUC, C_{max} & $t_{1/2}$.
    -The RLD insert reported that the influence of food on the absorption was not apparent. See FTR comment below.
-Bio. acceptable letter-out date 10/3/96

10. 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.

Date of Review: 1/7/97

Date of Submission: 11/26/96 [container-FPL, insert-printer's proof]

Primary Reviewer:
Jacqueline White, Pharm.D. Date: 1/17/97

Secondary Reviewer: Date: 1/17/97

Team Leader: Date: 1/21/97

cc:

ANDA: 74872
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes/JGrace/ (no cc)
njg/1/17/97/x:\new\...Lederle...74872tap.1
Review

APPROVAL SUMMARY

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

ANDA Number: 74-872

Date of Submission: February 12, 1997

Applicant's Name: ESI Lederle Inc.

Established Name: Acyclovir Capsules, 200 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?
- 12 copies FPL insert labeling
- 12 copies FPL container labels/100s
- 9 copies FPL contaienr labels/1000s

Container Labels: Satisfactory in final print as of 11/26/96 submission 100s and 1000s.

Professional Package Insert Labeling: Satisfactory in FPL as of 2/12/97

NOTE: The firm plans to combine their insert labeling for their capsule and tablet drug products post-approval.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Zovirax Capsules

NDA Number: 18828

NDA Drug Name: acyclovir capsules

NDA Firm: Glaxo Wellcome Inc.

Date of Approval of NDA Insert and supplement #: Revised insert labeling for NDA 18828/S-019, approved 1/8/97 and revised 5/96.

Has this been verified by the MIS system for the NDA?
Yes
Was this approval based upon an OGD labeling guidance? No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels: Acyclovir capsules
Basis of Approval for the Carton Labeling: n/a

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?	X		
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 from RLD].	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 NOTES TO THE CHEMIST]			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)	x		
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)			
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® (Glaxo Welcome Inc: Revised insert labeling for NDA 18828/S-019, approved 1/8/97 and revised 5/96.

2. Dispensing recommendations:

   PF[#4,July-Aug.1996]: Preserve in tight containers.
   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:

   PF[#4,July-Aug.1996]: Preserve in tight containers.
   NDA: Store at 15° to 25°C (59° to 77°F) and protect from moisture.
   ANDA: Store between 15° - 25°C (59° - 77°F). Protect from light and moisture.

3. Patents/Exclusivity

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

4. The firm revised the capsule imprints described in the HOW SUPPLIED section and they are consistent with the firm's finished dosage form capsule description.
[Vol. 1.1, 11/26/96 submission]
[See NOTES TO THE CHEMIST]

5. Components/Composition

The list of inactive ingredients in the DESCRIPTION section are NOT consistent with the Components and Composition section.
[Vol. B1.2, p.1636 & 1804]
[See NOTES TO THE CHEMIST]

6. Container/Closure
100s - CRC
100s - nonCRC
1000s- nonCRC
[Vol. B1.3, section XIV]

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 should be deleted; [to be consistent with other ANDA's for acyclovir capsules insert labeling]. This ANDA is for the capsule formulation only.
NOTE: The firm plans to combine their insert labeling for both thier capsule and tablet drug product post-approval.

9. Bioequivalence/Pharmacokinetic data

-Both fasting & fed studies were done. See Bio. review dated 10/3/96.
-Fasting study
    -ANDA & RLD C_{max} & t_{max} were comparable to each other. The C_{max} was comparable to one of the RLD studies found in the insert labeling. Steady state plasma levels were reported in the RLD insert, however neither t_{max} nor $t_{1/2}$ were listed. ANDA & RLD t_{max} & $t_{1/2}$ were comparable to each other.
-Food study

-It was reported that food appears to increase t_{max} and decrease AUC, C_{max} & $t_{1/2}$.
-The RLD insert reported that the influence of food on the absorption was not apparent. See FTR comment below.
-Bio. acceptable letter-out date 10/3/96

10. 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.

11. The listing of inactive ingredients for the capsule imprinting ink is consistent with the updated ingredient list submitted by the firm on 3/20/97.

12. The chemist confirms that the imprints listed in HOW SUPPLIED are correct (3/20/97).

Date of Submission: 2/12/97

Primary Reviewer:
Jacqueline White, Pharm.D. — Date: 3/27/97

Team Leader: — Date: 3/27/97

cc:

ANDA 74-872
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes/JGrace/ (no cc)
njg/3/27/97/x:\new\...Lederle...74872ap.1
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-872

CHEMISTRY REVIEWS

1. CHEMIST'S REVIEW NO. 1

2. ANDA 74-872

3. NAME AND ADDRESS OF APPLICANT
ESI Lederle, Inc.
401 North Middletown Road
Pearl River, NY 10965-1299

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Burroughs Wellcome's ZOVIRAX®
(NDA 18-828). Patent certification and exclusivity statement are provided (pp. 007-008).

Final approval date is January 25, 1985.

U.S. Patent No. 4,199,574 expires April 22, 1997

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Acyclovir Capsules

7. PROPRIETARY NAME
Zovirax®

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		FDA	
Orig. submission	3/27/96	Acknowledgement letter	2/16/96
		CSO review	3/29/96
		Labeling	10/10/96
		Bioequivalency	9/30/96

10. PHARMACOLOGICAL CATEGORY
Indicated in the treatment of initial episodes and the management of recurrent episodes of genital herpes, also indicated for the treatment of herpes zoster (shingles) and chickenpox (valicella).

11. Rx or OTC
℞

12. RELATED DMF(s)
DMF #

[redacted]

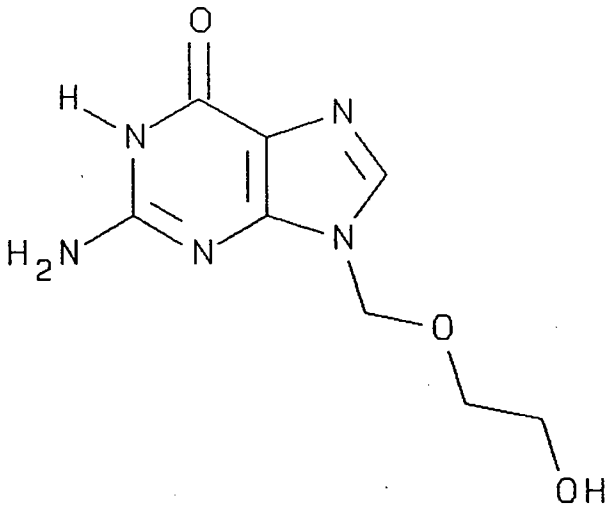
13. DOSAGE FORM
Capsules **(HARD GELATIN)**

14. STRENGTH
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

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



9-[(2-Hydroxyethoxy)methyl]guanine. CAS [59277-89-3]

Drug substance is an official USP 23 item. Drug product is not an official USP 23 items.

16. RECORDS AND REPORTS None

17. COMMENTS

a. Application contains CMC deficiencies
b. Labeling is unsatisfactory, dated 10/10/96
c. Bio is **satisfactory**, letter issued 10/3/96
d. Status of DMF ———is unsatisfactory
e. Methods validation for the drug product has been submitted to the Northeast Regional Laboratory (NY) for evaluation, 10/16/96
f. Drug Substance does not require Methods validation
g. Establishment evaluation found satisfactory, dated 7/19/96.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is **NOT APPROVABLE.** The amendment will be MAJOR.

19. REVIEWER:
Raymond Brown

DATE COMPLETED:
October 21, 1996

RBrown 10/30/96

APPEARS THIS WAY
ON ORIGINAL

Redacted 12 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

(pp. 4-15)

36. ORDER OF REVIEW
The supplemental application covered by this review was taken in order of receipt.

Yes _____ No ___X___

If no, please explain.
Assigned as part of Inter-Branch transfer to deal with workload imbalance.

cc: ANDA 74-828
Division File
FIELD COPY
DUP File

Endorsements:

HFD-645/R.Brown/10/21/96 R Brown 10/30/96
HFD-645/J.Simmons/10/22/96 J Simmons 10.30.96

F/T by pah/10/30/96
x:\new\firmsam\lederle\ltrs&rev\74828.naf

NOT APPROVABLE

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1 (pp 17-18)

1. CHEMIST'S REVIEW NO. 2

2. ANDA **74-872**

3. NAME AND ADDRESS OF APPLICANT
ESI Lederle, Inc.
401 North Middletown Road
Pearl River, NY 10965-1299

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Burroughs Wellcome's ZOVIRAX®
(NDA 18-828). Patent certification and exclusivity statement are provided (pp. 007-008).

Final approval date is January 25, 1985.

U.S. Patent No. 4,199,574 expires April 22, 1997

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Acyclovir Capsules

7. PROPRIETARY NAME
Zovirax®

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		FDA	
Orig. submission	3/27/96	Acknowledgment letter	2/16/96
		CSO review	3/29/96
		Labeling review	10/10/96
		Bioequivalency	9/30/96
		Deficiency letter	11/04/96
Amendment (major)	11/26/96	Method validation	12/13/96
		Labeling review	1/07/97

This review covers submission dated 11/26/96.

10. PHARMACOLOGICAL CATEGORY
Indicated in the treatment of initial episodes and the management of recurrent episodes of genital herpes, also indicated for the treatment of herpes zoster (shingles) and chickenpox (valicella).

11. Rx or OTC
℞

12. RELATED DMF(s)
DMF # [redacted]

[redacted]

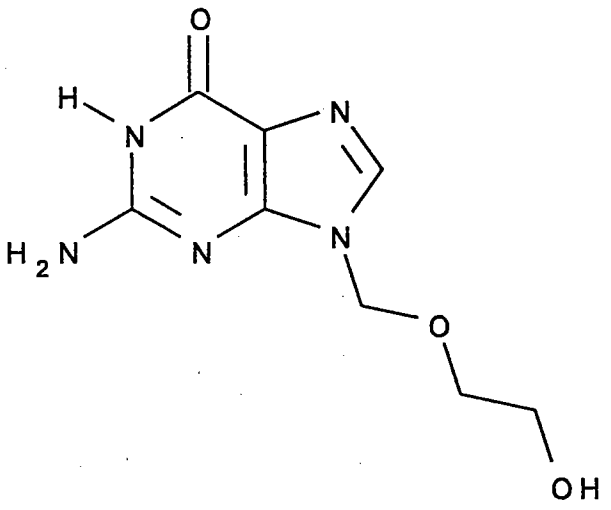
13. DOSAGE FORM
Capsules **(HARD GELATIN)**

14. STRENGTH
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

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



9-[(2-Hydroxyethoxy)methyl]guanine. CAS [59277-89-3]

Drug substance is an official USP 23 item. Drug product is not an official USP 23 item.

16. RECORDS AND REPORTS None

17. COMMENTS

a. Labeling is satisfactory, dated 1/17/97
b. Bio is **satisfactory**, letter issued 10/3/96
c. DMF ——— is satisfactory, dated 1/31/97
d. Methods validation for drug product conducted by the Northeast Regional Laboratory (NY) has been found suitable for regulatory analysis, dated 12/23/96
e. Drug Substance does not require Methods validation
f. Establishment evaluation found satisfactory, dated 7/19/96.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVE

19. REVIEWER: Raymond Brown

DATE COMPLETED: February 10, 1997

APPEARS THIS WAY
ON ORIGINAL

Redacted 13 page(s)

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CHEMISTRY REVIEW #2

(pp 4-16)

31. SAMPLES AND RESULTS **Satisfactory** -
Bulk Drug Substance - Methods validation is not required because this item is compendial.

Drug Product - Methods validation is required because Acyclovir Capsules is not USP. Methods validation package found suitable for regulatory analysis, dated 12/23/96.

32. LABELING **Satisfactory** -
See review of professional labeling conducted by Jacqueline White, concurred by John Grace, dated 1/07/97.

33. ESTABLISHMENT INSPECTION **Satisfactory** -
An **ESTABLISHMENT EVALUATION REQUEST** has been issued, dated 3/29/96, to the Division of Compliance has found the CGMP status of [redacted] and ESI Lederle, Inc. 401 North Middletown Road, Pearl River, NY **acceptable**, dated 7/19/96.

34. BIOEQUIVALENCY STATUS **Satisfactory** - (pp. 99.58-2305)
See review of two Bioequivalence studies and dissolution data conducted by S.P. Shrivastava, concurred by Keith K. Chan, Ph.D., dated 9/30/96. **SATISFACTORY letter issued 10/3/96**

35. ENVIRONMENT IMPACT CONSIDERATION (Vol. 1.9, pp. 2304-2305)
Satisfactory -

Applicant has requested a categorical exclusion from the requirements to prepare and submit an Environmental Assessment statement, under 21 CFR, Section 25.24(c)(1). Applicant states "since the drug product is not intended to be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect".

Applicant has submitted a certification of compliance which states " we are in compliance with all emission requirements set forth in permits applicable to the manufacture of Acyclovir Capsules 200 mg, at our facility in Pearl River, NY, as well as emission requirements set forth in state, and local statutes and regulations applicable to the manufacture of Acyclovir Capsules 200 mg, at our facility in Pearl River, NY.

36. ORDER OF REVIEW
The supplemental application covered by this review was taken in order of receipt.

Yes _____ No ____X_____

If no, please explain.

Assigned as part of Inter-Branch transfer to deal with workload imbalance.

cc: ANDA 74-872
Division File
FIELD COPY

Endorsements:

HFD-645/R.Brown/2/10/97 R Brown 3/11/97
HFD-645/J.Simmons/UVenkatarm/2/13/97 U V. Venkataram for
F/T by pah/3/6/97 3/26/97
x:\new\firmsam\lederle\ltrs&rev\74872.apf

DMF CHECKLIST FOR ANDA 74-872 - REVIEW #2

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/ [redacted]	1	Sat.	1/3/97
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	II/ [redacted]	4		
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	III/ [redacted]	4		
	Comments:			
[redacted]	II/ [redacted]	4		
	Comments:			

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no relevant revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Checklist page 1 of 1.

Raymond Brown
Reviewer

Raymond Brown
Signature

2/10/97
Date

DIVISION REVIEW SUMMARY

ANDA 74-872 **DRUG PRODUCT:** Acyclovir

FIRM: ESI Lederle, Inc. **DOSAGE FORM:** Capsules (Oral)

STRENGTH: 200 mg

CGMP STATEMENT/EIR UPDATE STATUS: Satisfactory -
A **ESTABLISHMENT EVALUATION REQUEST** issued, dated 3/29/96, to the Division of Compliance has found the cGMP status of [redacted] and ESI Lederle, Inc., 401 North Middletown Road, Pearl River NY. **acceptable**, dated 7/19/96.

BIO INFORMATION: Satisfactory -
The Division of Bioequivalence has found that the studies demonstrate that ESI Lederle's acyclovir, 200 mg capsules, are bioequivalent to the reference product Zovirax® 200 mg capsules, manufactured by Burroughs Wellcome. See Bio review dated 09/30/96.

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Satisfactory -

Drug substance is a compendia item. Methods validation is not required.

Drug Product - Methods validation found suitable for regulatory analysis, dated 12/23/96.

STABILITY: Satisfactory -
Applicant has submitted stability data for a production batch, lot #93265-0100 accelerated condition (40°C/75%RH) stability data tested at 0, 1, 2 and 3 months on the smallest (100 tabs, 90cc bottle) and the largest (1000 tabs, 960cc bottle) HDPE marketed container sizes. The components in the *unit of issue package* are identical to the trade package style except for the press and turn feature. No intermediate container size indicated. The data are within the specified limits. The stability protocol is adequate and within FDA guidelines. The containers used in stability studies are the same as those in container section (vol. 1.8, pp. 2021-2098). An expiration dating of 24 month has been granted.

LABELING: Satisfactory -
See Review of Professional Labeling conducted by Jacqueline white, concurred by John Grace, dated 1/27/97.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Satisfactory - Lot #93265-0100 (——— NDS lots #QD05045, QD05047 and QD05048 used, Rec'd #J6628, J6725 and J6726 respectively) is a ——— capsule production batch. DMF —— was found satisfactory, dated 1/31/97. ~~The waiver of an in-vivo bioequivalence study requirement was granted.~~ AB 3/24/97

SIZE OF STABILITY BATCHES - Satisfactory - Lot #93265-0100 is a ——— capsule production batch, actually produced ——— capsules, packaging yield —— %. Batch reconciliation for ——————————————— yield is —— % and encapsulation is —— % of theoretical, respectively. The entire batch was encapsulated. The batch size meets the Office of Generic Drug's policy #22-90 which requires a minimum 100,000 units batch or 10% of the proposed production batch size, whichever is greater. The batch was manufactured using production scale equipment under production conditions.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
The proposed production batch size is ——— capsules (see vol, 1.7. pp. 1820-1870). The manufacturing process is the same as for the ——— batch size.

RECOMMENDATION:
APPROVE

RBrown 3/11/97

cc: 74-872
Ray Brown/2/10/97
Brenda T. Arnwine/UVenkataram/2/13/97
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F/T by pah/3/6/97
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3/11/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-872

BIOEQUIVALENCE REVIEWS

SEP 30 1996

Acyclovir Capsule, 200 mg
ANDA #74-872
Reviewer: S.P. Shrivastava
WP #74872SDW.396

ESI-Lederle, Inc.
Pearl River, NY
Submitted:
March 27, 1996

REVIEW OF TWO BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA

I. BACKGROUND

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside analog with *in vivo* and *in vitro* inhibitory activity against (in decreasing order) herpes simplex types 1 and 2 viruses, varicella zoster virus, Epstein-Barr virus, and cytomegalovirus. Acyclovir is converted by enzymes present in virus-infected cells into an active form, acyclovir triphosphate, which interrupts viral DNA replication. Acyclovir capsules and suspension are indicated for treatment of initial episodes and management of recurrent herpes simplex virus genitalis in certain patients. The capsule, suspension, and tablet dosage forms are indicated for treatment of acute herpes zoster and chicken pox.

Acyclovir oral absorption is slow, variable, and incomplete, with absolute bioavailability estimated at about 15-30%. Peak blood concentrations occur approximately 1.5-2.5 hours following oral dosing. There are no active metabolites. Studies in which 0.5 to 15 mg/kg were administered I.V. to patients with normal renal function yielded elimination half-lives of 2 to 3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine.

Acyclovir is marketed as Zovirax^{R} (Burroughs-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 400 mg and 800 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 ml (NDA #19-909, 12/22/89).

In this submission, the firm has submitted two bioequivalence studies, and dissolution testing data.

II. SUMMARY OF BIOEQUIVALENCE STUDY PROTOCOLS

A. Single-Dose Fasting Study

1. Protocol # 95-098 MA

This randomized, single-dose, two-way crossover study was conducted with 30 healthy male volunteers in accordance with the Protocol. Six subjects, #6, 13, 15, 25, 27, and 30 were found positive in drug screen prior to Period 2 of the study. Four subjects, Sub 6, 15, 27, and 30 returned two weeks later, and Sub #13 and 25 did not return to complete phase two of the study. Thus 28 subjects completed the study.

In each period, subjects received a single 200 mg dose of either Lederle's acyclovir capsules or BW's Zovirax^{R} Capsules following an overnight fast. There was a one-week wash-out period between treatments. Blood samples were collected pre-dose and for 24 hours after each dose. Plasma concentrations of acyclovir was measured by a fully validated HPLC procedure. Pharmacokinetic and statistical analyses were performed to compare the test and reference treatments.

2. Objective of the study

The objective of this study was to determine the bioequivalence of two acyclovir formulations after administration of single doses to healthy volunteers under fasting conditions.

3. Study design: Randomized, single-dose, two-way crossover study under fasting conditions.

4. Study sites

Clinical study: [redacted]
Analytical study:

5. Study dates:

Clinical study:	12/2/95-12/10/95 (All subjects Except Subject #6, 15, 27, and 30)
	12/2/95-12/24/95 (Make-up group, Subject #6, 15, 27, and 30)
Analytical study:	12/14/95-1/12/96
Storage Time:	41 Days

6. Investigators:

Principal Investigator - [redacted] Ph.D.
Analytical Chemist - [redacted], Ph.D.
Study Monitor - [redacted], Pharm.D.

A. Test: 200 mg Acyclovir Capsules (Lederle, Lot #93265-0100);
Exp. Date - 10/30/96. Batch size - [redacted] capsules; Potency - 99.5%.

B. Reference: 200 mg Zovirax^{R} Capsules (Burroughs Wellcome, Lot #5P2223);
Exp. Date 6/30/96. Potency - 97.5%.

7. Dosing: All doses were administered with 180 ml of room temperature water following an overnight fast.

8. Subjects: The 30 subjects who entered in this study were normal healthy male volunteers aged 18-40 years, weighing at least 60 kg, and within 10% of their ideal body weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection

of the subjects.

Twenty-eight subjects completed both arms of the study. Subjects #13 and 25 failed to return to Period 2 of the study. In addition, Subjects #6, 15, 27 and, 30 were found positive in drug screen prior to dosing for Period 2, and they were dosed one week later. The reviewer analyzed the data with and without subject #6, 15, 27 and 30.

9. Food and fluid intake: Standard lunch was served 5 hours post-dose and dinner was served as scheduled on each day of drug administration. The drug products were administered with 180 mL of tap water. Water was allowed *ad lib.* one hour pre-dose and 2 hours post-dose.

10. Washout period: One week.

11. Blood samples: In each period, 10 mL of blood samples were collected in Vacutainers at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours. Plasma was separated and all plasma samples were stored frozen at -20°C until ready for analysis.

12. Subject safety monitoring: Subjects were asked to spontaneously report any signs or symptoms that might be related to the drug products.

13. Adverse reactions: On each dosing period subjects were asked to report any signs or symptoms judged to be drug related.

14. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for acyclovir. 90% confidence intervals were calculated for AUC_{0-t} , AUC0-∞ and C_{max}.

B. Limited-Food Study

1. Protocol # 95-099 MA

2. Study design: Randomized, single-dose, three-way crossover study under fasting/non-fasting conditions.

3. Study Sites and Investigators: Site, Study Monitor, and Analytical Chemist same as in Fasting Study. Principal Investigator for this study was ———— M.D.

4. Study dates: Clinical study - 12/1/95-12/16/95
Analytical study - 12/27/95-1/9/96
Max. Storage Period: 40 Days

5. Treatments:

A. Test: 200 mg Acyclovir Capsules (Lederle, Lot #93265-0100) under non-fasting conditions, Exp. Date - 10/30/96.

B. Reference: 200 mg Zovirax^{R} Capsules (Burroughs Wellcome, Lot #5P2223) under non-fasting conditions; Exp. Date - 6/30/96.

C. Test: 200 mg Acyclovir Capsules (Lederle, Lot #93265-0100) under fasting conditions.

6. Dosing: All doses were administered with 180 mL of water at room temperature following an overnight fast or within 5 minutes after consuming the breakfast depending on the dosing schedule.

7. Subjects: Twenty-one subjects entered the study and 19 completed the three phases. Subjects #10 did not check-in for Period 2, and Subject 17 was dropped due to concurrent illness prior to Period 3 dosing, respectively.

   The subjects screened were normal healthy male volunteers aged 19-40 years, and were within 10% of their ideal body weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

8. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 180 mL of tap water. Water was allowed *ad lib.* one hour pre-dose and 2 hours post-dose.

9. Wash-out period: One week.

10. Blood samples: Same as in the fasting study.

III. VALIDATION OF ASSAY METHOD FOR PLASMA SAMPLES

Methods:

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information from

BIOEQUIVALENCE REVIEW

Table 3. Intra-day variability

Theoretical Conc, ng/mL	30	300	1125
n	6	6	6
Variability, %CV	6.1	0.7	0.6

e. Absolute Recovery: Percent extracted vs. unextracted, data are given in Table 4.

Table 4. Acyclovir Recovery Data

Theoretical Conc, ng/mL	10	250	1500
n	6	6	6
Recovery, %	—	—	—
%CV	9.5	3.4	1.0

f. Stability of Acyclovir : Stability was checked under various conditions, including reinjection after 19 hrs, refrigeration at 2-8 ^{0}C, in biological matrix at bench-top for 25 hours, freeze-thaw cycles, heating at 56 ^{0}C for one hour at water bath, and long-term stability at -20 ^{0}C for 55 weeks. The stability data are acceptable (Table 5).

Table 5. Stability Under Various Sample Storage Conditions

Storage Test	**Conc. ng/mL**	**Storage Period**	**Temperature**	**Recov.**
System-Check	30	23 Hrs	Room	101.3
(Autosampler)	300			97.0
(n=4)	1125			92.0
Three Freeze-Thaw	30	-------	Room/-20 °C	98.7
Cycles (n=6)	300			98.3
	1125			100.0
Bench-Top	30	25 Hours	Room	101.3
(n=6)	300			95.0
	1125			93.7
Long-Term Stab.	30	55 Weeks	-20 °C	103.0
(n=6)	300			102.2
	1125			103.1

IV. RESULTS

A. Single-Dose Fasting Study

1. **Blood/Plasma Drug Concentration:** During Period 2, Subjects #6, 15, 27, and 30 were found positive in drug screen, therefore, they were dosed one week later. These subjects should not belong to the same study period. So, they were analyzed in three ways by the reviewer.

   (a) 28 Subjects in two treatments, three periods (Table 6, Attachment 1).
   (b) 28 Subjects in two treatments, two periods (Table 9).
   (c) 24 Subjects, two periods (excluding Subjects #6, 15, 27, and 30; Tables 12, Attachment 2).

2. **Pharmacokinetic Parameters**: Mean PK parameters for 28 subjects three periods, 28 subjects two periods, and 24 subjects two periods (without Subject #6, 15, 27, and 30) are given in Tables 7-8, 10-11 and 13-14, respectively. Individual data submitted for all 28 subjects are given in Attachments 3-4. Since the correct analysis is to treat the 28 subjects in three periods, following summary statements mainly apply to those results from 28 subjects (Tables 6-8).

- The 90% CI for LAUCs and LC_{max} are within 80-125% when all 28 subjects are included (Tables 8, 11). However, when Subjects #6, 15, 27 and 30 are excluded, LC_{max} does not meet the 90% CI criteria (Table 14). LC_{max} for the test product is 10% lower than the reference drug.

- Individual Test/Reference ratios for AUC_{0-t} ranged between 0.36-2.96 with an average of 1.08 and CV of 53%.

- Individual Test/Reference ratios for AUC_{0-inf} ranged between 0.37-2.81 with an average of 1.06 and CV of 48%.

- Individual Test/Reference ratios for C_{max} ranged between 0.42-2.52 with an average of 1.00 and CV of 45%.

- Individual Test/Reference ratios for T_{max} ranged between 0.42-4.50 with an average of 1.32 and CV of 62%.

- The ratios of AUC_{0-t}/AUC_{0-inf} ranged between 0.87-0.98 with an average of 0.95 and CV of 2.6%.

- Individual PK parameters and summary data submitted by the firm are given in

Attachments-3-4.

3. Adverse Reaction: No serious or unexpected adverse reactions were reported.

Sign/Symptom	Test	Reference	Drug Related
Headache	2	1	Probable/Possible
Light-Headed	0	1	Probable/Possible
Vomiting	0	1	Possible

The *in vivo* fasting study is acceptable.

TABLE 6. PLASMA CONCENTRATION OF ACYCLOVIR IN FASTING SUBJECTS (N=28, THREE PERIOD)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	21.60	25.63	17.17	25.15	1.26
0.67	176.07	101.37	162.22	78.10	1.09
1	262.25	108.66	281.88	116.81	0.93
1.33	300.40	109.20	337.39	142.85	0.89
1.67	312.75	112.57	369.57	175.80	0.85
2	312.00	124.85	354.57	171.39	0.88
2.5	302.16	132.27	318.84	153.92	0.95
3	273.57	130.94	278.71	140.68	0.98
4	217.96	112.57	219.78	123.92	0.99
5	177.88	96.69	175.92	105.46	1.01
6	136.29	78.59	135.89	79.58	1.00
8	85.82	44.62	86.89	47.19	0.99
10	52.61	23.73	55.63	28.57	0.95
12	35.41	14.40	35.88	16.72	0.99
16	15.76	8.69	16.59	8.56	0.95
20	6.82	7.21	7.03	7.39	0.97
24	3.26	5.30	2.23	4.91	1.47

1=TEST, 2=REFERENCE

TABLE 7. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, N=28, THREE PERIOD)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1985.97	791.53	2059.62	891.50	0.96
AUCT	1904.21	791.77	1973.62	896.35	0.96
CMAX	361.75	133.43	400.88	166.99	0.90
KE	0.17	0.05	0.17	0.04	1.03
LAUCI	1849.27	0.38	1885.80	0.43	0.98
LAUCT	1762.18	0.40	1788.82	0.46	0.99
LCMAX	338.86	0.37	366.98	0.44	0.92
THALF	4.42	1.56	4.41	1.23	1.00
TMAX	1.90	0.89	1.59	0.65	1.19

1=TEST, 2=REFERENCE

TABLE 8. LSMEANS AND 90% CONFIDENCE INTERVALS (N=28, THREE PERIOD)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	2123.02	2165.04	82.34	113.78
AUCT	2050.56	2086.18	81.96	114.62
CMAX	392.71	424.29	77.93	107.18
LAUCI	2038.82	2029.24	85.15	118.55
LAUCT	1967.07	1943.04	85.11	120.41
LCMAX	379.25	399.37	80.04	112.66

1=TEST, 2=REFERENCE

TABLE 9. PLASMA CONCENTRATION OF ACYCLOVIR IN FASTING SUBJECTS (N=28)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	21.60	25.63	17.17	25.15	1.26
0.67	176.07	101.37	162.22	78.10	1.09
1	262.25	108.66	281.88	116.81	0.93
1.33	300.40	109.20	337.39	142.85	0.89
1.67	312.75	112.57	369.57	175.80	0.85
2	312.00	124.85	354.57	171.39	0.88
2.5	302.16	132.27	318.84	153.92	0.95
3	273.57	130.94	278.71	140.68	0.98
4	217.96	112.57	219.78	123.92	0.99
5	177.88	96.69	175.92	105.46	1.01
6	136.29	78.59	135.89	79.58	1.00
8	85.82	44.62	86.89	47.19	0.99
10	52.61	23.73	55.63	28.57	0.95
12	35.41	14.40	35.88	16.72	0.99
16	15.76	8.69	16.59	8.56	0.95
20	6.82	7.21	7.03	7.39	0.97
24	3.26	5.30	2.23	4.91	1.47

1=TEST, 2=REFERENCE

TABLE 10. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, N=28)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1985.97	791.53	2059.62	891.50	0.96
AUCT	1904.21	791.77	1973.62	896.35	0.96
CMAX	361.75	133.43	400.88	166.99	0.90
KE	0.17	0.05	0.17	0.04	1.03
LAUCI	1849.27	0.38	1885.80	0.43	0.98
LAUCT	1762.18	0.40	1788.82	0.46	0.99
LCMAX	338.86	0.37	366.98	0.44	0.92
THALF	4.42	1.56	4.41	1.23	1.00
TMAX	1.90	0.89	1.59	0.65	1.19

1=TEST, 2=REFERENCE

TABLE 11. LSMEANS AND 90% CONFIDENCE INTERVALS (N=28)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	1985.97	2059.62	83.96	108.89
AUCT	1904.21	1973.62	83.43	109.54
CMAX	361.75	400.88	78.40	102.08
LAUCI	1849.27	1885.80	86.25	111.49
LAUCT	1762.18	1788.82	86.03	112.81
LCMAX	338.86	366.98	80.75	105.59

1=TEST, 2=REFERENCE

TABLE 12. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS (N=24)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	21.71	26.18	16.00	24.90	1.36
0.67	170.14	87.27	162.77	76.03	1.05
1	259.58	99.25	281.25	112.29	0.92
1.33	300.57	110.12	332.12	132.83	0.91
1.67	314.90	117.67	368.87	172.31	0.85
2	314.18	132.84	352.07	167.90	0.89
2.5	303.07	141.57	317.76	153.98	0.95
3	271.72	139.53	277.29	139.90	0.98
4	212.20	117.11	220.16	125.39	0.96
5	173.33	101.66	175.56	106.65	0.99
6	134.15	83.82	136.35	80.48	0.98
8	85.15	47.82	87.87	48.40	0.97
10	51.80	25.24	56.75	29.37	0.91
12	35.25	15.24	36.37	17.06	0.97
16	15.68	8.48	17.14	8.35	0.91
20	6.24	7.21	7.03	7.39	0.89
24	2.88	5.15	2.10	4.85	1.37

1=TEST, 2=REFERENCE

TABLE 13. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, N=24)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1962.13	841.23	2063.62	890.05	0.95
AUCT	1881.41	842.60	1976.08	893.75	0.95
CMAX	361.55	139.44	401.42	160.20	0.90
KE	0.17	0.05	0.17	0.04	1.04
LAUCI	1810.48	0.40	1901.88	0.41	0.95
LAUCT	1723.57	0.42	1805.40	0.43	0.95
LCMAX	336.66	0.39	373.70	0.38	0.90
THALF	4.38	1.54	4.42	1.21	0.99
TMAX	1.81	0.80	1.60	0.67	1.13

1=TEST, 2=REFERENCE

TABLE 14. LSMEANS AND 90% CONFIDENCE INTERVALS (N=24)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	1967.54	2072.09	81.02	108.88
AUCT	1886.67	1984.54	80.50	109.63
CMAX	361.24	400.93	77.20	103.00
LAUCI	1819.08	1908.24	83.50	108.83
LAUCT	1732.36	1811.94	83.28	109.76
LCMAX	336.84	373.26	78.76	103.40

1=TEST, 2=REFERENCE

B. Limited Food Study

A total of 21 subjects participated in the study, and 19 completed the study successfully. Two subjects, Subject #10 did not check-in for Period 2, and Subject #17 was dropped due to concurrent illness.

1. Blood/Plasma Drug Concentration

The average plasma concentration data, test/reference ratios, and plasma profiles are given in Tables 15-16 and Attachment-5. Test Fed/Reference Fed ratios during 1-24 hours are 0.41-1.22.

2. Pharmacokinetic Parameters

- Average pharmacokinetic parameters and test/reference (food) ratios are given in Tables 17-20.
- The ratios of average test/reference (food) for AUCs and C_{max} are within 0.8-1.2 as required (Tables 18).
- ANOVA analysis showed no significant period effect on AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}.
- Individual PK parameters are given in Attachments 6-8.
- Food appears to decrease the AUCs, C_{max}, and T_{half}, and increase T_{max}.

3. **Adverse Reaction:** No difference between test fed and reference fed were found.

Sign/Symptom	Test-Fed	Reference-Fed	Test-Fasting	Drug Related
Headache	2	2	3	Probable
Vomiting	0	1	0	Possible

The *in vivo* non-fasting study is acceptable.

TABLE 15. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	0.00	0.00	0.00	0.00	31.99	42.53
0.67	5.25	10.53	22.57	47.74	170.44	120.05
1	35.57	39.56	87.10	96.59	283.54	136.18
1.33	105.22	104.55	175.30	105.46	362.23	171.60
1.67	191.89	148.40	265.38	107.79	391.03	195.21
2	252.00	161.48	313.57	113.63	391.83	202.74
2.5	295.28	126.83	342.84	101.83	349.66	194.44
3	315.87	82.83	326.68	93.75	312.96	193.72
4	293.23	78.18	262.45	77.89	254.25	156.43
5	236.99	84.87	205.66	62.56	195.74	129.75
6	175.92	64.14	152.99	49.62	147.05	100.26
8	101.85	38.70	91.29	30.88	92.45	54.82
10	61.64	23.55	55.51	19.56	58.62	32.70
12	39.98	16.96	36.47	13.08	39.02	20.89
16	19.29	9.44	18.85	8.40	20.37	11.10
20	8.63	8.77	7.08	9.08	10.78	8.34
24	4.27	6.59	4.98	6.84	5.57	8.01

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 16. RATIO OF TEST/REFERENCE MEAN PLASMA ACYCLOVIR LEVELS
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.33	.	0.00	0.00
0.67	0.23	0.03	0.13
1	0.41	0.13	0.31
1.33	0.60	0.29	0.48
1.67	0.72	0.49	0.68
2	0.80	0.64	0.80
2.5	0.86	0.84	0.98
3	0.97	1.01	1.04
4	1.12	1.15	1.03
5	1.15	1.21	1.05
6	1.15	1.20	1.04
8	1.12	1.10	0.99
10	1.11	1.05	0.95
12	1.10	1.02	0.93
16	1.02	0.95	0.93
20	1.22	0.80	0.66
24	0.86	0.77	0.90

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 17. TEST MEAN/REFERENCE MEAN (ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	2030.75	598.10	2025.40	536.71	2377.89	1089.06
AUCT	1944.28	582.95	1926.74	515.80	2194.16	1123.83
CMAX	361.19	105.67	375.37	87.60	432.18	206.31
KE	0.17	0.05	0.16	0.06	0.16	0.06
LAUCI	1961.33	0.26	1954.47	0.28	2164.66	0.45
LAUCT	1875.87	0.26	1857.74	0.28	1938.25	0.52
LCMAX	348.66	0.26	365.33	0.24	375.42	0.61
THALF	4.44	1.41	4.82	1.67	5.05	2.08
TMAX	2.83	0.83	2.49	0.82	1.80	0.85

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 18. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.00	0.85	0.85
AUCT	1.01	0.89	0.88
CMAX	0.96	0.84	0.87
KE	1.04	1.07	1.03
LAUCI	1.00	0.91	0.90
LAUCT	1.01	0.97	0.96
LCMAX	0.95	0.93	0.97
THALF	0.92	0.88	0.95
TMAX	1.14	1.58	1.39

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 19. LSMEANS AND 90% CONFIDENCE INTERVALS
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LSMEAN3	LOWCI12	UPPCI12	LOWCI13
PARAMETER						
AUCI	2051.25	2045.14	2423.13	85.39	115.21	72.07
AUCT	1957.59	1945.88	2207.47	83.86	117.35	73.92
CMAX	359.92	377.35	430.91	77.04	113.71	67.47
LAUCI	1977.88	1978.61	2204.63	87.62	114.04	78.64
LAUCT	1885.52	1882.92	1948.21	85.27	117.60	82.41
LCMAX	346.97	368.70	373.59	76.24	116.16	75.24

TABLE 20. LSMEANS AND 90% CONFIDENCE INTERVALS
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	UPPCI13	LOWCI23	UPPCI23
PARAMETER			
AUCI	97.24	71.81	96.99
AUCT	103.44	73.39	102.91
CMAX	99.58	71.51	103.63
LAUCI	102.35	78.67	102.39
LAUCT	113.66	82.30	113.50
LCMAX	114.64	79.95	121.82

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

V. FORMULATION

Table 21. shows the composition of the test products, 200 mg Acyclovir Capsules by Lederle.

The ingredients used in the test product are within the IIG (1996) limits. The executed batch size was [redacted] capsules.

[NOT FOR RELEASE UNDER F.O.I.]

Table 21. Composition of Lederle's Acyclovir Capsules

Ingredient	Test	Reference
Acyclovir, USP	200.000	200.000
Silicon Dioxide [redacted] NF	[redacted]	----
Cellulose Microcrystalline, NF	[redacted]	----
Magnesium Stearate, NF	[redacted]	[redacted]
Povidone USP [redacted]	[redacted]	----
Sodium Starch Glycolate, NF	[redacted]	----
[redacted][1], USP	0.000	----
Ink Black	For Printing	For Printing
Lactose	----	[redacted]
Sodium Lauryl Sulfate	----	[redacted]
Starch, Corn	----	[redacted]
Unspecified ingredient	----	PNG[2]
Dye FDC Blue #2	----	PNG
Titanium Dioxide	----	PNG
Gelatin	----	PNG

1 Used in the manufacturing process, but does not appear in the final product.

2 PNG = Potency and grade not given.

VI. *IN VITRO* RESULTS (DISSOLUTION)

The capsules meet the dissolution requirement of Q=NLT —% in 30 minutes (Table 22).

TABLE 22. *In Vitro* Dissolution Testing

Method: Used FDA method. USP method not available.
Apparatus I (Basket) **RPM: 100** **No. of Units: 12**
Medium: water **Volume:** 900 mL
Reference Drug: Zovirax[R] **Manufacturer:** Burroughs-Wellcome
Assay Methodology: UV Absorbance @ — nm.

Sampling Time	Test Product			Reference Product		
(Minutes)	Mean % Dissol	Range	CV	Mean % Dissol	Range	CV
	Lot #93265-0100		Strength 200 mg	Lot # 5P2223		
10	76		20.5	61		22.2
20	86		11.5	81		5.0
30	92		6.3	90		6.8
40	95		4.0	97		7.3

*Dissolution results are acceptable according to the Acceptance Table on page 1793 of USP XXIII (1995).

VII. COMMENTS

1. The HPLC peaks for acyclovir standards are without any interferences. However, a number of peaks for plasma samples have shoulders on the descending side of the peak (see pages 410, 448, 465, 467, 1421, 1451, 1470, 1496, 1498, etc.). In future, such interferences should be avoided. It decreases the accuracy of the data obtained.

2. The Sections on Analytical Performance for Protocol (pages 247 and 971) indicate that external standard technique was used for calibration purposes. However, Sections on Study Support Validation Raw Data (pages 307 and 1032) indicate that a ———— ———— was used for internal standard (I.S.) and for calculating ratios, etc. If such operations are used to accommodate the computer software requirements, the firm should make appropriate statement in the analytical section to avoid any confusion.

VIII. RECOMMENDATIONS

1. The *in vivo* bioequivalence studies, under fasting and non-fasting conditions, conducted by ESI-Lederle on its acyclovir capsules, 200 mg strength, Lot #93265-0100, comparing it to Burroughs-Wellcome's Zovirax^{R}, 200 mg Capsules, Lot #5P2223, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that ESI-Lederle's acyclovir, 200 mg capsules, are bioequivalent to the reference product, Zovirax^{R} 200 mg capsules, manufactured by Burroughs-Wellcome.

2. The dissolution testing conducted by ESI-Lederle, on its acyclovir, 200 mg capsules, Lot #93265-0100, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The testing should be conducted in 900 mL Purified Water using USP XXIII Apparatus I (Basket) at 100 R.P.M. The test product should meet the following specifications:

   Not less than —% (Q) of the labeled amount of acyclovir is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability and *in vitro* dissolution testing requirements for its acyclovir 200 mg capsules, and the application is acceptable.

The firm should be informed of the comments and recommendations.

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar Date 9/30/1996

Concur: Date: 9/30/96

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

Attachments-8

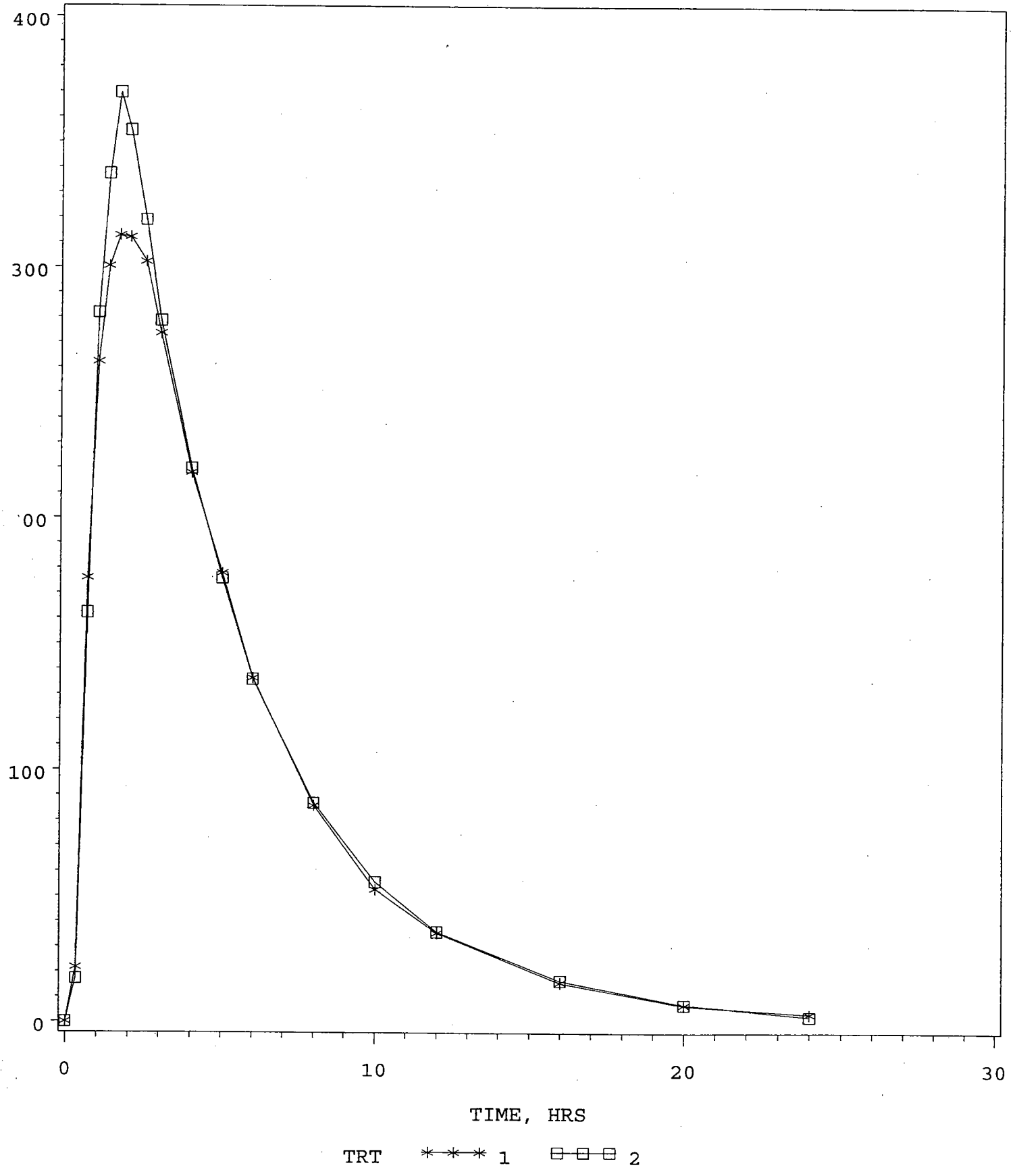
SPS/sps/7-24-96/74872SDW.396

cc: ANDA #74872 (Original, Duplicate) HFD-600 (DHare), HFD-630, HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

Attachment - 1

FIG P-1. ACYCLOVIR CAPSULES: PLASMA LEVELS

ACYCLOVIRCAPSULES, 200 MG, ANDA #74-872
UNDER FASTING CONDITIONS
DOSE=1 X 200 MG

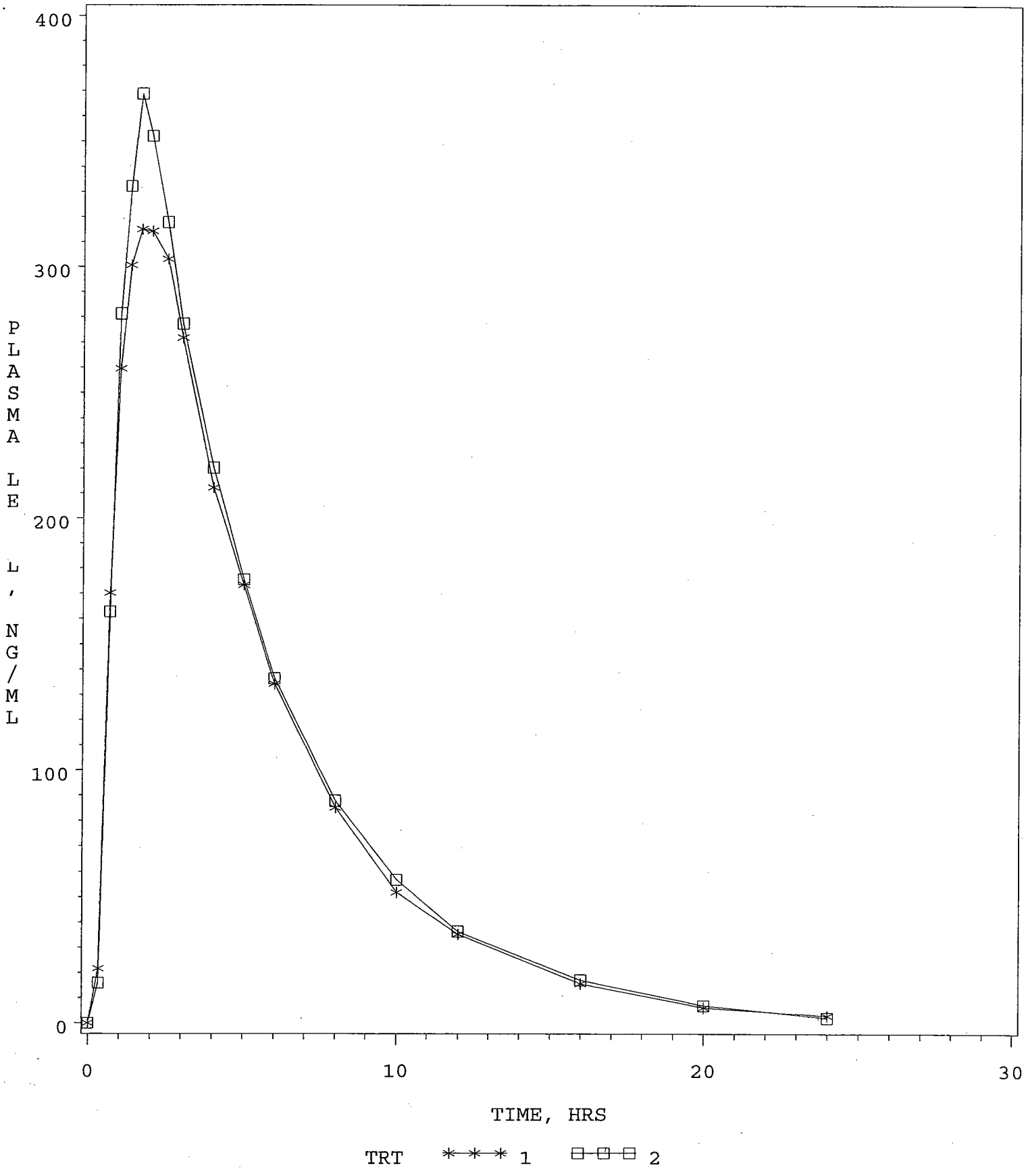


1=TEST PRODUCT(ESI-LEDERLE) 2=REFERENCE PRODUCT(BURROUGHS-WELLCOME)

Attachment-2

FIG P-1. ACYCLOVIR CAPSULES: PLASMA LEVELS (N=24)

ACYCLOVIR CAPSULES, 200 MG, ANDA #74-872
UNDER FASTING CONDITIONS
DOSE=1 X 200 MG



1=TEST PRODUCT(ESI-LEDERLE) 2=REFERENCE PRODUCT(BURROUGHS-WELLCOME)

Table 4

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations for Acyclovir 200 mg Capsule (ESI Lederle)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	BA	2									
2	AB	1									
3	AB	1									
4	BA	2									
5	BA	2									
6	AB	1									
7	BA	2									
8	AB	1									
9	AB	1									
10	BA	2									
11	BA	2									
12	AB	1									
14	AB	1									
15	AB	1									
16	BA	2									
17	BA	2									
18	AB	1									
19	BA	2									
20	AB	1									
21	BA	2									
22	AB	1									
23	BA	2									
24	AB	1									
26	BA	2									
27	AB	1									
28	BA	2									
29	AB	1									
30	BA	2									
Mean			361.8	1.90	1904.2	1986.0	0.1733	4.42	5.826	7.474	7.523
S.D.			133.4	0.89	791.8	791.5	0.0505	1.56	0.371	0.398	0.381
C.V.(%)			36.9	46.71	41.6	39.9	29.1276	35.17	6.372	5.326	5.069
S.E.M.			25.2	0.17	149.6	149.6	0.0095	0.29	0.070	0.075	0.072
N			28.0	28.00	28.0	28.0	28.0000	28.00	28.000	28.000	28.000
Minimum											
Maximum											

Attachment - 3

Table 5

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations for Zovirax(R) 200 mg Capsule (Burroughs Wellcome Co.)

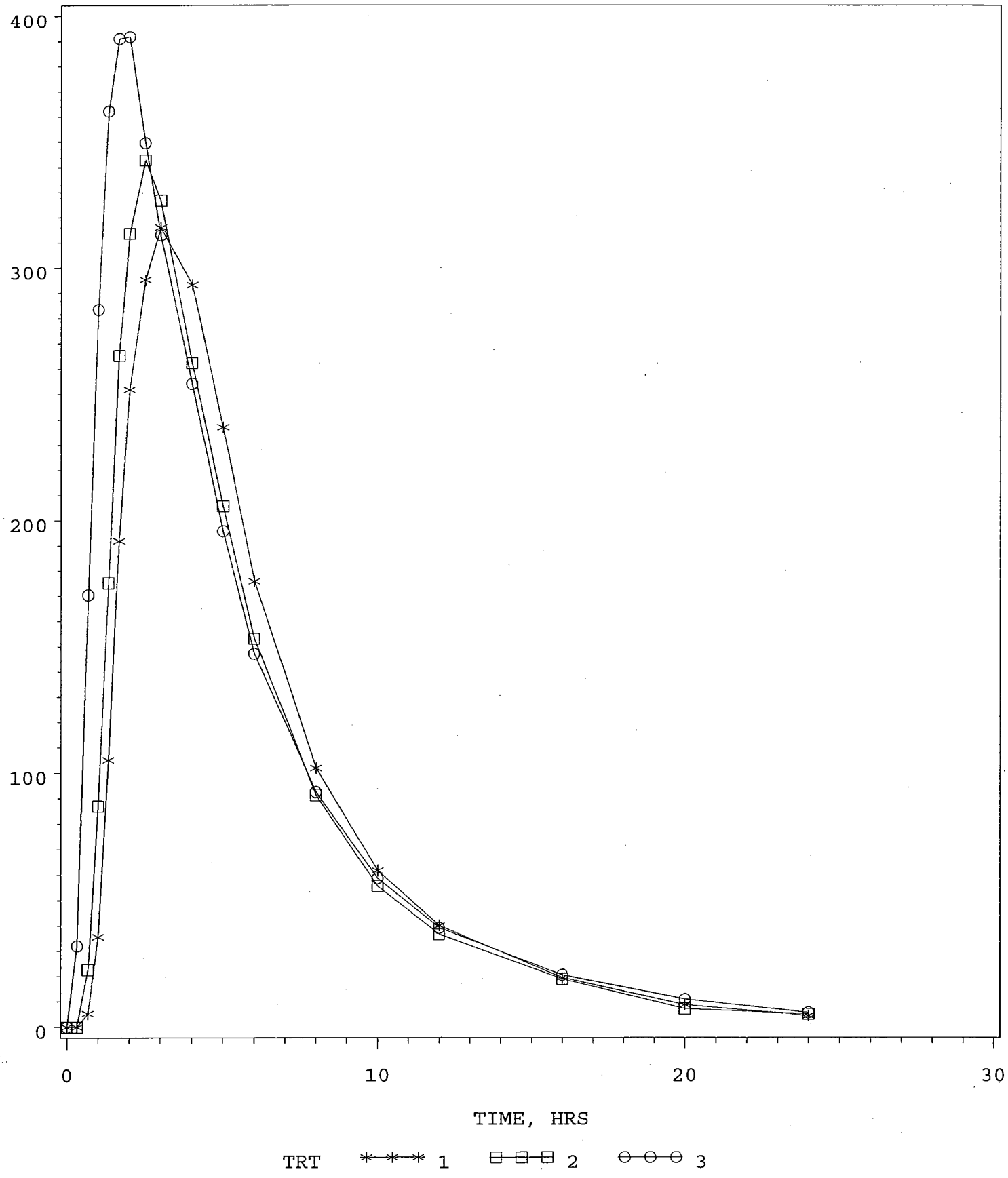
Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	BA	1									
2	AB	2									
3	AB	2									
4	BA	1									
5	BA	1									
6	AB	2									
7	BA	1									
8	AB	2									
9	AB	2									
10	BA	1									
11	BA	1									
12	AB	2									
14	AB	2									
15	AB	2									
16	BA	1									
17	BA	1									
18	AB	2									
19	BA	1									
20	AB	2									
21	BA	1									
22	AB	2									
23	BA	1									
24	AB	2									
26	BA	1									
27	AB	2									
28	BA	1									
29	AB	2									
30	BA	1									
Mean			400.9	1.59	1973.6	2059.6	0.1678	4.41	5.905	7.489	7.542
S.D.			167.0	0.65	896.4	891.5	0.0413	1.23	0.443	0.457	0.431
C.V.(%)			41.7	41.11	45.4	43.3	24.6074	27.80	7.499	6.106	5.711
S.E.M.			31.6	0.12	169.4	168.5	0.0078	0.23	0.084	0.086	0.081
N			28.0	28.00	28.0	28.0	28.0000	28.00	28.000	28.000	28.000
Minimum											
Maximum											

Attachment - 4

Attachment - 5

FIG P-2. ACYCLOVIR CAPSULES: PLASMA LEVELS

ACYCLOVIR CAPSULES, 200 MG, ANDA #74-872
UNDER NON-FASTING CONDITIONS
DOSE=1 X 200 MG



1=TEST FED (ESI-LEDERLE) 2=REFERENCE FED (BURROUGHS-WELLCOME) 3=TEST FASTING (ESI-LEDERLE)

Table 5

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations
for Acyclovir 200 mg Capsule (ESI Lederle, fed)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	CBA	3									
2	CAB	2									
3	BAC	2									
4	BCA	3									
5	ACB	1									
6	ABC	1									
7	ACB	1									
8	BCA	3									
9	ABC	1									
11	CAB	2									
12	CBA	3									
13	ACB	1									
14	CAB	2									
15	CBA	3									
16	BAC	2									
18	ABC	1									
19	BCA	3									
20	CAB	2									
21	ABC	1									
Mean			361.2	2.83	1944.3	2030.7	0.1699	4.44	5.854	7.537	7.581
S.D.			105.7	0.83	583.0	598.1	0.0487	1.41	0.264	0.265	0.261
C.V.(%)			29.3	29.15	30.0	29.5	28.6729	31.66	4.516	3.516	3.447
S.E.M.			24.2	0.19	133.7	137.2	0.0112	0.32	0.061	0.061	0.060
N			19.0	19.00	19.0	19.0	19.0000	19.00	19.000	19.000	19.000
Minimum											
Maximum											

Attachment - 6

Table 6

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations
for Zovirax(R) 200 mg Capsule (Burroughs Wellcome Co.)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	CBA	2									
2	CAB	3									
3	BAC	1									
4	BCA	1									
5	ACB	3									
6	ABC	2									
7	ACB	3									
8	BCA	1									
9	ABC	2									
11	CAB	3									
12	CBA	2									
13	ACB	3									
14	CAB	3									
15	CBA	2									
16	BAC	1									
18	ABC	2									
19	BCA	1									
20	CAB	3									
21	ABC	2									
Mean			375.4	2.49	1926.7	2025.4	0.1628	4.82	5.901	7.527	7.578
S.D.			87.6	0.82	515.8	536.7	0.0611	1.67	0.244	0.285	0.282
C.V.(%)			23.3	32.86	26.8	26.5	37.5094	34.58	4.132	3.786	3.715
S.E.M.			20.1	0.19	118.3	123.1	0.0140	0.38	0.056	0.065	0.065
N			19.0	19.00	19.0	19.0	19.0000	19.00	19.000	19.000	19.000
Minimum											
Maximum											

Attachment - 7

Table 7

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations
for Acyclovir 200 mg Capsule (ESI Lederle, fasting)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	CBA	1									
2	CAB	1									
3	BAC	3									
4	BCA	2									
5	ACB	2									
6	ABC	3									
7	ACB	2									
8	BCA	2									
9	ABC	3									
11	CAB	1									
12	CBA	1									
13	ACB	2									
14	CAB	1									
15	CBA	1									
16	BAC	3									
18	ABC	3									
19	BCA	2									
20	CAB	1									
21	ABC	3									
Mean			432.2	1.80	2194.2	2377.9	0.1582	5.05	5.928	7.570	7.680
S.D.			206.3	0.85	1123.8	1089.1	0.0586	2.08	0.611	0.521	0.445
C.V.(%)			47.7	47.42	51.2	45.8	37.0574	41.17	10.310	6.880	5.796
S.E.M.			47.3	0.20	257.8	256.7	0.0138	0.49	0.140	0.119	0.105
N			19.0	19.00	19.0	18.0	18.0000	18.00	19.000	19.000	18.000
Minimum											
Maximum											

Attachment - 8

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #74-872 **SPONSOR** ESI-Lederle

DRUG: Acyclovir **DOSAGE FORM:** Capsules

STRENGTH(S): 200 mg

TYPE OF STUDY: SINGLE-DOSE x FASTING/FED x

STUDY SITE: _____ NOT A FIRST GENERIC

STUDY SUMMARY

Single-dose fasting study

Parameter	Test	Ref.	Ratio	90%CI
LAUCi ng.hr/mL	1849.27	1885.80	0.98	85.15-118.55
LAUCt ng.hr/mL	1762.18	1788.82	0.99	85.11-120.41
Lcmax ng/mL	338.86	366.98	0.92	80.04-112.66
Tmax Hr.	1.90	1.59	1.19	
Thalf hr.	4.42	4.41	1.00	
Non-Fasting Study				
AUCi	2030.75	2025.40	1.00	
AUCt	1944.28	1926.74	1.01	
Cmax	361.19	375.37	0.96	
Tmax	2.83	2.49	1.14	
Thalf	4.44	4.82	0.92	

DISSOLUTION Test [mean (range)] Ref.

	Test	Ref.
10 min	76	61
20 min	86	81
30 min	92	90
40 min	95	97

PRIMARY REVIEWER: S.P. Shrivastava, Ph.D. **BRANCH:** II

INITIAL: _____ **DATE:** 9/12/96

BRANCH CHIEF: S. Nerurkar, Ph.D **BRANCH:** II

INITIAL: _____ **DATE:** 9/30/1996

DIRECTOR: Keith K. Chan, Ph.D.

DIVISION OF BIOEQUIVALENCE

INITIAL: _____ **DATE:** 9/30/96

DIRECTOR: Douglas L. Sporn

OFFICE OF GENERIC DRUGS

INITIAL: N/A **DATE:** _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-872

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

I initiated a call to ESI Lederle Inc. on 2/3/97 and left a message for N. Tantillo, that my call was in reference to labeling comments for ANDA 74872.

S. Peritore returned the call to our Office and I informed him of the labeling comments under "revisions needed post-approval" on the tentative approval summary [submission date 11/26/96]. He asked if any of these labeling comments would apply to their tablet application. I informed him which comments would apply to their tablet application. He was also informed to submit revised insert labeling as a telephone amendment.

DATE 2/3/97

ANDA NUMBER
74 872

IND NUMBER

TELECON

INITIATED BY **MADE**
_X APPLICANT/ _ BY
SPONSOR **TELE.**

x_ FDA _ IN PERSON

PRODUCT NAME
acyclovir capsules

FIRM NAME
ESI Lederle Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
S. Peritore

TELEPHONE NUMBER
914 723 4137

SIGNATURE
Jacqueline Wist, Rand 2/3/97

ANDA/AADA OFFICE LEVEL APPROVAL ROUTING SUMMARY

ANDA # 74-872
AADA #
Drug Acyclovir
Dosage Form CAPSULES
Strength 200mg
Applicant BSI Lederle
Proposed Action AP TA

REVIEWER:	Draft RECEIPT	Final ACTION
1. Project Manager T. Ama Review Support Branch	Date 3/5/97 Initials	Date 3/12/97 Initials

Original Rec'd date 3/28/96
Date Acceptable for Filing " " 7/28/96
Open Amendment Date(s) 11/26/96, 2/12/97
Chemistry Reviewer R Blewer
Supervisor T Simmons
Bio Reviewer S.P. Srivastava
Supervisor S. Nerurkar
Date of Office Level Bio Review 9/30/96
Pending Legal Case Yes____ No✓
Comments:

EER Status Acceptable 7/19/96 ✓
OAI Status Yes____ No ✓
Patent Certification ☐ II ☐ Cert. Let. exp. 4/22/97
Citizen Petition Yes____ No✓ If YES attach Email from Project Manager to Petition Coordinator of pending approval

2. Director of Chem. I or II Office of Generic Drugs	Date 3/17/97 Initials	Date 3/24/97 Initials

Comments: Chemistry is satisfactory

3. Office Level Chem Review **(1st Generic Only)** Div. Dir. of Chem I or II	Date Initials	Date Initials

Comments: Not first generic. Rweet

4. P. Rickman Supv., Reg. Support Branch	Date 3/25/97 Initials	Date 3/25/97 Initials

Contains certification required by the GDEA if sub after 6/1/92 ✓
Yes✓ No____ //// Determination of involvement? Yes____ No✓
Paragraph 4 Certification ____Yes ✓No (checklist)
Comments:
patent 574 will expire on 4/22/97 TA letter
No exclusivity issues

5. J. Phillips Director Division of LPS Office of Generic Drugs	Date 3/26/97 Rweet Initials	Date 3/27/97 JPhillips Initials

Comments:
This is for a tentative approval (patent 574 expires on 4/22/97). Acceptable EER dated 7/19/96 (Vol 1.1) No O.A.I. Alert in EES as of this date. OC requested to provide "Overall Recommendation" for EES prior to final approval. CMC and methods validation acceptable for approval. Bio-testing and Fed studies reviewed and found acceptable-Office level sign off dated 9/30/96 (K.Chan). FPL Acceptable 3/27/97 (100's and 500's). No contested correspondence or Citizens Petitions pending - Recommend: Tentative Approval OK for IA (TD)

6. G.Johnston
Deputy Director
Office of Generic Drugs
Patent Cert - P_4 - Yes ___ No ✓
Petition status NONE
Pend. Legal Actions - Yes ___ No ✓
Comments: OK to approve

Date 3/27/97 Initials G
Date 3/27/97 Initials G

7. D. Sporn
Director
Office of Generic Drugs

R. Williams, MD
1st Generic ___
PD or clinical for BE ___
Special Scientific or Reg Issues ___
Comments:

Date ___ Initials ___
Date 3/27/97 Initials ___

8. T. Ames
Project Manager
Div Chem II, Branch 7

Date 3/27/97 Initials
Date ___ Initials ___

Company Notified
5:50 Time notified of approval via telephone
6:09 Time notified of approval via facismile

LETTER SIGNED: ___
(Name and Date)

(revision date 8-14-96) (X:\wpfile\welsh\rout2.rec)

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-872

CORRESPONDENCE

ESI LEDERLE

505(b)(2) Incomplete
for Info
3/27/96

RECEIVED

MAR 28 1996

GENERIC DRUGS

March 27, 1996

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Acyclovir Capsules, 200 mg

Dear Sir/Madam:

We are submitting a complete Abbreviated New Drug Application pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules, 200 mg.

This application provides for the manufacture, processing, labeling and packaging of Acyclovir Capsules at our Pearl River, New York facility. Documents contained in this application are on letterhead from Lederle Laboratories and ESI Lederle. Other documents reference Wyeth-Ayerst Laboratories. All are affiliated companies under common ownership and control of American Home Products Corporation.

This application, which contains 9 unnumbered volumes, is organized in the format suggested in the Office of Generic Drugs' Policy and Procedure Guide No. 30-91, entitled "Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application".

The reference listed drug product in this application is the Burroughs Wellcome product Zovirax® Capsules 200 mg. The active ingredient, dosage form, strength and route of administration of our proposed product are the same as those of the reference drug product. A side-by-side comparison of our proposed product labeling to the reference drug product labeling is included in this application. The proposed product, like the reference product, will be marketed as a prescription drug as stated in the labeling.

The reference drug is not entitled to a period of marketing exclusivity. It is covered by a US patent expiring April 22, 1997, as published in "Approved Drug Products with Therapeutic Equivalence Evaluations, 15th Edition". This application contains a paragraph III certification with respect to the claimed US Patent 4,199,574 which will expire April 22, 1997. We request that approval of this application be made effective on expiration of this patent.

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000 Fax: (914) 732-5114

To demonstrate the bioequivalence of ESI Lederle's Acyclovir Capsules, two bioequivalence studies were conducted. One study is entitled "2-Way Crossover Bioequivalence Study of ESI Lederle and Burroughs Wellcome (Zovirax®) 200 mg Acyclovir Capsules in Fasting Volunteers" and the other study is entitled "3-Way Crossover Bioequivalence Study of ESI Lederle and Burroughs Wellcome (Zovirax®) 200 mg Acyclovir Capsules in Fed and Fasting Volunteers". The two completed studies are included in Section VI of this application. The study data are contained on a floppy disk submitted with the orange pharmacokinetic review copy of this application. A hard copy printout of this data also accompanies the disk. This data is in the format specified in the Division of Bioequivalence guidance, entitled "Informal Guidance on the Submission of Data for Bioequivalence Studies in Computer Format" dated 12/15/87.

As required under 21 CFR 314.94(a)(7)(iii), each *in vivo* bioequivalence study in this application contains a description of the analytical and statistical methods used in each study, and statements that each study was conducted in compliance with the institutional review board regulations in 21 CFR Part 56, and the informed consent regulations in 21 CFR Part 50.

We are using Acyclovir USP drug substance manufactured by ——————— ——————— acting as their US agent. This application contains letters from ——————— authorizing FDA to refer to the DMF (———) on behalf of ESI Lederle Inc and authorizing ——————— to be their US agent.

The submission batch size was ——————— capsules. The anticipated production batches are the same size as the submission batch.

The submission batch was packaged in the containers proposed for marketing. Acyclovir capsules 200 mg will be supplied in trade packages of 100s and 1000s, and in unit-of-issue 100s. All operations will be performed at our Lederle facility in Pearl River, New York.

Since aspects related to our facilities will be evaluated by FDA's field investigational staff, and not by drug application reviewers, this application does not contain references to a Type 1 DMF, nor does it contain a description of our facilities related to the content of a Type 1 DMF. However, we do provide a brief, general description of our facilities, operations and controls.

With respect to analytical methods, three copies of the method validation package are being submitted with this application since we are proposing our own methods of testing for the drug product, which is not a compendial article.

In accordance with 21 CFR 314.94 requiring the submission by applicants of an additional copy of the chemistry, manufacturing and controls section of applications to the field office, we are providing a field copy directly to the FDA New York District Office. We certify that the field copy is a true copy of the chemistry, manufacturing and controls section of our application.

This application contains a certification statement with respect to convictions or persons debarred under 21 USC 335a(a) or (b).

Please contact the undersigned if you need any additional information.

Sincerely,

Nicholas C. Tantillo
Director
Regulatory Affairs and Compliance
ESI Lederle

cc: NY District Office

ANDA 74-872

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

APR 10 1996

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Acyclovir Capsules, 200 mg

DATE OF APPLICATION: March 27, 1996

DATE OF RECEIPT: March 28, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Timothy Ames
Project Manager
(301) 594-1841

Sincerely yours,

Jerry Phillips 4/10/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-872
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB _____ date
HFD-615/WRussell, CSO _____ date
HFD-647/JSimmons, Sup. Chem _____ date
File\x:\new\firmsam\ESI\ltrs&rev\74872
F/T hrw 4-3-96
ANDA Acknowledgement Letter!

ANDA 74-872

OCT - 3 1996

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

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The testing should be conducted in 900 mL Purified Water using USP 23 Apparatus I (Basket) at 100 R.P.M. The test product should meet the following specifications:

   > Not less than —% (Q) of the labeled amount of acyclovir is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-872, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File

Letter Out, Bio Acceptable

Endorsements:

S. Shrivastava 10/2/96
S. Nerurkar 10/2/96
M. Anderson 10/2/96 STM for

DRAFTED: STM 10/02/96 X:\WPFILE\BIO\FINAL\N74872.APP

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-872

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

NOV 4 1996

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.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1.

2.

3.

4.

5. [redacted]

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.

Please note and acknowledge the following:

Please be advised that you have the option to use 25°-30°C with ambient relative humidity or ICH proposed conditions of 25° ± 2°C and 60% ± 5% relative humidity.

Drug Master File ——— is currently deficient and the DMF holder has been advised of the deficiencies. A satisfactory resolution of the DMF deficiencies is required by the holder prior to the approval of this application. In your response, please provide a statement from the DMF holder indicating all issues communicated to the holder by the Agency have been addressed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond

to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

10/1/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 74-872
DUP Jacket
FIELD COPY
Division File
HFD-600/Reading File

Endorsements:

HFD-645/RBrown/10/21/96
HFD-645/JSimmons/10/22/96
HFD-613/JWhite/
HFD-613/TAmes
X:\WPFILE\KIM\BROWN\74-872L.ORG
F/T by pah/10/30/96
X:\new\firmsam\lederle\ltrs&rev\74872.naf
NOT APPROVABLE: MINOR

APPEARS THIS WAY
ON ORIGINAL

1 copy out

ESi LEDERLE

NEW CORRESPONDENCE

November 22, 1996

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRES

Re: ANDA 74-872
Acyclovir Capsules, 200 mg

Dear Sir/Madam:

We have on this day submitted samples of our drug product to the New York District office, as requested by the Supervisory chemist there. Attached is a copy of the letter submitted with the various samples and documents in support of our application.

Please add this document to our application. Thank you.

Sincerely,

Nicholas C. Tantillo
Director, Regulatory Affairs

RECEIVED
NOV 2 5 [illegible]
GENERIC DRUGS

RECEIVED
NOV 2 5 [illegible]
GENERIC DRUGS

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000 Fax: (914) 732-5114

AM Noted. (2) next labeling Reviewer (1) then 1st to Chemistry Reviewer

ESiLEDERLE

12/12/96

MINOR AMENDMENT

NDA ORIG AMENDMENT
N/AM FPL

November 26, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Acyclovir Capsules
200 mg
ANDA #74-872

Dear Sir/Madam:

We refer to our 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 refer also to your comment letter dated November 4, 1996, which outlined deficiencies noted in our application, and a telephone contact on November 6, 1996 between Ray Brown of your office and Nicholas Tantillo of this office.

We understand our responses are considered a Minor Amendment. Our responses are as follows:

A. CHEMISTRY DEFICIENCIES

COMMENT 1: [ ]

REPLY: Attached for inclusion in SECTION XIV of our application are [ ]

COMMENT 2a: [ ]

REPLY: [ ]

RECEIVED
NOV 2 ? 1996
GENERIC DRUGS

Nicholas 12.6.96

401 North Middletown Rd., Pearl River, NY 10965-1299 Tel: (914) 732-5000 Fax: (914) 732-5114

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

11/26/1996 ESI LEDERLE LETTER

B. LABELING DEFICIENCIES:

REPLY: Our labeling has been revised in accordance with your recommendations and after a telephone discussion on November 6, 1996 between Mr. John Grace of the Labeling Review Branch and Sal Peritore from this office.

Attached for inclusion in SECTION V of our application are twelve (12) copies of our final printed container labels (U5831) and twelve (12) copies insert labeling (CI 4845, issued November 25, 1996). Further, we have included a side-by-side comparison of this proposed labeling with the previous submission of March 27, 1996, with all differences annotated and explained, as requested.

Please note that the description of the capsules changed in the HOW SUPPLIED Section. The printing will be modified for marketed product to incorporate the identifier "511" instead of '————', and "mg" is added after "...200" The revised monograph and the revised master production formula contain this changed description..

We note your comment regarding the CLINICAL PHARMACOLOGY section. We plan to combine the inserts for the tablet and capsule dosage forms, but we do not want the approval of one application contingent upon approval of the other. We will combine inserts for tablets and capsules after approval of our applications and submit a post-approval supplement.

General comments - Please note and acknowledge the following:
Please be advised that you have the option to use 25° - 30° with ambient relative humidity or ICH proposed conditions of 25° ± 2° and 60% ± 5% relative humidity.

Reply: We note and acknowledge your comment regarding our option to use 25° - 30° with ambient relative humidity or ICH proposed conditions of 25° ± 2° and 60% ± 5% relative humidity.

Drug Master File——is currently deficient and the DMF holder has been advised of the deficiencies. A satisfactory resolution of the DMF deficiencies is required by the holder prior to the approval of this application. In your response, please

provide a statement from the DMF holder indicating all issues communicated to the holder by the Agency have been addressed.

Reply: The Drug Master File holder, _____ has provided a letter indicating all issues communicated to it have been addressed Attached for inclusion in section VIII of our application is a copy of that letter.

In accordance with 21 CFR 314.94(d)(5) requiring the submission by applicants of an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy of this amendment directly to the FDA New York District Office. We certify that the field copy is a true copy of this amendment to our application.

We trust that we have adequately addressed your comments. We look forward to a prompt review and approval of this application.

Sincerely,

Nicholas C. Tantillo
Director, Regulatory Affairs
914-732-4137

cc FDA NY District Office

Package insert See Note on "marked up" P.1 ...
Labeling satisfactory in FPL 3/18/97

ESI LEDERLE

TELEPHONE AMENDMENT

NDA ORIG AMENDMENT

AF

February 12, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Acyclovir Capsules
200 mg
ANDA 74-872

Gentlemen:

We refer to our abbreviated new drug application for Acyclovir Capsules, 200 mg, and the telephone call from Dr. Jacqueline White of February 3, 1997, requesting changes to the package insert labeling to be submitted as a telephone amendment.

We have revised the DESCRIPTION, CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION sections and are providing twelve (12) final printed copies of our revised package insert **(CI 4845, Issued February 6, 1997)** as requested. Also enclosed is a side-by-side comparison of this version with the previously submitted version showing the changes.

We trust this amendment will lead to a quick approval of our application.

Sincerely,

Salvatore P. Peritore, R.Ph., M.S.
Associate Director
Regulatory Affairs

/eg
(a:fda:7acyccap)

Enclosures

RECEIVED

FEB 13 1997

GENERIC DRUGS

FAX AMENDMENT

March 20, 1997

Raymond Brown
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Acyclovir Capsules
ANDA 74-872

Via Fax: 301-443-3839

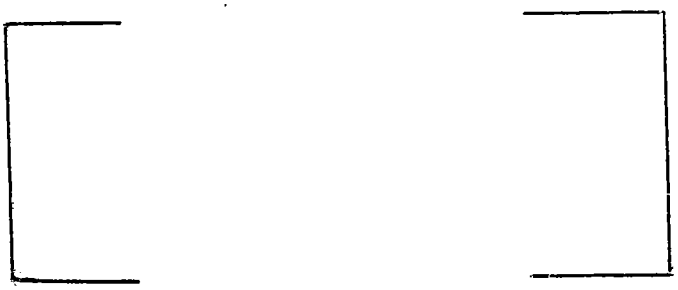
Dear Sir:

In response to a telephone request to us by Ms. Cassandra Sharrod, we are providing the following ingredients in the black inks used by ——— for capsule shell imprint:

MANUFACTURER - ———————————

continued ...

2



Attached are copies of —— Product Specifications for each of these inks.

Sincerely,

Nicholas Tantillo
Director, Regulatory Affairs
ESI LEDERLE

Attachments

/eg
(r:fda:7acycpfx)