# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number : 074828**

**Trade Name : ACYCLOVIR 200MG CAPSULES**

**Generic Name: Acyclovir 200mg Capsules**

**Sponsor :Lemmom Company**

**Approval Date: April 22, 1997**

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 074828**

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# CENTER FOR DRUG EVALUATION AND RESEARCH

## Application Number 074828

## APPROVAL LETTER

ANDA 74-828

APR 22 1997

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

Dear Ms. Jaskot:

This is in reference to your abbreviated new drug application dated December 28, 1995, 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 amendment dated March 26, 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 the application is approved. The Division of Bioequivalence has determined you 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 changes 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 you 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,

Douglas L. Sporn 4-22-97
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074828

## FINAL PRINTED LABELING

NDC 0093-0044-01

# ACYCLOVIR
## Capsules
## 200 mg

Each capsule contains:
Acyclovir, USP 200 mg

**Caution:** Federal law prohibits dispensing without prescription.

100 CAPSULES

LEMMON

**Usual Dosage:** See package insert for full prescribing information.

Store at 15° to 25°C (59° to 77°F).

Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L19054 PG Iss. 9/96

LEMMON COMPANY
Sellersville, PA 18960

N 3 0093-0044-01 4 00


NDC 0093-0044-10

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L19055 PG Iss. 9/96

LEMMON COMPANY
Sellersville, PA 18960

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0044

ACYCLOVIR CAPSULES, 200 mg

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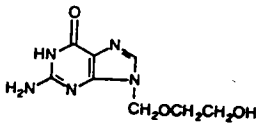
**DESCRIPTION**

Acyclovir is an antiviral drug. Acyclovir capsules are for oral administration. Each capsule contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose (monohydrate), sodium lauryl sulfate, and magnesium stearate. The capsule shell consists of gelatin, FD&C Blue No. 2, D&C Red No. 33, and titanium dioxide. The imprinting ink contains pharmaceutical glaze (modified) in SD-45, titanium dioxide, ethylene glycol, monoethyl ether, lecithin, and simethicone.

The chemical name of acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine; it has the following structural formula:



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

Acyclovir is a white, crystalline powder with 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 herpesviruses 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 man, 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 5.9-13.5 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 of 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.[11-19] 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 0.17-1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85-3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells of P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with $ID_{50}$ values ranging from 2.3-17.6 mcg/mL (plaque reduction, HEF cells) to 1.82-56.8 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/m$^2$ and 600 mg/m$^2$, in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

In a multi-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 of 6 volunteers, the influence of food on the absorption 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 psycho-social 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 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy. Re-evaluation 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 re-evaluation.

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

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

**Herpes-Zoster Infections:** In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to 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 one month and one 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.

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**WARNINGS**

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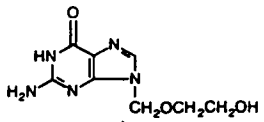
## DESCRIPTION

Acyclovir is an antiviral drug. Acyclovir capsules are for oral administration. Each capsule contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose (monohydrate), sodium lauryl sulfate, and magnesium stearate. The capsule shell consists of gelatin, FD&C Blue No. 2, D&C Red No. 33, and titanium dioxide. The imprinting ink contains pharmaceutical glaze (modified) in SD-45, titanium dioxide, ethylene glycol, monoethyl ether, lecithin, and simethicone.

The chemical name of acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine; it has the following structural formula:



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**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/m$^2$ and 600 mg/m$^2$, in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

In a multi-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 of 6 volunteers, the influence of food on the absorption 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 psycho-social 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 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy. Re-evaluation 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 re-evaluation.

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

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 one month and one 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%).[35] 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 man 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 acyclovir treatment 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 acyclovir treatment of chickenpox would have any effect on either decreasing or increasing the incidence of 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:** Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

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

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

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

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

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically 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 one-month study and were 24 to 48 times human levels in the six-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 spermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels).

**Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[42] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

**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 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%) and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%) and paresthesia (0.8%). Adverse events reported by 329 patients during the third year include 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 hr 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:** 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 re-evaluation. See **INDICATIONS AND USAGE** and **PRECAUTIONS** for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

**Intermittent Therapy:** 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 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

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

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

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

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

**Hemodialysis:** For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a six-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 200 mg are available in a #1 capsule with a dark blue body and a dark blue cap, imprinted "93" and "044" on both the cap and the body, in bottles of 100 and 1000.

Store between 15° to 25°C (59° to 77°F).

Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

**CAUTION:** Federal law prohibits dispensing without prescription.

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Manufactured By:
**LEMMON COMPANY**
Sellersville, PA 18960

Printed in USA
Rev. C 3/97

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER 074828**

**CHEMISTRY REVIEW(S)**

1. CHEMIST'S REVIEW NO. 3

2. ANDA 74-828

3. NAME AND ADDRESS OF APPLICANT
Lemmon Company
650 Cathill Road
Sellersville, PA 18960

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

**Final approval date is January 25, 1985.**

**U.S. Patent No. 4199574, 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 | 12/28/95 | Refused to file letter | 2/16/96 |
| Amendment | 2/26/96 | | |
| | | Acknowledgment letter | 3/12/96 |
| | | CSO review | 1/26/96 |
| | | Bio review #1 | 6/20/96 |
| | | Bio letter | 7/16/96 |
| | | Labeling review #1 | 7/16/96 |
| | | Deficiency letter | 9/09/96 |
| Amendment (major) | 10/14/96 | Labeling review #2 | 11/08/96 |
| | | Bio review #2 | 11/18/96 |
| | | Methods validation report | 11/19/96 |
| | | Bio acceptable letter | 11/21/96 |
| Amendment (minor) | 12/11/96 | Deficiency (facsimile) | 1/21/97 |
| | | | 1/22/97 |

This review covers submission dated 01/29/97.

10. PHARMACOLOGICAL CATEGORY
For the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients. Also for the treatment of herpes zoster (shingles) and chickenpox (valicella).

11. Rx or OTC
Rx

12. RELATED DMF(s)

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

14. STRENGTH
**200 mg**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074828

## BIOEQUIVALENCE REVIEW(S)

ANDA 74-828

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville PA 18960

NOV 2 1 1996

Dear Madam:

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 interim dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less thar of the labeled amount of acyclovir in the dosage form 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,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 18 1996



| | |
|---|---|
| Acyclovir Capsules | Lemmon |
| 200 mg Capsules | Sellersville, PA |
| ANDA #74-828 | Submission Date: |
| Reviewer: Moo Park | July 26, 1996 |
| Filename: 74828SDF.796 | |

Review of a BE Study under Nonfasting Conditions

I. Objectives

Review of Lemmon's 3-way crossover *in vivo* bioequivalence study comparing its 200 mg strength Acyclovir Capsules to Burroughs Wellcome's 200 mg strength Zovirax Capsules under nonfasting/ fasting conditions.

II. Background

The firm had submitted an acceptable *in vitro* dissolution data and acceptable 2-way crossover *in vivo* bioequivalence study under fasting conditions (submission date: 12/28/95; review date: 6/20/96).

III. Summary of Bioequivalence Study Procedures

BE Study under Nonfasting Conditions

1. Protocol #B-05065

2. Objective of the study:

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

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

4. Study sites:

   Clinical study:

   Analytical study:

   PK and Statistics:

5. Study dates:

Clinical study: 10/20/95-11/9/95
Analytical study: 1/10/96-1/23/96

6. Investigators:

Clinical:

Analytical:

PK and Statistics:

7. Drug Products:

A. Test: 200 mg Acyclovir Capsules (Lemmon, Lot #0554-014)

B. Reference: 200 mg Zovirax® Capsules (Burroughs Wellcome, Lot #4x1896; exp date: 11/97)

8. Dosing: All doses were administered with 240 ml of room temperature water.

Treatment #1: 200 mg (1 x 200 mg) of test product with water after an overnight fast of at least 10 hours.

Treatment #2: 200 mg (1 x 200 mg) of test product with water after a high fat breakfast preceded by an overnight fast of at least 9.5 hours.

Treatment #3: 200 mg (1 x 200 mg) of reference product with water after a high fat breakfast preceded by an overnight fast of at least 9.5 hours.

9. Subjects: Eighteen (18) subjects who were recruited in this study were normal healthy male volunteers in the age range of 18-45 years, and within 10% of their ideal 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. Subjects #16 and 18 did not participate in the study. Therefore, this study was initiated and completed with 16 subjects. Subject #17 was unable to participate in period 3 due to personal reasons. This subject started and completed the period 3 six days later than the other subjects.

10. Confinement: The subjects were housed and fed at the clinical facility from the evening prior to each treatment until 14 hours

following dosing.

11. Food and fluid intake: Standard lunch was served 4 hours post-dose. The drug products were administered with 240 mL of water. Water was allowed ad lib. from 2 hours post-dose.

Standard breakfast used in the study:

| | |
|---|---|
| one | buttered English Muffin |
| one | fried egg |
| one | slice of American cheese |
| one | slice of Canadian bacon |
| one | serving of hash brown potatoes |
| six | fluid ounces (180 mL) of orange juice |
| eight | fluid ounces (240 mL) of whole milk |

12. Washout period: One week.

13. Blood samples: In each period, 10 mL of blood samples were collected at 0, 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, and 14 hours. Plasma was separated and all plasma samples were stored frozen at -20°C until analyzed.

14. Subject safety monitoring: Blood pressure and heart rate were monitored at baseline and at 2 and 14 hours post-dose in each period. No significant changes were reported.

15. Adverse reactions: Two adverse reactions (headaches) were reported by subject #17 in periods 1 and 2, both with the test product. No actions were taken.

16. Analytical procedure: Plasma samples were assayed by a

19. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for acyclovir. Test/reference ratios were calculated for log-transformed AUCT, AUCI and CMAX.

IV. <u>Validation of Assay Method for Plasma Samples</u>

V. *In Vivo* BE Study Results with Statistical Analysis

Study under nonfasting conditions

A total of 18 subjects were recruited for the study but only 16 participated in the study and 16 subjects completed three periods of study successfully. Subject #17 was unable to participate in period 3 due to personal reasons. This subject started and completed the period 3 six days later than the other subjects.

Two adverse reactions (headaches) were reported by subject #17 in periods 1 and 2, both with the test product. No actions were taken.

1. Mean plasma levels

The mean plasma levels for the test and reference products under nonfasting conditions are comparable as shown in Table 2 and Fig. P-1. The test/reference ratios (RMEAN23) for the mean plasma levels under nonfasting conditions were close to 1 for most of the time points. Under nonfasting conditions, the mean Cmax (mean Tmax) was 365 ng/mL (3 hrs.) and 332 ng/mL (3 hrs.) for the test and reference products, respectively. Under fasting conditions, the mean Cmax of the test product was 384 ng/mL at 2-2.5 hours, indicating slight degree of food effect.

Table 2. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FAST; MEAN2=TEST-FOOD; MEAN3=REF-FOOD
RMEAN23=T/R RATIO UNDER NONFASTING CONDITIONS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

| | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 |
|---|---|---|---|---|---|---|
| TIME HR | | | | | | |
| 0 | 1.73 | 6.93 | 0.00 | 0.00 | 0.00 | 0.00 |
| 0.25 | 2.03 | 8.13 | 0.00 | 0.00 | 0.00 | 0.00 |
| 0.5 | 68.42 | 56.84 | 0.00 | 0.00 | 4.59 | 12.91 |
| 0.75 | 175.13 | 110.32 | 16.79 | 25.07 | 39.78 | 65.81 |
| 1 | 265.95 | 158.04 | 61.43 | 62.92 | 101.28 | 122.86 |
| 1.25 | 323.38 | 196.31 | 126.90 | 100.27 | 161.69 | 157.99 |
| 1.5 | 354.81 | 195.97 | 200.17 | 129.53 | 217.22 | 156.46 |
| 1.75 | 373.00 | 183.96 | 272.85 | 152.64 | 261.74 | 147.29 |
| 2 | 384.06 | 157.19 | 327.03 | 165.54 | 301.48 | 139.02 |
| 2.5 | 383.69 | 180.62 | 357.19 | 134.79 | 330.00 | 112.87 |
| 3 | 333.50 | 145.81 | 364.69 | 92.84 | 332.63 | 99.31 |
| 4 | 259.56 | 124.50 | 296.94 | 100.19 | 281.63 | 83.15 |
| 6 | 146.52 | 66.59 | 159.06 | 46.06 | 149.00 | 41.71 |
| 8 | 93.72 | 41.86 | 90.63 | 24.69 | 86.41 | 23.40 |
| 10 | 61.16 | 27.62 | 57.91 | 15.21 | 55.51 | 15.12 |
| 12 | 40.72 | 19.23 | 38.24 | 10.44 | 37.84 | 9.58 |
| 14 | 26.03 | 17.47 | 24.56 | 13.14 | 20.44 | 15.10 |

(CONTINUED)

| | RMEAN12 | RMEAN13 | RMEAN23 |
|---|---|---|---|
| TIME HR | | | |
| 0 | . | . | . |
| 0.25 | . | . | . |
| 0.5 | . | 14.91 | 0.00 |
| 0.75 | 10.43 | 4.40 | 0.42 |
| 1 | 4.33 | 2.63 | 0.61 |
| 1.25 | 2.55 | 2.00 | 0.78 |
| 1.5 | 1.77 | 1.63 | 0.92 |
| 1.75 | 1.37 | 1.43 | 1.04 |
| 2 | 1.17 | 1.27 | 1.08 |
| 2.5 | 1.07 | 1.16 | 1.08 |
| 3 | 0.91 | 1.00 | 1.10 |
| 4 | 0.87 | 0.92 | 1.05 |
| 6 | 0.92 | 0.98 | 1.07 |
| 8 | 1.03 | 1.08 | 1.05 |
| 10 | 1.06 | 1.10 | 1.04 |
| 12 | 1.06 | 1.08 | 1.01 |
| 14 | 1.06 | 1.27 | 1.20 |

## 2. Pharmacokinetic parameters

The test/reference ratios (RMEAN23) for the non-transformed and log-transformed AUCT, AUCI and CMAX under nonfasting conditions range 1.04-1.12 as shown in Tables 3-4 and met the requirements of the Agency.

Table 3. ARITHMETIC MEANS AND RATIOS
MEAN1=TEST-FAST; MEAN2=TEST-FOOD; MEAN3=REF-FOOD
RMEAN23=T/R RATIO UNDER NONFASTING CONDITIONS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

| | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 |
|---|---|---|---|---|---|---|
| PARAMETER | | | | | | |
| AUCI | 2236.44 | 834.52 | 2049.06 | 459.75 | 1960.94 | 457.33 |
| AUCT | 2070.44 | 800.94 | 1901.50 | 435.96 | 1815.81 | 434.94 |
| CMAX | 466.94 | 184.22 | 439.00 | 102.61 | 394.75 | 105.24 |
| KE | 0.19 | 0.02 | 0.20 | 0.03 | 0.21 | 0.03 |
| LAUCI | 2092.02 | 0.38 | 1996.02 | 0.24 | 1910.18 | 0.24 |
| LAUCT | 1924.83 | 0.40 | 1849.94 | 0.25 | 1766.73 | 0.24 |
| LCMAX | 437.00 | 0.37 | 426.92 | 0.25 | 381.12 | 0.28 |
| THALF | 3.62 | 0.39 | 3.48 | 0.59 | 3.42 | 0.70 |
| TMAX | 1.92 | 0.87 | 2.59 | 0.71 | 2.44 | 0.84 |

(CONTINUED)

| | RMEAN12 | RMEAN13 | RMEAN23 |
|---|---|---|---|
| PARAMETER | | | |
| AUCI | 1.09 | 1.14 | 1.04 |
| AUCT | 1.09 | 1.14 | 1.05 |
| CMAX | 1.06 | 1.18 | 1.11 |
| KE | 0.95 | 0.93 | 0.98 |
| LAUCI | 1.05 | 1.10 | 1.04 |
| LAUCT | 1.04 | 1.09 | 1.05 |
| LCMAX | 1.02 | 1.15 | 1.12 |
| THALF | 1.04 | 1.06 | 1.02 |
| TMAX | 0.74 | 0.79 | 1.06 |

Table 4.LSMEANS AND RATIOS
LSM1=TEST-FAST; LSM2=TEST-FOOD; LSM3=REF-FOOD
RLSM23=T/R RATIO UNDER NONFASTING CONDITIONS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

| | LSM1 | LSM2 | LSM3 | RLSM12 | RLSM13 | RLSM23 |
|---|---|---|---|---|---|---|
| PARAMETER | | | | | | |
| AUCI | 2204.07 | 2004.43 | 1919.94 | 1.10 | 1.15 | 1.04 |
| AUCT | 2039.87 | 1859.51 | 1776.45 | 1.10 | 1.15 | 1.05 |
| CMAX | 459.57 | 429.90 | 386.70 | 1.07 | 1.19 | 1.11 |
| LAUCI | 2050.94 | 1949.32 | 1865.16 | 1.05 | 1.10 | 1.05 |
| LAUCT | 1885.86 | 1805.58 | 1723.36 | 1.04 | 1.09 | 1.05 |
| LCMAX | 427.94 | 417.54 | 372.34 | 1.02 | 1.15 | 1.12 |

VI. Comments

1. Study under nonfasting conditions (200 mg capsules):

The mean plasma levels for the test and reference products under nonfasting conditions are comparable. The test/reference ratios (RMEAN23) for the mean plasma levels under nonfasting conditions were close to 1 for most of the time points. Under nonfasting conditions, the mean Cmax (mean Tmax) was 365 ng/mL (3 hrs.) and 332 ng/mL (3 hrs.) for the test and reference products, respectively. Under fasting conditions, the mean Cmax of the test product was 384 ng/mL at 2-2.5 hours, indicating slight degree of food effect.

The test/reference ratios (RMEAN23) for the non-transformed and log-transformed AUCT, AUCI and CMAX under nonfasting conditions range 1.04-1.12 as shown in Tables 3-4 and met the requirements of the Agency.

2. Assay validation: Pre-study validation and within-study validation are acceptable.

3. Adverse reaction (200 mg capsules): No clinically significant adverse reactions were reported.

4. *In vivo* bioequivalence study under fasting conditions (submission date: 12/28/95) was acceptable.

5. The formulation and in vitro testing results including the dissolution data reviewed under the fasting study were acceptable.

VII. Deficiencies

None.

VIII. Recommendations

1. The *in vivo* bioequivalence study conducted by Lemmon on its Acyclovir Capsules, 200 mg strength, lot #0544-014, comparing it to Burroughs Wellcome's Zovirax® Capsules, 200 mg strength, lot #4x1896,under nonfasting conditions has been found acceptable by the Division of Bioequivalence. The study demonstrates that Lemmon's Acyclovir Capsules, 200 mg strength, is bioequivalent to Burroughs Wellcome's Zovirax® Capsules, 200 mg strength under nonfasting conditions.

2. The firm has already conducted an acceptable *in vivo* bioequivalence study under fasting conditions on its Acyclovir Capsules, 200 mg strength, lot #0544-014, comparing it to Burroughs Wellcome's Zovirax® Capsules, 200 mg strength, lot #4x1896 (submission date: 12/28/95; review date: 6/20/96).

3. The FDA dissolution testing conducted by Lemmon on its Acyclovir Capsules, 200 mg strength, lot #0544-014, and Burroughs Wellcome's Zovirax® Capsules, 200 mg strength, lot #4x1896, has been found acceptable (submission date: 12/28/95; review date: 6/20/96).

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

5. From the bioequivalence point of view the firm has met the *in vivo* bioequivalence and *in vitro* dissolution testing requirements and the studies are acceptable.

The firm should be informed of the recommendations.

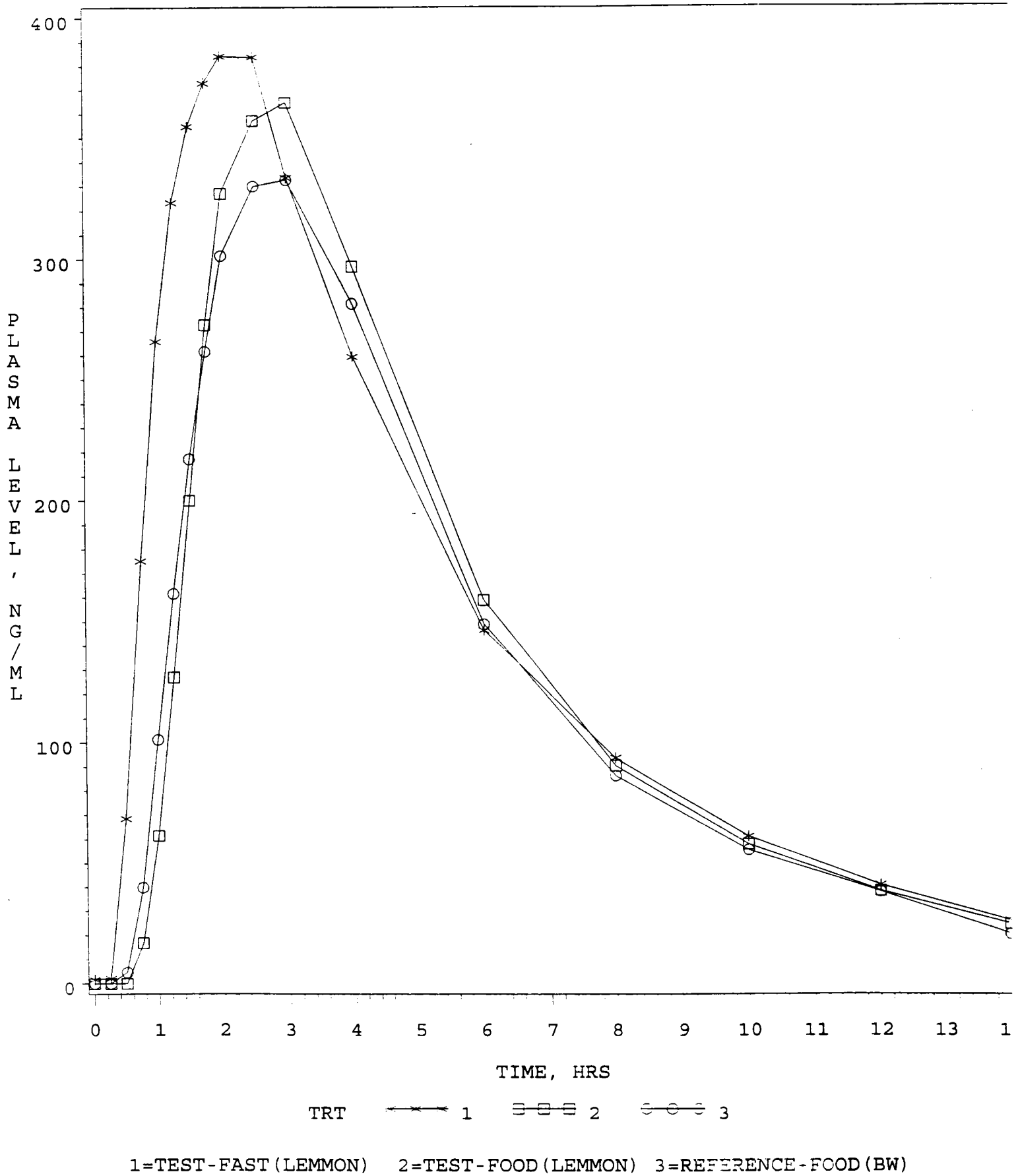
Moo Park, Ph.D. ✓
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATP' _____ 11/18/96

Concur: _____ Date: 11/18/96
Rabindra Patnaik, Ph.D.
Acting Director

# FIG P-1. PLASMA ACYCLOVIR LEVELS

ACYCLOVIR CAPSULES, 200 MG, ANDA #74-828
UNDER NONFASTING CONDITIONS
DOSE=200 MG



ON

JUN 20 1996



| | |
|---|---|
| Acyclovir Capsules | Lemmon |
| 200 mg Capsules | Sellersville, PA |
| ANDA #74-828 | Submission Date: |
| Reviewer: Moo Park | December 28, 1995 |
| Filename: 74828SD.D95 | |

Review of a BE Study and Dissolution Data

I. Objectives

Review of Lemmon's *in vivo* bioequivalence study comparing its 200 mg strength Acyclovir Capsules to Burroughs Wellcome's 200 mg strength Zovirax Capsules under fasting conditions. The firm submitted *in vitro* dissolution data for review.

Study under non-fasting conditions should also be submitted for review.

II. 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 IV 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 (Burroughs-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 800 mg and 400 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 ml (NDA #19-909, 12/22/89).

III. Summary of Bioequivalence Study Procedures

BE Study under Fasting Conditions

1. Protocol #B-05055

2. Objective of the study:

   The objective of this study was to determine the bioequivalence of two acyclovir capsule 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:

   Analytical study:

   PK and Statistics:

5. Study dates:

   Clinical study: 7/27/95 (Period 1)
   8/3/95 (Period 2)

   Analytical study: 8/17/95-9/21/95

6. Investigators:

   Clinical:

   Analytical:

   PK and Statistics:

7. Drug Products:

   A. Test: 200 mg Acyclovir Capsules (Lemmon, Lot #0554-014)

   B. Reference: 200 mg Zovirax® Capsules (Burroughs Wellcome, Lot #4x1896)

8. Dosing: All doses were administered with 240 ml of room

temperature water following an overnight fast.

9. Subjects: Thirty-two (32) subjects who entered in this study were normal healthy male volunteers in the age range of 18-45 years, and within 10% of their ideal 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. Thirty (30) subjects completed the entire clinical portion of the study.

10. Confinement: The subjects were housed and fed at the clinical facility from the evening prior to each treatment until 14 hours following dosing.

11. Food and fluid intake: Standard lunch was served 4 hours post-dose. The drug products were administered with 240 mL of water. Water was allowed ad lib. from 2 hours post-dose.

12. Washout period: One week.

13. Blood samples: In each period, 10 mL of blood samples were collected at 0, 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, and 14 hours. Plasma was separated and all plasma samples were stored frozen at -20°C until analyzed.

14. Subject safety monitoring: Blood pressure and heart rate were monitored at baseline and at 2 and 14 hours post-dose in each period. No significant changes were reported.

15. Adverse reactions: Ten adverse reactions (test: 5/2 subjects; reference: 4/3 subjects) were reported. No action was required.

16. Analytical procedure: Plasma samples were assayed by a

19. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for acyclovir. 90% confidence intervals were calculated for log-transformed AUCT, AUCI and CMAX.

IV. <u>Validation of Assay Method for Plasma Samples</u>

V. *In Vivo* BE Study Results with Statistical Analysis

Study under fasting conditions

A total of 34 subjects were recruited for the study but only 32 participated in the study and 30 subjects completed two periods of study successfully. There were two drop-outs: Subjects #4 and 34 did not complete the 2nd period due to illness.

Adverse reactions were followed according to the protocol of the study. No clinically significant adverse reactions were reported: Ten adverse reactions (test: 5/2 subjects; reference: 4/3 subjects) were reported. No action was required.

1. Mean plasma levels

The mean plasma levels for the test and reference products are comparable as shown in Table 3 and Fig. P-1. The test/reference ratios (RMEAN12) for the mean plasma levels were close to 1 for most of the time points.

Table 3. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| TIME HR | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | . |
| 0.25 | 6.07 | 20.09 | 1.57 | 5.98 | 3.87 |
| 0.5 | 106.12 | 96.65 | 80.05 | 98.62 | 1.33 |
| 0.75 | 237.74 | 131.72 | 188.58 | 160.92 | 1.26 |
| 1 | 321.03 | 171.26 | 271.77 | 166.94 | 1.18 |
| 1.25 | 393.86 | 198.60 | 349.93 | 188.17 | 1.13 |
| 1.5 | 408.83 | 200.09 | 372.50 | 159.06 | 1.10 |
| 1.75 | 435.07 | 191.25 | 415.90 | 169.75 | 1.05 |
| 2 | 399.87 | 151.62 | 414.23 | 160.53 | 0.97 |
| 2.5 | 367.87 | 151.86 | 429.67 | 186.17 | 0.86 |
| 3 | 349.47 | 142.90 | 383.80 | 145.71 | 0.91 |
| 4 | 273.93 | 124.13 | 304.01 | 124.83 | 0.90 |
| 6 | 160.72 | 68.17 | 174.48 | 62.43 | 0.92 |
| 8 | 103.60 | 44.76 | 110.99 | 36.64 | 0.93 |
| 10 | 68.75 | 29.13 | 71.37 | 24.97 | 0.96 |
| 12 | 46.10 | 17.70 | 48.98 | 12.32 | 0.94 |
| 14 | 32.32 | 12.95 | 33.49 | 15.23 | 0.97 |

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=TEST/REF RATIO

2. Pharmacokinetic parameters

The test/reference ratios for the non-transformed and log-transformed AUCT, AUCI and CMAX range 0.95-1.01 as shown in Table 4. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the 80-125% range as shown in Table 5.

Table 4. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 2444.20 | 843.09 | 2565.83 | 769.88 | 0.95 |
| AUCT | 2273.13 | 820.60 | 2375.83 | 744.09 | 0.96 |
| CMAX | 503.63 | 178.38 | 510.00 | 197.87 | 0.99 |
| KE | 0.20 | 0.03 | 0.20 | 0.03 | 1.01 |
| LAUCI* | 2315.06 | 0.33 | 2435.10 | 0.35 | 0.95 |
| LAUCT* | 2142.27 | 0.35 | 2240.86 | 0.37 | 0.96 |
| LCMAX* | 475.02 | 0.35 | 472.31 | 0.41 | 1.01 |
| THALF | 3.50 | 0.60 | 3.55 | 0.66 | 0.99 |
| TMAX | 1.76 | 0.57 | 2.09 | 0.79 | 0.84 |

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 5. LSMEANS AND 90% CONFIDENCE INTERVALS

| | LSMEAN1 | LSMEAN2 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|
| PARAMETER | | | | |
| AUCI | 2444.20 | 2565.83 | 85.27 | 105.25 |
| AUCT | 2273.13 | 2375.83 | 85.42 | 105.93 |
| CMAX | 503.63 | 510.00 | 86.93 | 110.57 |
| LAUCI | 2315.06 | 2435.10 | 85.61 | 105.57 |
| LAUCT | 2142.27 | 2240.86 | 85.55 | 106.83 |
| LCMAX | 475.02 | 472.31 | 88.51 | 114.28 |

VI. Formulation

Table 6. shows the composition of the test products, 200 mg Acyclovir Capsules by Lemmon. The reference product contains corn starch, lactose, magnesium stearate and sodium lauryl sulfate. The test and reference formulations are qualitatively same.

Table 6. Composition of Lemmon's Acyclovir Capsules

| Ingredient | Amount, mg |
|---|---|
| Acyclovir, USP 23 | 200 |
| Lactose monohydrate, NF 18 | |
| Corn starch, NF 18 | |
| Sodium lauryl sulfate, NF 18 | |
| Magnesium stearate, NF 18 | |
| Total | 430 |

VII. In Vitro Testing

1. Potency and content uniformity

Assay and content uniformity data are summarized for the test and reference products in Table 8. The batch size of the test product was capsules.

Table 7. Potency and Content Uniformity

| Product | Lot No. | Potency, % | Content uniformity (%CV) |
|---|---|---|---|
| Zovirax, 200 mg exp. 11/97 | 4x1896 | 96.4 | 97.1 (2.1) |
| Test, 200 mg | 0554-014 | 100.3 | 100.6 (3.9) |

2. Dissolution testing data

Lemmon established its own dissolution method for the test product. The dissolution testing was performed in 900 mL of water using apparatus 1 (basket) at 100 rpm with dissolution specifications of NLT dissolved in 30 minutes (see Table 8). FDA method is different from the Lemmon method in its tolerances. The tolerances of the FDA method is NLT in 30 minutes as shown below:

FDA method:

Medium: 900 mL water
Apparatus 1 (basket) at 100 rpm
Tolerances: NLT in 30 minutes

The dissolution data summarized in Table 8 for the test and reference products meet the FDA specifications.

VIII. Comments

1. Study under fasting conditions (200 mg capsules):

A total of 34 subjects were recruited for the study but only 32 participated in the study and 30 subjects completed two periods of study successfully. There were two drop-outs: Subjects #4 and 34 did not complete the 2nd period due to illness.

The mean plasma levels for the test and reference products are comparable. The test/reference ratios (RMEAN12) for the mean plasma levels were close to 1 for most of the time points. The test/reference ratios for the non-transformed and log-transformed AUCT, AUCI and CMAX range 0.95-1.01. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the 80-125% range.

2. Assay validation: Pre-study validation and within-study validation are acceptable.

3. Adverse reaction (200 mg capsules): No clinically significant adverse reactions were reported: Ten adverse reactions (test: 5/2 subjects; reference: 4/3 subjects) were reported. No action was required.

4. The batch size of the 200 mg test product was capsules.

5. The formulation of the 200 mg test product does not contain inactive ingredients which may adversely affect its bioavailability.

6. The dissolution data for the test and reference products met the FDA specifications. The firm is recommended to adopt the FDA tolerances of

IX. Deficiencies

1. Study under non-fasting conditions should be submitted for review.

2. The following is recommended for future submissions:

(1) ASCII data should be space delimited.

(2) Submit SAS printout for log-transformed PK parameters.

X. Recommendation

The *in vivo* bioequivalence study conducted by Lemmon on its Acyclovir Capsules, 200 mg strength, lot #0544-014, comparing it to Burroughs Wellcome's Zovirax® Capsules, 200 mg strength, lot #4x1896, has been found incomplete by the Division of Bioequivalence.

The firm should be informed of the deficiencies #1-2 and recommendation.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

6/20/96

Concur: Date: 24-96

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

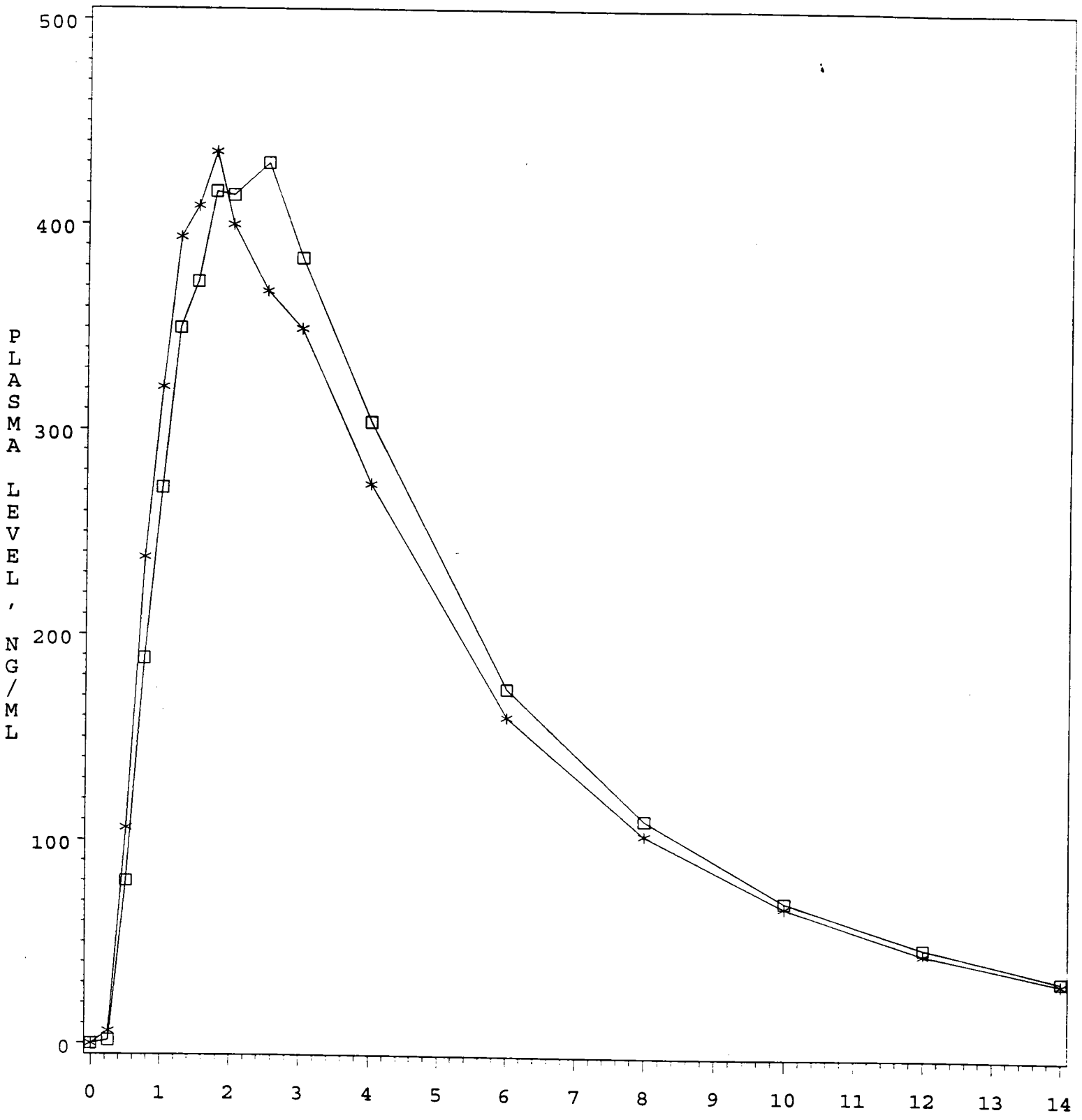
cc: ANDA #74-828 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Mhatre, Park), Drug File, Division File

File history: Draft(5/21/96);Final (6/18/96)

| Table 8. *In Vitro* Dissolution Testing Data | | | | | | |
|---|---|---|---|---|---|---|
| I. General Information | | | | | | |
| Drug Product (Generic Name) | Acyclovir Capsules | | | | | |
| Strength | 200 mg | | | | | |
| ANDA Number | 74-828 | | | | | |
| Applicant | Lemmon | | | | | |
| Reference Drug Product | Burroughs Wellcome's 200 mg strength Zovirax® Capsules | | | | | |
| II. Method for Dissolution Testing | | | | | | |
| Medium and Volume | 900 mL water | | | | | |
| Apparatus and rpm | Basket, 100 rpm | | | | | |
| Time | 30 min | | | | | |
| Tolerances | | | | | | |
| Assay Method | | | | | | |
| III. Dissolution Data (%) | | | | | | |
| Time | Test Product<br>Lot No:0554-014<br>Strength:200<br>No of Units:12 | | | Reference Product<br>Lot No:4x1896<br>Strength:200<br>No of Units:12 | | |
| Min | Mean | Range | %CV | Mean | Range | %CV |
| 5 | 18.7 | | 41 | 24.2 | | 22 |
| 10 | 58.8 | | 18 | 66.1 | | 11 |
| 15 | 88.2 | | 7.0 | 83.7 | | 7.8 |
| 30 | 101.0 | | 2.8 | 95.5 | | 5.1 |
| | | | | | | |
| | | | | | | |

# FIG P-1. PLASMA ACYCLOVIR LEVELS

ACYCLOVIR CAPSULES, 200 MG, ANDA #74-828
UNDER FASTING CONDITIONS
DOSE=200 MG




1=TEST PRODUCT(LEMMON) 2=REFERENCE PRODUCT(BW)