# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number : 074658**

**Trade Name : ACYCLOVIR TABLETS**

**Generic Name: Acyclovir Tablets 400mg and 800mg**

**Sponsor : Lek Pharmaceutical and Chemical Co**

**Approval Date: April 22, 1997**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION 074658

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074658

# TENTATIVE APPROVAL LETTER

M Bennett

ANDA 74-658

MAR 27 1997

LEK Pharmaceutical and Chemical Company d.d.
Attention: A. Gašperlin
333 Sylvan Avenue, 2nd Floor
Englewood Cliffs, NJ 07632

Dear Sir:

This is in reference to your abbreviated new drug application dated April 3, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Tablets, 400 mg and 800 mg.

Reference is also made to your amendments dated September 14, 1995, October 22, 1996, and January 27 and February 19, 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, please 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,

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

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 074658**

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APR 12 1997

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Dear Sir:

This is in reference to your abbreviated new drug application dated April 3, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Tablets, 400 mg and 800 mg.

Reference is also made to your correspondence 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 your Acyclovir Tablets, 400 mg and 800 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Tablets, 400 mg and 800 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,

/S/

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 074658

## FINAL PRINTED LABELING

481840

Lot & Mnf. date:

Exp. date:

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

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

Made in Slovenia

7 0 6 4 1 2 4 9 9 0 6 6

NDC 48866-4990-6

# Acyclovir Tablets

Each tablet contains 400 mg

Store between 15° and 25°C (59° and 77°F). Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP.

lek

1000 Tablets

Manufactured by
Lek Pharmaceutical and
Chemical Company d.d.
Verovškova 57, Ljubljana, Slovenia

OPEN HERE

2

NDC 48866-4990-6

**Acyclovir Tablets**

Each tablet contains **400 mg**

[illegible] between 1[illegible] and 2[illegible]C (59° [illegible]) [illegible] from light and moisture. Dispense in a tight, light-resistant container as defined in the USP.

[illegible] **1000 Tablets**

[illegible] Slovenia

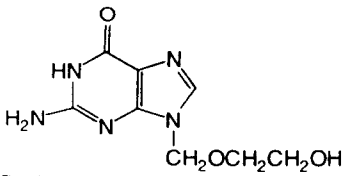
# ACYCLOVIR TABLETS
# ACYCLOVIR CAPSULES

**DESCRIPTION:** Acyclovir capsules and tablets are formulations of an antiviral drug for oral administration. Each capsule of Acyclovir contains 200 mg of acyclovir and the inactive ingredients colloidal silicon dioxide, lactose monohydrate, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and talc. The capsule shell consists of gelatin, titanium dioxide and water. Printed with edible black ink contains black iron oxide.

Each 800 mg tablet of Acyclovir contains 800 mg of acyclovir and the inactive ingredients colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

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

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



The molecular formula of acyclovir is $C_8H_{11}N_5O_3$. 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.[11-19] 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 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

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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 different 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 5 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 and tablets are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

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

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

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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 is contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

**WARNINGS:** Acyclovir capsules and tablets 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 and tablets 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 acyclovir treatment of chickenpox 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:** 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

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.[36]

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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 and tablets 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 acyclovir treatment of chickenpox 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:** Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 5 times a day (dosing appropriate for treatment of herpes zoster) or

200 mg given orally 5 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see 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 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 aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels).

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

**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

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 (0.8%), rash (0.8%), vomiting (0.6%), and flatulence (0.4%). The 496 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, one 400 mg tablet) 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

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

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

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

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

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

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

| Normal Dosage Regimen | Creatinine Clearance (mL/min/1.73 $m^2$) | 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 (white, opaque cap and body) containing 200 mg acyclovir and printed with „ACY 200" on cap and body - Bottle of 100 (NDC 48866-4990-0), and of 1000 (NDC 48866-4990-7).

Acyclovir tablets (white to off-white, unscored, bar-shaped) containing 800 mg acyclovir and engraved with „ACY 800" - Bottle of 100 (NDC 48866-4982-1), and of 1000 (NDC 48866-4990-5).

Acyclovir tablets (white to off-white, unscored, oval) containing 400 mg acyclovir and engraved with „ACY 400" - Bottle of 100 (NDC 48866-4986-5) and of 1000 (NDC 48866-4990-6).

Store between 15° and 25°C (59° and 77°F). Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP. CAUTION: Federal law prohibits dispensing without prescription.

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Lot & Mnf. date:

Exp. date:

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

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

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# Acyclovir Tablets

Each tablet contains 800 mg

Store between 15° and 25°C (59° and 77°F). Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP.

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**100 Tablets**

Manufactured by
Lek Pharmaceutical and
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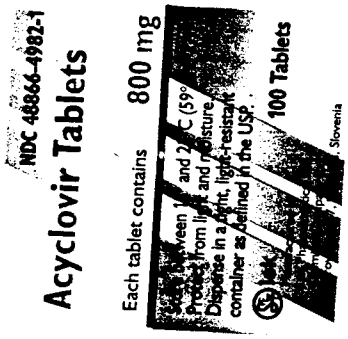
Verovškova 57, Ljubljana, Slovenia



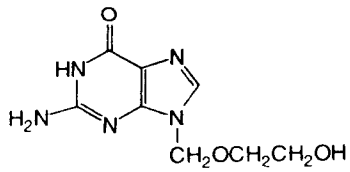

# ACYCLOVIR TABLETS
# ACYCLOVIR CAPSULES

**DESCRIPTION:** Acyclovir capsules and tablets are formulations of an antiviral drug for oral administration. Each capsule of Acyclovir contains 200 mg of acyclovir and the inactive ingredients colloidal silicon dioxide, lactose monohydrate, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and talc. The capsule shell consists of gelatin, titanium dioxide and water. Printed with edible black ink contains black iron oxide.

Each 800 mg tablet of Acyclovir contains 800 mg of acyclovir and the inactive ingredients colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

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

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




The molecular formula of acyclovir is $C_8H_{11}N_5O_3$. 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 nucleoside 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.[11-19] 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 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 1.6 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes sim-

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, 5 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 different 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 and tablets are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

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

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

associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).[34]

**Chickenpox:**
In a double-blind, placebo-controlled efficacy study in 118 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.

**CONTRAINDICATIONS:** Acyclovir is contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

**WARNINGS:** Acyclovir capsules and tablets 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 and tablets 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 acyclovir treatment of chickenpox 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:** Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 5 times a day (dosing appropriate for treatment of herpes zoster) or

200 mg given orally 5 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see 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 (35 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 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 aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels).

**Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[42] In the 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 (6.0%), 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 496 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.)

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***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, one 400 mg tablet) 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

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

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

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

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

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

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

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

**Hemodialysis:** For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 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 (white, opaque cap and body) containing 200 mg acyclovir and printed with „ACY 200" on cap and body - Bottle of 100 (NDC 48866-4990-0), and of 1000 (NDC 48866-4990-7).

Acyclovir tablets (white to off-white, unscored, bar-shaped) containing 800 mg acyclovir and engraved with „ACY 800" - Bottle of 100 (NDC 48866-4982-1), and of 1000 (NDC 48866-4990-5).

Acyclovir tablets (white to off-white, unscored, oval) containing 400 mg acyclovir and engraved with „ACY 400" - Bottle of 100 (NDC 48866-4966-5) and of 1000 (NDC 48866-4990-6).

Store between 15° and 25°C (59° and 77°F). Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP. CAUTION: Federal law prohibits dispensing without prescription.

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Lek,
Pharmaceutical and Chemical Company d.d.
Ljubljana, Slovenia
Printed in Slovenia

February 1997

481866

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074658

## CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Application Review

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-658

3. NAME AND ADDRESS OF APPLICANT
Lek Pharmaceutical and Chemical Company d.d.
Verovškova 57
61107 Ljubljana
Slovenia

4. LEGAL BASIS for ANDA SUBMISSION
ZOVIRAX® tablets, 800 mg/tablet
ZOVIRAX® tablets, 400 mg/tablet
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Patent #4199574 expires April 22, 1997. No exclusivities are listed.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Acyclovir USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

| | | |
|---|---|---|
| 4/3/95 | Original Submission. | |
| 6/25/95 | Amendment - | Addition of 400 mg tablet. |
| 2/15/96 | Amendment - | Response to Agency's letter of 10/19/95. |
| 6/17/96 | Amendment - | Submission in response to commitment in 2/15/96 Amendment. |
| 10/18/96 | Amendment - | Response to Agency's letter of 10/4/96. |
| **1/27/97** | **Amendment -** | **Response to Agency's Facsimile of 1/17/97.** |
| **2/19/97** | **Amendment -** | **Response to Labeling Telephone Amendment request.** |

FDA:

| | |
|---|---|
| 5/31/95 | Receipt Acknowledged. |
| 10/19/95 | Issuance of Not Approvable letter. |
| 1/16/96 | Issuance of Bioequivalence Deficiency letter. |

| | |
|---|---|
| 9/25/96 | Issuance of Bioequivalence No Further Questions letter. |
| 10/4/96 | Issuance of Not Approvable letter. |
| 1/17/97 | Issuance of Facsimile Minor Amendment. |
| 2/4/97 | Telephone Amendment request, Labeling. |

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

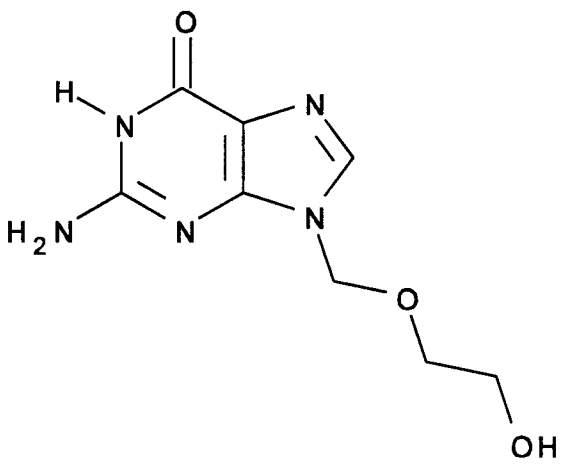
(b)4 - Confidential Business

13. DOSAGE FORM
Tablet for
Oral Administration

14. POTENCIES
400 mg/tablet
800 mg/tablet

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP
$C_8H_{11}N_5O_3$; M.W. = 225.21
CAS [59277-89-3]




1. 9-[(2-Hydroxyethoxy)methyl]guanine.

2. 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]-

USP: White to off-white crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in 0.1 N hydrochloric acid; sparingly soluble in water; insoluble in alcohol.

Merck: Crystals from methanol, mp 256.5° - 257°. $LD_{50}$ in mice (mg/kg): > 10,000 orally; 1000 i.p.

16. RECORDS AND REPORTS

| | |
|---|---|
| 7/25/95 | Labeling review, C. Hoppes. |
| 8/31/95 | Chemistry review #1, G.J. Smith. |
| 12/5/95 | Bioequvalence review, M. Park. |
| 7/11/96 | Labeling review, J. Grace. |
| 8/14/96 | Chemistry review #2, G.J. Smith. |
| 9/13/96 | Bioequivalence review, M. Park. |
| 11/4/96 | Labeling review, C. Hoppes. |
| 12/10/96 | Chemistry review #3, G.J. Smith. |
| 2/27/97 | Labeling review, J. White. |

17. COMMENTS

The firm has resolved all major questions regarding the chemistry, manufacturing and controls sections of the application.

Labeling was found to be satisfactory.

The Division of Bioequivalence found the 800 mg tablet equivalent to the listed drug and granted a waiver for the 400 mg tablet - 9/13/96.

An acceptable EIR was issued by the Office of Compliance.

Methods Validation was found satisfactory.

DMF for drug substance was satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application may be granted Tentative Approval.

19. REVIEWER: Glen Jon Smith

DATE COMPLETED: March 3, 1997

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074658

## BIOEQUIVALENCE REVIEW(S)

D W

ANDA 74-658

LEK Pharmaceuticals
and Chemical Company d.d.
Attention: Andrej Gasperlin
Authorized U.S. Agent
333 Sylvan Avenue, 2nd Floor
Englewood Cliffs, NJ 07632

SEP 2 5 1996

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 Tablets 400 mg and 800 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 dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)4 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,

/S/

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

SEP 3 1996 DIV

| | |
|---|---|
| Acyclovir Tablets | LEK |
| 400 and 800 mg Tablets | Ljubljana, Slovenia |
| ANDA #74-658 | Submission Date: |
| Reviewer: Moo Park | February 15, 1996 |
| Filename: 74658A.296 | |

## Review of an Amendment

### I. Objectives

Review of Lek's amendment to its original submission of two *in vivo* bioequivalence studies comparing its 800 mg strength Acyclovir Tablets to Burroughs Wellcome's 800 mg strength Zovirax Tablets under fasting and non-fasting conditions (submission date: 4/3/1995). The firm submitted *in vitro* dissolution data for the 400 and 800 mg tablets for review in the amendment.

### II. Review of Data and Comments

1. Review of *in vitro* dissolution data:

   The firm was asked to perform the comparative dissolution testing using 900 mL water as the dissolution medium in apparatus 2 at 50 rpm. Tolerances are NLT (b)4 (Q) in 30 minutes. The data submitted for the 400 mg and 800 mg tablets met the FDA specifications as shown in Table 1.

2. Waiver is granted for the 400 mg tablets.

### III. Deficiency

None.

### IV. Recommendations

1. The *in vivo* bioequivalence studies conducted under fasting and non-fasting conditions by LEK on its Acyclovir Tablets, 800 mg strength, lot #1150794, comparing it to Burroughs Wellcome's 800 mg strength Zovirax[R] Tablets, 800 mg strength, lot #3X1653, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Lek's Acyclovir Tablets, 800 mg strength, is bioequivalent to Burroughs Wellcome's Zovirax[R] Tablets, 800 mg strength.

2. The dissolution testing conducted by Lek on its Acyclovir Tablets, 400 mg strength, lot #1010794 and 800 mg strength, lot #1150794, is acceptable. The formulation for the 400 mg strength tablets is proportionally similar to the 800 mg strength tablets of the test product which underwent two

acceptable bioequivalence studies (submission date: 4/3/1995). Waiver of in vivo bioequivalence study requirements for the 400 mg strength tablets of the test product is granted. The 400 mg strength tablets of the test product are therefore deemed bioequivalent to Burroughs Wellcome's Zovirax[R] Tablets, 400 mg strength.

3. 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 II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)4 of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view the firm has met the *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

The firm should be informed of the recommendations.

/S/

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

RD INITIALED RMHATRE /S/
FT INITIALED RMHATRE 8/21/96

Concur: /S/ Date: 9/13/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

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

File history: Draft(8/16/96);Final (8/20/96)

| Table 1. *In Vitro* Dissolution Testing Data | |
|---|---|
| I. General Information | |
| Drug Product (Generic Name) | Acyclovir Tablets |
| Strength | 400 and 800 mg |
| ANDA Number | 74-658 |
| Applicant | LEK |
| Reference Drug Product | Burroughs Wellcome's 400 and 800 mg strength Zovirax[R] Tablets |
| II. FDA Method for Dissolution Testing | |
| Medium and Volume | 900 mL water |
| Apparatus and rpm | Paddle, 50 rpm |
| Time | 30 min |
| Tolerances | (b)4 - |
| Assay Method | (b)4 - |

III. Dissolution Data (%)

| Time | Test Product<br>Lot No:1010794<br>Strength:400 mg<br>No of Units:12 | | | Reference Product<br>Lot No:401421<br>Strength:400 mg<br>No of Units:12 | | |
|---|---|---|---|---|---|---|
| Min | Mean | Range | %CV | Mean | Range | %CV |
| 10 | 59.4 | (b)4 - Confidential Business | 13.8 | 86.3 | (b)4 - Confidential Business | 4.2 |
| 20 | 88.1 | | 5.1 | 94.2 | | 2.2 |
| 30 | 93.9 | | 2.1 | 96.8 | | 1.5 |

| Time | Test Product<br>Lot No:1150794<br>Strength:800 mg<br>No of Units:12 | | | Reference Product<br>Lot No:3x1653<br>Strength:800 mg<br>No of Units:12 | | |
|---|---|---|---|---|---|---|
| Min | Mean | Range | %CV | Mean | Range | %CV |
| 10 | 70.4 | (b)4 - Confidential Business | 11.1 | 77.8 | (b)4 - Confidential Business | 7.1 |
| 20 | 91.2 | | 3.8 | 91.0 | | 6.0 |
| 30 | 95.3 | | 2.8 | 96.1 | | 2.3 |

ANDA 74-658

JAN 16 1996

LEK Pharmaceutical
and Chemical Company d.d
Attention: Andrej Gasperlin
Authorized U.S. Agent
333 Sylvan Avenue, 2nd Floor
Englewood Cliffs, NJ 07632

Dear Sir:

**Reference is made to the Abbreviated New Drug Application submitted on April 3, June 27, September 14, 1995, for Acyclovir Tablets 400 mg and 800 mg.**

**The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:**

1. The comparative dissolution methodology was not acceptable. Dissolution should be conducted using the following methodology for both the 400 mg and 800 mg test and reference listed drugs:

| | |
|---|---|
| Apparatus: | USP Paddle |
| RPM: | 50 rpm |
| Medium: | Deaerated Water |
| Volume: | 900 mL |
| Sampling Times: | 10, 20, and 30 minutes |

2. Mean and %CV should be provided for the future submission of content uniformity data for test and reference products.

3. The bioequivalence study summary and reports are very unclear. For example, the clinical study section for the 800 mg tablets (pages 151-173, vol 1.1) should contain a detailed account of the clinical study including: the conduct of the study, problems, protocol deviations and medical events. Summary table of bioequivalence data (p. 96) needs the addition of non-transformed data. Also, clear descriptions of each entry are needed within the table. The summary of validation section (pages 191-286) presents analytical validation data in either tabular or graphic format but without the appropriate descriptions.

**NOTE:**

**Because of poor format, an excessive amount the reviewers time was spent in locating the information needed for proper evaluation.**

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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

DEC 5 1995



Acyclovir Tablets

400 mg and 800 mg Tablets

ANDA #74-658

Reviewer: Moo Park

Filename: 74658SDW.495

LEK

Ljubljana, Slovenia

Submission Date:

April 3, 1995

June 27, 1995
September 14, 1995

# Review of Two BE Studies, Dissolution Data and a Waiver Request

## I. Objectives

Review of Lek's two *in vivo* bioequivalence studies comparing its 800 mg strength Acyclovir Tablets to Burroughs Wellcome's 800 mg strength Zovirax Tablets under fasting and non-fasting conditions. The firm submitted *in vitro* dissolution data 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 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 (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

A. BE Study under Fasting Conditions

1. Protocol # N/A

2. Study # 21/93/ACI-2

3. Brief description of the study

This randomized, single-dose, two-way crossover study was conducted with 28 healthy male volunteers in accordance with the Protocol. In each period, subjects received a single 800 mg dose of either LEK's Acyclovir Tablets or BW's Zovirax Tablets following an overnight fast. There was a one-week washout between treatments. Blood samples were collected pre-dose and over 24 hours after each dose. Plasma concentrations of acyclovir was measured by a fully validated (b)4 procedure. Pharmacokinetic and statistical analyses were performed to compare the test and reference treatments.

4. 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.

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

6. Study sites:

Clinical study:

Analytical study:

(b)4 - Confidential Business

7. Study dates:

Clinical study: 10/22/94-10/23/94 (Period 1)
10/29/94-10/30/94 (Period 2)

Analytical study: N/A

8. Investigators:

(b)4 - Confidential Business

Institute for Chemistry.

9. Drug Products:

A. Test: 800 mg Acyclovir Tablets (LEK, Lot #1150794)

B. Reference: 800 mg Zovirax® Tablets (Burroughs Wellcome, Lot #3X1653)

10. Dosing: All doses were administered with 200 ml of room temperature water following an overnight fast.

11. Subjects: The 28 subjects who entered in this study were normal healthy male volunteers in the age range of 20-40 years, and within 15% 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.

12. Confinement: During the confinement periods of this study, the subjects were housed and fed at the clinical facility.

13. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 200 mL of tap water. 200 mL of soft drink containing no xanthin was provided at 2 hours post-dose. Water was allowed ad lib. after 4 hours post-dose.

14. Washout period: One week.

15. Blood samples: In each period, 10 mL of blood samples were collected at 0, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours. Plasma was separated and all plasma samples were stored frozen at -18°C until transfer to the laboratory for analysis.

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

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

19. Analytical procedure: Plasma samples were packaged in a freezer and shipped to the analytical laboratory. The plasma samples were assayed by [redacted](b)4 - Confidential[redacted]

20. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for acyclovir. 90% confidence intervals were calculated for AUCt,

AUCi and Cmax.

B. BE Study under Non-fasting Conditions

1. Protocol # N/A

2. Study # 9426 ACI-4

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

4. Study sites:

Clinical study:

Analytical study:

(b)4 - Confidential Business

5. Study dates:

Clinical study: 11/12/94-11/13/94 (Period 1)
11/19/94-11/20/94 (Period 2)
11/26/94-11/27/94 (Period 3)

Analytical study: N/A

6. Investigators:

(b)4 - Confidential Business

7. Treatments:

A. Test: 800 mg Acyclovir Tablets (LEK, Lot #1150794) under non-fasting conditions.

B. Reference: 800 mg Zovirax[R] Tablets (Burroughs Wellcome, Lot #3X1653) under non-fasting conditions.

C. Test: 800 mg Acyclovir Tablets (LEK, Lot #1150794) under fasting conditions.

8. Dosing: All doses were administered with 200 ml of room temperature water following an overnight fast or 10 minutes after consuming the breakfast depending on the dosing schedule.

9. Subjects: The 16 subjects who were entered in this study were normal healthy male volunteers in the age range of 20-35 years, and within 15% 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.

10. Confinement: During the confinement periods of this study, the subjects were housed and fed at the clinical facility.

11. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 200 mL of tap water. 200 mL of soft drink containing no xanthin was provided at 2 hours post-dose. Water was allowed ad lib. after 4 hours post-dose.

12. Washout period: One week.

13. Blood samples: In each period, 10 mL of blood samples were collected at 0, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours. Plasma was separated and all samples were stored frozen at -18°C until analysis.

IV. Validation of Assay Method for Plasma Samples

(b)4 - Confidential Business

(b)4 - Confidential Business

(b)4 - Confidential Business

(b)4 - Confidential Business

(b)4 - Confidential Business

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

A. Study under fasting conditions

A total of 28 subjects participated in the study and completed two periods of study successfully. There was no drop-out and there was no missing sample.

Adverse reactions were followed according to the protocol of the study. No clinically significant adverse reactions were reported except four subjects (Subjects #15, 17, 19 and 28) showing elevated total bilirubin and Subject #20 showing elevated SGOT.

1. Mean plasma levels

The mean plasma levels for the test and reference products are comparable as shown in Table 9. The test/reference ratios (RMEAN12) for the mean plasma levels range from 0.83 to 1.22.

Table 9. 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 | . |
| 0.33 | 0.16 | 0.14 | 0.13 | 0.13 | 1.22 |
| 0.67 | 0.46 | 0.21 | 0.41 | 0.21 | 1.12 |
| 1 | 0.61 | 0.21 | 0.59 | 0.23 | 1.04 |
| 1.33 | 0.67 | 0.23 | 0.64 | 0.25 | 1.04 |
| 1.67 | 0.66 | 0.25 | 0.65 | 0.25 | 1.02 |
| 2 | 0.65 | 0.28 | 0.63 | 0.23 | 1.03 |
| 2.5 | 0.61 | 0.27 | 0.58 | 0.22 | 1.05 |
| 3 | 0.53 | 0.24 | 0.52 | 0.23 | 1.01 |
| 4 | 0.42 | 0.23 | 0.41 | 0.22 | 1.03 |
| 6 | 0.22 | 0.12 | 0.24 | 0.13 | 0.92 |
| 8 | 0.14 | 0.07 | 0.14 | 0.08 | 1.01 |
| 10 | 0.08 | 0.06 | 0.09 | 0.06 | 0.98 |
| 12 | 0.06 | 0.05 | 0.06 | 0.05 | 0.91 |
| 24 | 0.02 | 0.03 | 0.02 | 0.03 | 0.83 |

UNIT: PLASMA LEVEL=MCG/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 PK parameters range 0.99-1.01 as shown in Table 10. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were all within the 80-125% range as shown in Table 11. The magnitude of the spread between the upper and lower confidence intervals, 30% for the Cmax and 40% for the AUCt and AUCi, indicates a large intra-subject variability or some other reasons.

Table 10.TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 4.13 | 1.88 | 4.10 | 1.79 | 1.01 |
| AUCT | 3.65 | 1.65 | 3.63 | 1.60 | 1.01 |
| CMAX | 0.77 | 0.26 | 0.76 | 0.25 | 1.01 |
| KE | 0.23 | 0.10 | 0.22 | 0.11 | 1.04 |
| LAUCI* | 3.74 | 0.45 | 3.75 | 0.42 | 1.00 |
| LAUCT* | 3.30 | 0.47 | 3.32 | 0.43 | 0.99 |
| LCMAX* | 0.72 | 0.36 | 0.71 | 0.38 | 1.01 |
| THALF | 4.44 | 3.59 | 4.65 | 3.54 | 0.95 |
| TMAX | 1.58 | 0.73 | 1.70 | 0.86 | 0.93 |

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

Table 11.LSMEANS AND 90% CONFIDENCE INTERVALS

| | LSMEAN1 | LSMEAN2 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|
| PARAMETER | | | | |
| AUCI | 4.13 | 4.10 | 79.23 | 122.17 |
| AUCT | 3.65 | 3.63 | 79.36 | 121.74 |
| CMAX | 0.77 | 0.76 | 87.43 | 115.02 |
| LAUCI | 3.74 | 3.75 | 81.56 | 121.74 |
| LAUCT | 3.30 | 3.32 | 81.33 | 121.69 |
| LCMAX | 0.72 | 0.71 | 87.78 | 117.31 |

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

3. Test/reference ratios for individual subjects

The test/reference ratios shown in Table 12 were summarized in Table 13. The mean ratios for AUCt and AUCi were both 1.2 with 60% CV and 57% CV, respectively. The mean ratio for Cmax was 1.13 with 51% CV. This indicates that the test product's AUC and Cmax for the indivisuals are 20% and 13% higher, respectively, than the reference product's AUC and Cmax.

Table 12. Test Product/Reference Product Ratios for Individual Subjects

| OBS | SUB | SEQ | RAUCT12 | RAUCI12 | RCMAX12 | RTMAX12 | RKE12 | RTHALF12 |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | (b)4 - Confidential Business | | | | | |
| 2 | 2 | 1 | | | | | | |
| 3 | 3 | 2 | | | | | | |
| 4 | 4 | 1 | | | | | | |
| 5 | 5 | 2 | | | | | | |
| 6 | 6 | 2 | | | | | | |
| 7 | 7 | 2 | | | | | | |
| 8 | 8 | 1 | | | | | | |
| 9 | 9 | 1 | | | | | | |
| 10 | 10 | 2 | | | | | | |
| 11 | 11 | 2 | | | | | | |
| 12 | 12 | 1 | | | | | | |
| 13 | 13 | 2 | | | | | | |
| 14 | 14 | 2 | | | | | | |
| 15 | 15 | 2 | | | | | | |
| 16 | 16 | 1 | | | | | | |
| 17 | 17 | 1 | | | | | | |
| 18 | 18 | 1 | | | | | | |
| 19 | 19 | 2 | | | | | | |
| 20 | 20 | 1 | | | | | | |
| 21 | 21 | 2 | | | | | | |
| 22 | 22 | 2 | | | | | | |
| 23 | 23 | 2 | | | | | | |
| 24 | 24 | 1 | | | | | | |
| 25 | 25 | 1 | | | | | | |
| 26 | 26 | 2 | | | | | | |
| 27 | 27 | 1 | | | | | | |
| 28 | 28 | 1 | | | | | | |

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

Table 13. Statistics on the Test/Reference Ratios

| Variable | N | Mean | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|
| RAUCT12 | 28 | 1.20 | 0.72 | (b)4 - Confidential Business | |
| RAUCI12 | 28 | 1.20 | 0.68 | | |
| RCMAX12 | 28 | 1.13 | 0.58 | | |
| RTMAX12 | 28 | 1.15 | 0.70 | | |
| RKE12 | 28 | 1.58 | 1.67 | | |
| RTHALF12 | 28 | 1.32 | 1.07 | | |

B. Study under non-fasting Conditions

A total of 16 subjects participated in the study and completed three periods of the study successfully. There was no drop-out and

there was no missing sample.

Adverse reactions were followed according to the protocol of the study. No clinically significant adverse reactions were reported except Subject #14 who showed elevated total bilirubin at post-dose laboratory test.

1. Mean plasma levels

Table 14 and Fig. P-2 show the plasma acyclovir-time data for the food study which indicate significant food effect on the absorption of acyclovir. The plasma levels under non-fasting conditions (MEAN1 and MEAN2) were much higher than those under fasting conditions (MEAN3). At 2 hours post-dose where the peak mean concentrations are observed, the ratios between the non-fasting and fasting mean plasma levels were 1.71 and 1.76 for the test and reference products, respectively. The plasma levels under non-fasting conditions were comparable between the test and reference products.

Table 14. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FOOD
MEAN2=REFERENCE-FOOD
MEAN3=TEST-FASTING

| | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 |
|---|---|---|---|---|---|
| TIME HR | | | | | |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 0.33 | 0.09 | 0.07 | 0.06 | 0.06 | 0.24 |
| 0.67 | 0.40 | 0.30 | 0.31 | 0.29 | 0.60 |
| 1 | 0.87 | 0.44 | 0.59 | 0.38 | 0.72 |
| 1.33 | 1.10 | 0.37 | 0.75 | 0.33 | 0.76 |
| 1.67 | 1.17 | 0.33 | 1.00 | 0.35 | 0.75 |
| 2 | 1.17 | 0.34 | 1.15 | 0.37 | 0.67 |
| 2.5 | 0.99 | 0.25 | 1.02 | 0.32 | 0.58 |
| 3 | 0.82 | 0.21 | 0.92 | 0.34 | 0.50 |
| 4 | 0.66 | 0.13 | 0.73 | 0.28 | 0.35 |
| 6 | 0.36 | 0.06 | 0.38 | 0.12 | 0.21 |
| 8 | 0.21 | 0.04 | 0.23 | 0.06 | 0.13 |
| 10 | 0.14 | 0.03 | 0.15 | 0.06 | 0.09 |
| 12 | 0.10 | 0.03 | 0.08 | 0.07 | 0.06 |
| 24 | 0.01 | 0.03 | 0.04 | 0.04 | 0.02 |

(CONTINUED)

| | SD3 | RMEAN12 | RMEAN13 | RMEAN23 |
|---|---|---|---|---|
| TIME HR | | | | |
| 0 | 0.00 | . | . | . |
| 0.33 | 0.09 | 1.43 | 0.36 | 0.25 |
| 0.67 | 0.17 | 1.29 | 0.67 | 0.52 |
| 1 | 0.30 | 1.47 | 1.21 | 0.82 |
| 1.33 | 0.36 | 1.48 | 1.45 | 0.98 |
| 1.67 | 0.39 | 1.17 | 1.57 | 1.34 |
| 2 | 0.36 | 1.02 | 1.75 | 1.72 |
| 2.5 | 0.30 | 0.97 | 1.71 | 1.76 |
| 3 | 0.24 | 0.89 | 1.65 | 1.86 |
| 4 | 0.16 | 0.90 | 1.88 | 2.09 |
| 6 | 0.08 | 0.96 | 1.70 | 1.78 |
| 8 | 0.05 | 0.92 | 1.58 | 1.73 |
| 10 | 0.05 | 0.95 | 1.64 | 1.72 |
| 12 | 0.05 | 1.21 | 1.70 | 1.41 |
| 24 | 0.03 | 0.24 | 0.50 | 2.09 |

UNIT: PLASMA LEVEL=MCG/ML TIME=HRS

2. <u>Pharmacokinetic parameters</u>

The test/reference ratios for the PK parameters under non-fasting conditions are shown as RMEAN12 in Table 15. The ratios for the log-transformed AUCt, AUCi and Cmax are 0.95, 0.92 and 1.03, respectively. The ratios met the requirements by the Agency.

Table 15. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)
MEAN1=TEST-FOOD
MEAN2=REFERENCE-FOOD
MEAN3=TEST-FASTING

| PARAMETER | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 |
|---|---|---|---|---|---|
| AUCI | 5.97 | 1.37 | 6.69 | 2.00 | 4.31 |
| AUCT | 5.50 | 1.22 | 5.91 | 1.75 | 3.72 |
| CMAX | 1.32 | 0.33 | 1.28 | 0.27 | 0.83 |
| KE | 0.23 | 0.07 | 0.17 | 0.11 | 0.17 |
| LAUCI* | 5.84 | 0.22 | 6.37 | 0.33 | 3.93 |
| LAUCT* | 5.38 | 0.21 | 5.65 | 0.32 | 3.36 |
| LCMAX* | 1.28 | 0.24 | 1.25 | 0.22 | 0.77 |
| THALF | 3.57 | 2.10 | 6.59 | 4.17 | 5.85 |
| TMAX | 1.74 | 0.51 | 1.90 | 0.66 | 1.32 |

(CONTINUED)

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

| PARAMETER | SD3 | RMEAN12 | RMEAN13 | RMEAN23 |
|---|---|---|---|---|
| AUCI | 1.84 | 0.89 | 1.39 | 1.55 |
| AUCT | 1.64 | 0.93 | 1.48 | 1.59 |
| CMAX | 0.34 | 1.04 | 1.59 | 1.53 |
| KE | 0.09 | 1.40 | 1.35 | 0.97 |
| LAUCI | 0.45 | 0.92 | 1.48 | 1.62 |
| LAUCT | 0.48 | 0.95 | 1.60 | 1.68 |
| LCMAX | 0.42 | 1.03 | 1.68 | 1.63 |
| THALF | 4.14 | 0.54 | 0.61 | 1.13 |
| TMAX | 0.53 | 0.92 | 1.31 | 1.43 |

C. Bioequivalence Data for 400 mg Strength

The Agency waives the requirements for *in vivo* bioequivalence study for the 400 mg strength tablets. However, LEK has completed the *in vivo* bioequivalence studies under fasting and non-fasting conditions. Examination of the data for the 400 mg tablets showed that the in vivo BE studies are acceptable. The 90% confidence intervals under fasting conditions and the test/reference ratios under non-fasting conditions for the pharmacokinetic parameters were summarized below as reference. A total of 28 subjects were

chosen for the fasting study and 27 subjects completed both periods. Subject #15 dropped out. For the non-fasting study, 16 subjects entered the study and completed the study.

1. 90% confidence intervals under fasting conditions

The test/reference ratios for the log-transformed AUCt, AUCi, and Cmax range 0.99-1.02 as shown in Table 16. The 90% confidence intervals for the log-transformed AUCt, AUCi, and Cmax met the 80-125% range as shown in Table 17.

Table 16. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

| | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 2.58 | 1.18 | 2.47 | 0.86 | 1.05 |
| AUCT | 2.28 | 1.17 | 2.16 | 0.82 | 1.06 |
| CMAX | 0.56 | 0.27 | 0.54 | 0.20 | 1.03 |
| KE | 0.23 | 0.05 | 0.26 | 0.08 | 0.92 |
| LAUCI* | 2.35 | 0.44 | 2.30 | 0.41 | 1.02 |
| LAUCT* | 2.01 | 0.53 | 1.99 | 0.44 | 1.01 |
| LCMAX* | 0.50 | 0.51 | 0.50 | 0.39 | 0.99 |
| THALF | 3.13 | 0.81 | 3.09 | 1.39 | 1.01 |
| TMAX | 1.51 | 0.61 | 1.34 | 0.79 | 1.12 |

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

Table 17. LSMEANS AND 90% CONFIDENCE INTERVALS

| | LSMEAN1 | LSMEAN2 | LOWCI12 | UPPCI12 |
|---|---|---|---|---|
| PARAMETER | | | | |
| AUCI | 2.58 | 2.47 | 88.03 | 121.56 |
| AUCT | 2.28 | 2.15 | 87.64 | 124.55 |
| CMAX | 0.56 | 0.54 | 86.02 | 121.76 |
| LAUCI | 2.35 | 2.30 | 86.41 | 121.60 |
| LAUCT | 2.01 | 1.98 | 83.55 | 123.06 |
| LCMAX | 0.50 | 0.50 | 81.97 | 119.59 |

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

2. Test/reference ratios of PK parameters under non-fasting conditions

The test/reference ratios for the PK parameters under non-fasting conditions are shown as RMEAN12 in Table 18. The ratios for the log-transformed AUCt, AUCi and Cmax are 1.01, 1.01 and 1.11, respectively. The ratios met the requirements by the Agency. Significant food effects were shown as with the 800 mg tablets.

Table 18. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)
MEAN1=TEST-FOOD
MEAN2=REFERENCE-FOOD
MEAN3=TEST-FASTING

| | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 |
|---|---|---|---|---|---|
| PARAMETER | | | | | |
| AUCI | 3.57 | 0.80 | 3.50 | 0.63 | 2.64 |
| AUCT | 3.31 | 0.78 | 3.25 | 0.62 | 2.36 |
| CMAX | 0.95 | 0.28 | 0.83 | 0.13 | 0.63 |
| KE | 0.28 | 0.05 | 0.28 | 0.03 | 0.27 |
| LAUCI | 3.49 | 0.22 | 3.45 | 0.17 | 2.50 |
| LAUCT | 3.23 | 0.23 | 3.20 | 0.18 | 2.20 |
| LCMAX | 0.91 | 0.28 | 0.82 | 0.16 | 0.58 |
| THALF | 2.54 | 0.43 | 2.50 | 0.25 | 2.85 |
| TMAX | 1.58 | 0.33 | 1.84 | 0.79 | 1.67 |

(CONTINUED)

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

| | SD3 | RMEAN12 | RMEAN13 | RMEAN23 |
|---|---|---|---|---|
| PARAMETER | | | | |
| AUCI | 0.85 | 1.02 | 1.36 | 1.33 |
| AUCT | 0.86 | 1.02 | 1.40 | 1.38 |
| CMAX | 0.22 | 1.14 | 1.52 | 1.33 |
| KE | 0.08 | 1.00 | 1.03 | 1.02 |
| LAUCI | 0.35 | 1.01 | 1.40 | 1.38 |
| LAUCT | 0.40 | 1.01 | 1.47 | 1.45 |
| LCMAX | 0.41 | 1.11 | 1.57 | 1.41 |
| THALF | 1.22 | 1.01 | 0.89 | 0.88 |
| TMAX | 0.79 | 0.86 | 0.95 | 1.11 |

## VI. Formulation

Table 19. shows the composition of the test products, 400 mg and 800 mg Acyclovir Tablets by LEK. The 400 mg and 800 mg strengths are exactly proportional in active and inactive ingredients.

The reference product contains FD&C Blue No.2, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Table 19. Composition of LEK's Acyclovir Tablets

| Ingredient | 400 mg tablet, mg | 800 mg tablet, mg |
|---|---|---|
| Acyclovir | 400 | 800 |
| Povidone | [redacted] | [redacted] |
| Microcrystalline cellulose | [redacted] | [redacted] |
| Sodium starch glycolate | [redacted] | [redacted] |
| Magnesium stearate | [redacted] | [redacted] |
| Colloidal silicon dioxide | [redacted] | [redacted] |
| Total tablet weight | 525 | 1050 |

VII. In Vitro Testing

1. Potency and content uniformity

Assay and content uniformity data are summarized for the test and reference products in Table 20. The batch size of the test product wa[redacted]

Table 20. Potency and Content Uniformity

| Product | Lot No. | Potency, % | Content uniformity (%CV) |
|---|---|---|---|
| Zovirax, 400 mg | 401421 | 98.15 | - |
| Test, 400 mg | 1010794 | 98.63 | - |
| Zovirax, 800 mg | 3X1653 | 99.54 | 99.19 (1.8) |
| Test, 800 mg | 1150794 | 96.08 | 100.1 (7.8) |

2. Dissolution testing data

The dissolution testing was performed in 900 mL of 0.1 N HCl using appa[redacted]s 2 (paddle) at 50 rpm with dissolution specifications of NLT [redacted] dissolved in 30 minutes. The FDA method calls for water as dissolution medium instead of 0.1 HCl used in the dissolution testing. The firm is recommended to perform the dissolution testing in water and submit the data for review.

VIII. Comments

1. Study under fasting conditions (800 mg tablets):

A total of 28 subjects participated in the study and completed two periods of study successfully. There was no drop-out and there was no missing sample.

The mean plasma levels for the test and reference products are comparable. The test/reference ratios for the non-transformed and log-transformed PK parameters range 0.99-1.01. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were all within the 80-125% range.

2. Study under non-fasting Conditions (800 mg tablets):

A total of 16 subjects participated in the study and completed three periods of the study successfully. There was no drop-out and there was no missing sample.

The plasma acyclovir-time data for the food study showed a significant food effect on the absorption of acyclovir. The plasma levels under non-fasting conditions were much higher than those under fasting conditions. At 2 hours post-dose where the peak mean concentrations were observed, the ratios between the non-fasting and fasting mean plasma levels were 1.71 and 1.76 for the test and reference products, respectively. The plasma levels under non-fasting conditions were comparable between the test and reference products. The test/reference ratios for log-transformed AUCt, AUCi and Cmax are 0.95, 0.92 and 1.03, respectively, under non-fasting conditions. The ratios for the The ratios met the requirements by the Agency.

3. Bioequivalence Data for 400 mg Strength:

The Agency waives the requirements for *in vivo* bioequivalence study for the 400 mg strength tablets. However, LEK has completed the *in vivo* bioequivalence studies under fasting (27 subjects) and non-fasting conditions (16 subjects). Examination of the data for the 400 mg tablets showed that the in vivo BE studies are acceptable.

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

5. Adverse reaction (800 mg tablets): Adverse reactions under fasting conditions were followed according to the protocol of the study. No clinically significant adverse reactions were reported except four subjects (Subjects #15, 17, 19 and 28) showing elevated total bilirubin and Subject #20 showing elevated SGOT. No clinically significant adverse reactions

were reported under the non-fasting conditions except Subject #14 who showed elevated total bilirubin at post-dose laboratory test.

6. The batch size of the 800 mg test product was [redacted] (b)4 - [redacted]

7. The formulations of the 400 mg and 800 mg test products are proportional in active and inactive ingredients.

8. The dissolution testing was done in 0.1 N H Cl. The firm is requested to use 900 mL water as the dissolution medium with apparatus 2 at 50 rpm.

9. Waiver for 400 mg tablets may be granted with the submission of acceptable dissolution data.

IX. Deficiencies

1. The firm is requested for the comparative dissolution testing to use 900 mL water as the dissolution medium with apparatus 2 at 50 rpm for the 400 and 800 mg tablets.

2. Mean and %CV should be provided for the future submission of content uniformity data for test and reference products.

3. Clear and comprehensive description of the *in vivo* studies and results are lacking in this submission. The firm should improve this aspect for future submissions.

X. Recommendation

The *in vivo* bioequivalence study conducted under fasting and non-fasting conditions by LEK on its Acyclovir Tablets, 800 mg strength, lot #1150794, comparing it to Burroughs Wellcome's 800 mg strength Zovirax® Tablets, 800 mg strength, lot #3X1653, has been found incomplete by the Division of Bioequivalence. The applicant should be informed of the deficiencies #1-3.

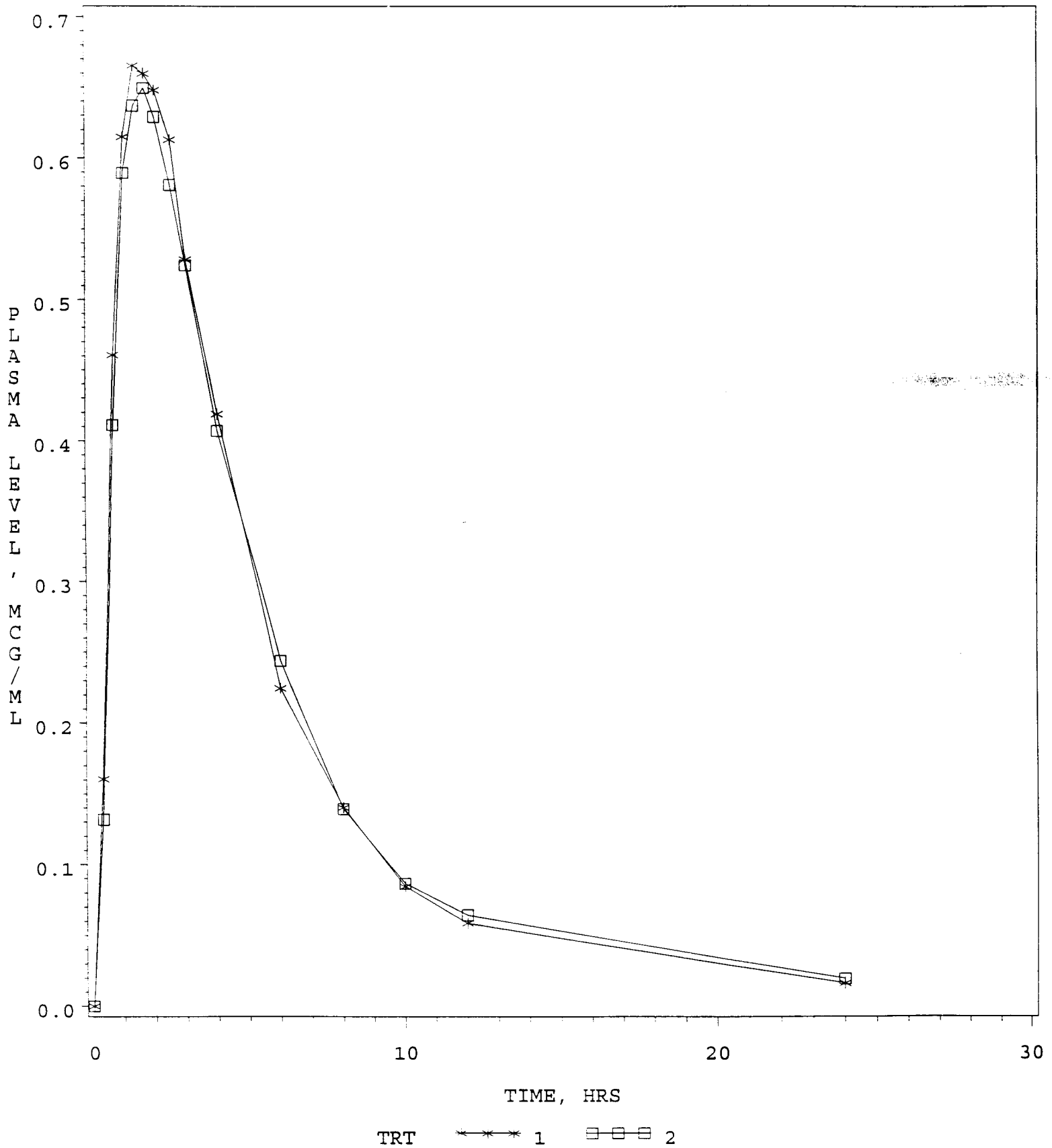
The firm should be informed of the deficiencies and recommendations.

[redacted] (b)4 - Confidential [redacted] Business [redacted]

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

# FIG P-1. PLASMA ACYCLOVIR LEVELS

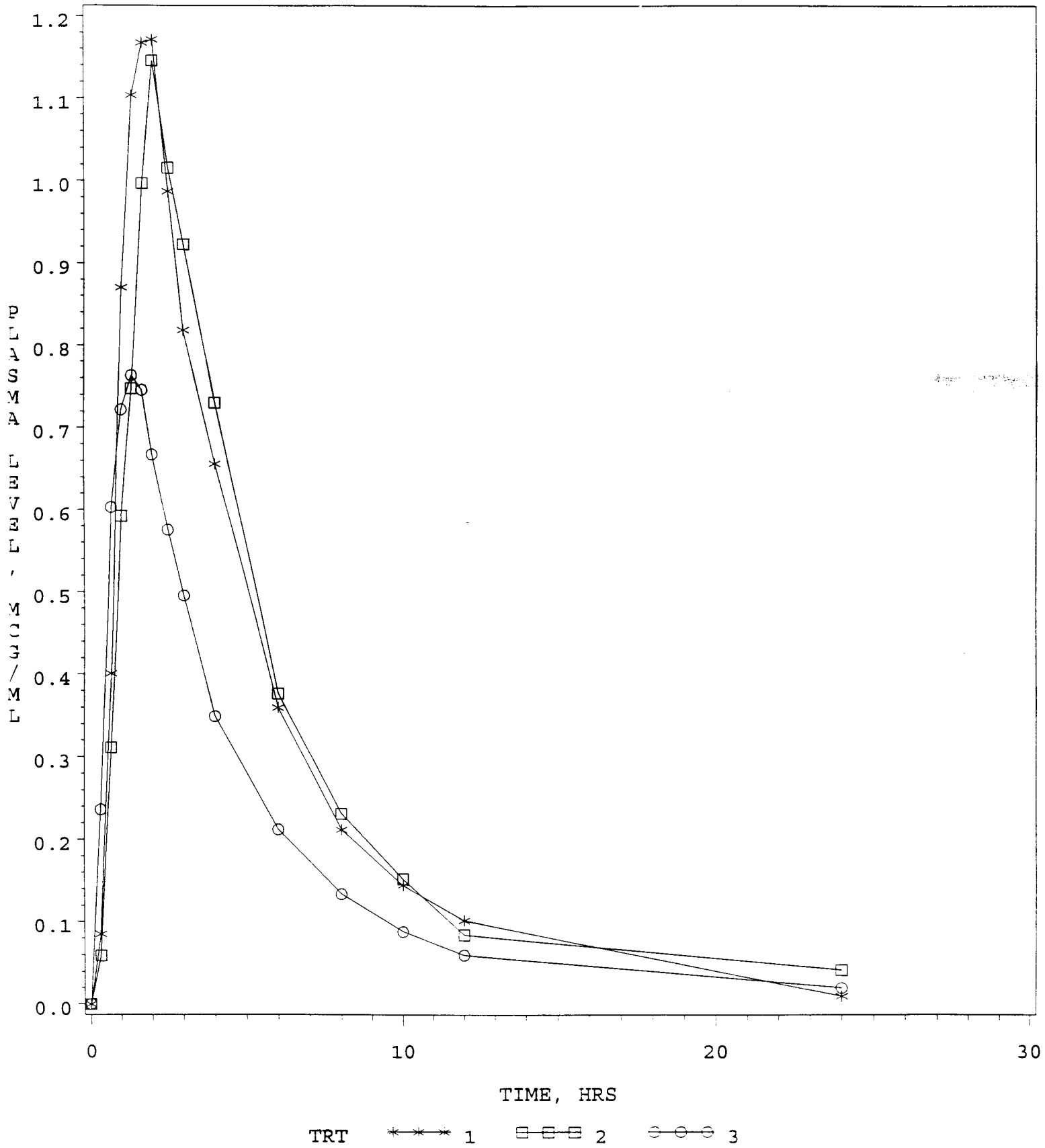
ACYCLOVIR TABLETS, 800 MG, ANDA #74-658
UNDER FASTING CONDITIONS
DOSE=800 MG




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

# FIG P-2. PLASMA ACYCLOVIR LEVELS

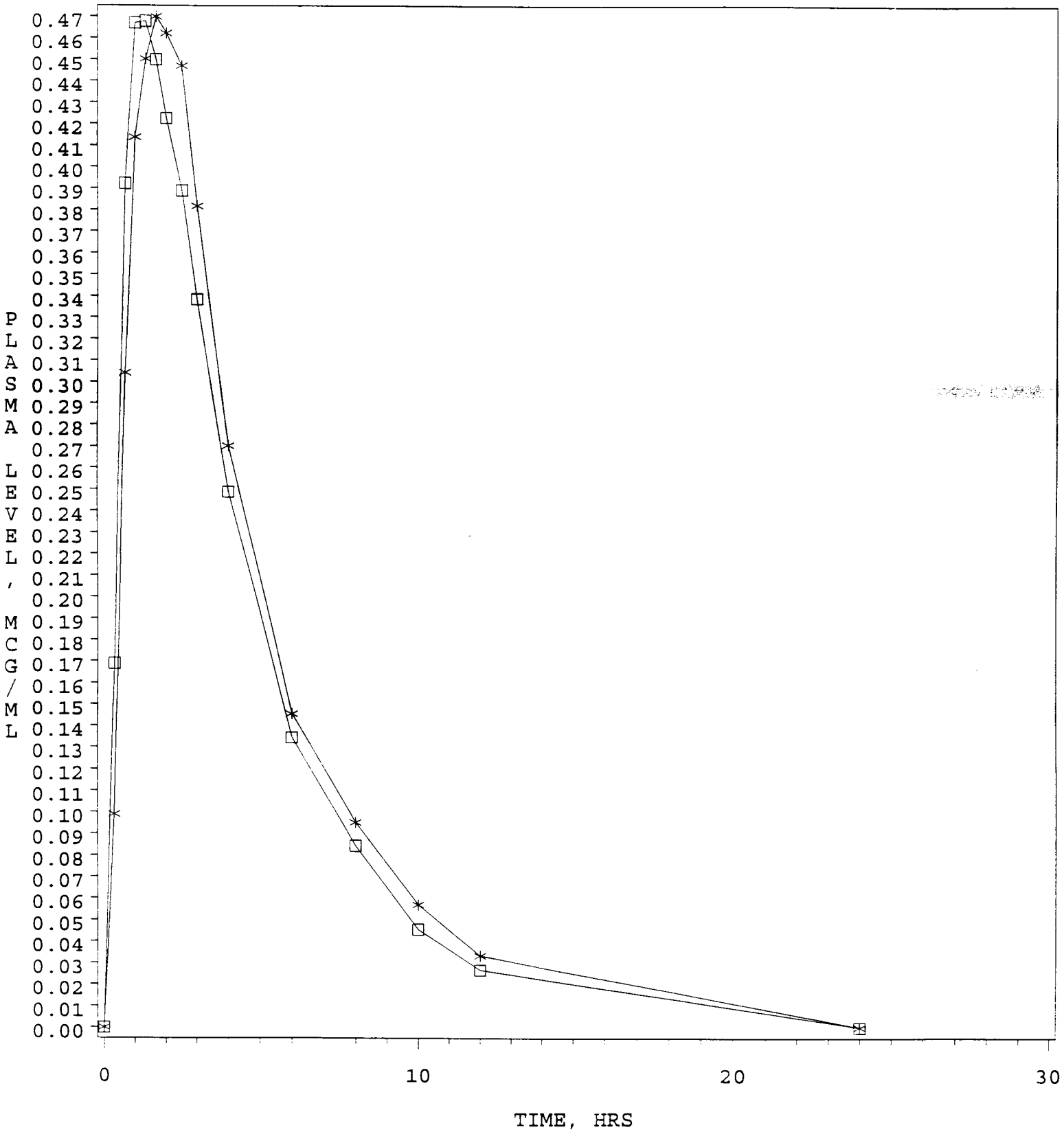
ACYCLOVIR TABLETS, 800 MG, ANDA #74-658
UNDER NON-FASTING CONDITIONS
DOSE=800 MG




1=TEST-NONFASTING(LEK) 2=REF-NONFASTING(BW) 3=TEST-FASTING(LEK)

# FIG P-3. PLASMA ACYCLOVIR LEVELS

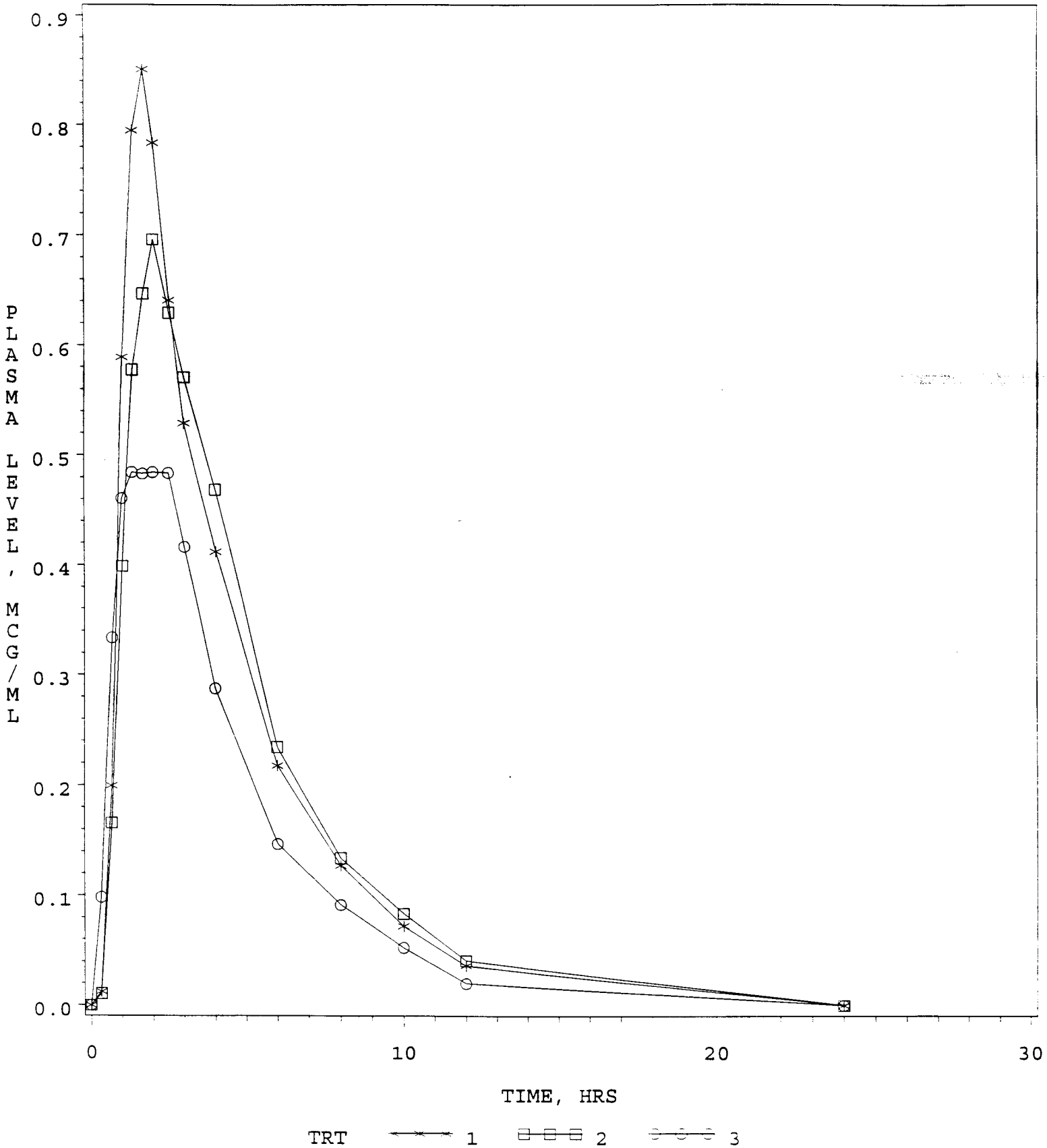
ACYCLOVIR TABLETS, 400 MG, ANDA #74-658
UNDER FASTING CONDITIONS
DOSE=400 MG




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

# FIG P-4. PLASMA ACYCLOVIR LEVELS

ACYCLOVIR TABLETS, 400 MG, ANDA #74-658
UNDER NON-FASTING CONDITIONS
DOSE=400 MG




1=TEST-NONFASTING(LEK) 2=REF-NONFASTING(BW) 3=TEST-FASTING(LEK)