

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75021

Trade Name Acyclovir Tablets 400mg and 800mg

Generic Name Acyclovir Tablets 400mg and 800mg

Sponsor Copley Pharmaceutical, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75021

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75021

APPROVAL LETTER

MAR 18 1998

Copley Pharmaceutical, Inc.
Attention: Isidoro Nudelman
25 John Road
Canton, MA 02021
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Dear Sir:

This is in reference to your abbreviated new drug application dated December 10, 1996, 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 October 20, 1997; February 10, and March 4, 1998.

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, respectively, 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,

3/16/98

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75021

FINAL PRINTED LABELING



NDC 38245-327-10

ACYCLOVIR TABLETS

Each tablet contains

400 mg

CAUTION: Federal law prohibits dispensing without prescription.
100 TABLETS

Copley Pharmaceutical, Inc.
Canton, MA 02021

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

Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.



N 38245-327-10 2

LOT:
EXP:

LAB716200



NDC 38245-327-25

ACYCLOVIR TABLETS

Each tablet contains

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS

Copley Pharmaceutical, Inc.
Canton, MA 02021

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

Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.



N 38245-327-25 6

LOT:
EXP:

LAB716300



NDC 38245-301-10

ACYCLOVIR TABLETS

Each tablet contains

800 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS



Copley Pharmaceutical, Inc.
Canton, MA 02021

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

Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.



N 38245-301-10 2
3

LOT:
EXP:

LAB715400



NDC 38245-301-25

ACYCLOVIR TABLETS

Each tablet contains

800 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS



Copley Pharmaceutical, Inc.
Canton, MA 02021

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

Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.



N 38245-301-25 6
3

LOT:
EXP:

LAB715500

ACYCLOVIR CAPSULES
ACYCLOVIR TABLETS

LEA506700
Revised: September 1997



LEA506700

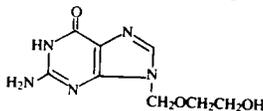
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DESCRIPTION: Acyclovir is an antiviral drug. Acyclovir capsules and tablets are formulations for oral administration. Each capsule of acyclovir contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose (monohydrate), magnesium stearate, sodium lauryl sulfate, pharmaceutical glaze, synthetic black iron oxide, propylene glycol, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, and D&C Yellow No. 10 Aluminum Lake. The capsule shell consists of gelatin, FD&C Blue No. 1 silicon dioxide, sodium lauryl sulfate and titanium dioxide. Printed with edible black ink.

Each 400 mg tablet of acyclovir contains 400 mg of acyclovir and the inactive ingredients FD&C Blue No. 2 Aluminum Lake, magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycolate.

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

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one; it has the following structural formula:



Acyclovir is a white crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and a molecular weight of 225.21. The maximum solubility in water at 37°C is 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25.

VIROLOGY: Mechanism of Antiviral Action: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). In cell culture, acyclovir's highest antiviral activity is against HSV-1, followed in decreasing order of potency against HSV-2 and VZV.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme 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. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities: The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals 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 (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/mL.

Drug Resistance: Resistance of VZV to antiviral nucleoside analogues can result from qualitative or quantitative changes in the viral TK or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to acyclovir have been recovered from patients with AIDS. In these cases, TK-deficient mutants of VZV have been recovered.

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Resistance of HSV to antiviral nucleoside analogues occurs by the same mechanisms as resistance to VZV. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY: Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in healthy volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in Table 1.

Table 1: Acyclovir Pharmacokinetic Characteristics (Range)

Parameter	Range
Plasma protein binding	9% to 33%
Plasma elimination half-life	2.5 to 3.3 hr
Average oral bioavailability	10% to 20% *

* Bioavailability decreases with increasing dose.

In one multiple-dose, cross-over study in healthy subjects (n=23), it was shown that increases in plasma acyclovir concentrations were less than dose proportional with increasing dose, as shown in Table 2. The decrease in bioavailability is a function of the dose and not the dosage form.

Table 2: Acyclovir Peak and Trough Concentrations at Steady State

Parameter	C_{max}	C_{min}
200 mg	0.83 mcg/mL	0.46 mcg/mL
400 mg	1.21 mcg/mL	0.63 mcg/mL
800 mg	1.61 mcg/mL	0.83 mcg/mL

There was no effect of food on the absorption of acyclovir (n=6); therefore, acyclovir capsules and tablets may be administered with or without food.

The only known urinary metabolite is 9-[(carboxymethoxy) methyl]guanine.

Special Populations: Adults with Impaired Renal Function: 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).

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

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase acyclovir half-life and systemic exposure. Urinary excretion and renal clearance were correspondingly reduced.

Clinical Trials: Initial Genital Herpes: Double-blind, placebo-controlled studies have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection and duration of lesion healing. The duration of pain and new lesion formation was decreased in some patient groups.

Recurrent Genital Herpes: Double-blind, placebo-controlled studies in patients with frequent recurrences (six or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 10 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of patients who received acyclovir 400 mg 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 patients showed that 71% to 87% were recurrence-free in each quarter.

Herpes Zoster Infections: In a double-blind

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Herpes Zoster Infections: In a double-blind, placebo-controlled study of immunocompetent patients with localized cutaneous zoster infection, acyclovir (800 mg five 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.

In a similar double-blind, placebo-controlled study, acyclovir (800 mg five 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).

Treatment was begun within 72 hours of rash onset and was most effective if started within the first 48 hours.

Adults greater than 50 years of age showed greater benefit.

Chickenpox: Three randomized, double-blind, placebo-controlled trials were conducted in 993 pediatric patients ages 2 to 18 years with chickenpox. All patients were treated within 24 hours after the onset of rash. In two trials, acyclovir was administered at 20 mg/kg four times daily (up to 3,200 mg per day) for 5 days. In the third trial, doses of 10, 15, or 20 mg/kg were administered four times daily for 5 to 7 days. Treatment with acyclovir shortened the time to 50% healing, reduced the maximum number of lesions, reduced the median number of vesicles, decreased the median number of residual lesions on day 28, and decreased the proportion of patients with fever, anorexia, and lethargy by day 2. Treatment with acyclovir did not affect varicella-zoster virus-specific humoral or cellular immune responses at 1 month or 1 year following treatment.

INDICATIONS AND USAGE:
Herpes Zoster Infections: Acyclovir is indicated for the acute treatment of herpes zoster (shingles).

Genital Herpes: Acyclovir is indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes.

Chickenpox: Acyclovir is indicated for the treatment of chickenpox (varicella).

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: Dosage adjustment is recommended when administering acyclovir to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

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.

Herpes Zoster: There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes Infections: Patients should be informed that acyclovir is not a cure for genital herpes. There are no data evaluating whether acyclovir will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

Chickenpox: 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. Drug Interactions: See CLINICAL PHARMACOLOGY: Pharmacokinetics.

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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 six times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally six times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics).

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

Acyclovir was tested in 16 genetic toxicity assays. No evidence of mutagenicity was observed in four microbial assays. Acyclovir demonstrated mutagenic activity in two *in vitro* cytogenetic assays (one mouse lymphoma cell line and human lymphocytes). No mutagenic activity was observed in five *in vitro* cytogenetic assays (three Chinese hamster ovary cell lines and two mouse lymphoma cell lines).

A positive result was demonstrated in one of two *in vitro* cell transformation assays, and morphologically transformed cells obtained in this assay formed tumors when inoculated into immunosuppressed, syngeneic, weaning mice. No mutagenic activity was demonstrated in another, possibly less sensitive *in vitro* cell transformation assay.

Acyclovir was clastogenic in Chinese hamsters at 380 to 760 times human dose levels. In rats, acyclovir produced a non-significant increase in chromosomal damage at 62 to 125 times human levels. No activity was observed in a dominant lethal study in mice at 36 to 73 times human levels.

Acyclovir did not 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 higher doses (50 mg/kg/day, s.c.) in rats and rabbits (11 to 22 and 16 to 31 times human levels, respectively) implantation efficacy, but not litter size, was decreased. In a rat peri- and post-natal study at 50 mg/kg/day, s.c., there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50 mg/kg/day, i.v. for 1 month (21 to 41 times human levels) or in dogs given 60 mg/kg/day orally for 1 year (six to 12 times human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or 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, rats were given three s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. In this test, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiological registry of acyclovir use during pregnancy has been ongoing since 1984. As of June 1996, outcomes of live births have been documented in 494 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when indicated.

Geriatric Use: Clinical studies of acyclovir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, and of concomitant disease or other drug therapy.

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 acyclovir 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Long-Term Administration: The most frequent adverse events reported in a clinical trial

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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) two times daily for 1 year in 586 patients treated with acyclovir were nausea (4.8%) and diarrhea (2.4%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), and headache (2.2%).

Herpes Zoster: The most frequent adverse event reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir five times daily for 7 to 10 days in 323 patients was malaise (11.5%). The 323 placebo recipients reported malaise (11.1%).

Chickenpox: The most frequent adverse event reported during three clinical trials of treatment of chickenpox with oral acyclovir at doses of 10 to 20 mg/kg four times daily for up to 5 to 7 days or 800 mg four times daily for 5 days in 495 patients was diarrhea (3.2%). The 498 patients receiving placebo reported diarrhea (2.2%).

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) is exceeded in the intratubular fluid. 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:

Acute Treatment of Herpes Zoster: 800 mg every 4 hours orally, five times daily for 7 to 10 days.

Genital Herpes: Treatment of Initial Genital Herpes: 200 mg every 4 hours, five times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg two times daily for up to 12 months, followed by re-evaluation. Alternative regimens have included doses ranging from 200 mg three times daily to 200 mg five times daily.

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

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

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.

Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

When therapy is indicated, it should be initiated at the earliest sign or symptom of chickenpox. There is no information about the efficacy of therapy initiated more than 24 hours after onset of signs and symptoms.

Patients With Acute or Chronic Renal Impairment: In patients with renal impairment, the dose of acyclovir capsules or tablets should be modified as shown in Table 3:

Table 3: Dosage Modification for Renal Impairment

				Normal Dosage
			200 mg ev 4 hours	
		400 mg ev 12 hour		
	800 mg ev 4 hours			

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Table 3: Dosage Modification for Renal Impairment

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
400 mg every 12 hours	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
800 mg every 4 hours	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
800 mg every 4 hours	10-25	800	every 8 hours
800 mg every 4 hours	0-10	800	every 12 hours

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

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.

Bioequivalence of Dosage Forms: Acyclovir suspension was shown to be bioequivalent to acyclovir capsules (n=20) and one acyclovir 800-mg tablet was shown to be bioequivalent to four acyclovir 200-mg capsules (n=24).

How Supplied: Acyclovir Capsules (blue, opaque cap and body) containing 200 mg acyclovir and printed with "Copley 299", Acyclovir 200". Bottle of 100 (NDC 38245-299-10).

Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.

Acyclovir Tablets (round, unscored, blue tablets) containing 400 mg acyclovir and debossed "Copley 327" on one side, plain on the other side - Bottle of 100 (NDC 38245-327-10) and Bottle of 250 (NDC 38245-37-25).

Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.

Acyclovir Tablets (capsule shaped, unscored, blue tablets) containing 800 mg acyclovir and debossed "Copley 301" on one side and plain on the other side - Bottle of 100 (NDC 38245-301-10) and Bottle of 250 (NDC 38245-310-25). **Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.**

CAUTION: Federal law prohibits dispensing without prescription.

Copley Pharmaceutical, Inc.
 Canton, MA 02021

Revised: September, 1997
 LEA 506700

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **75021**

CHEMISTRY REVIEW(S)

ANDA 75-021

1. CHEMISTRY REVIEW NO.: 2

2. ANDA # 75-021

3. NAME AND ADDRESS OF APPLICANT
Copley Pharmaceutical, Inc.
25 John Road
Canton, MA 02021

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Glaxo Wellcome's Zovirax® Tablets 400 mg and 800 mg. Patent expired on 4/22/97. No exclusivity remains.

A patent certification and exclusivity statement is also included p. 011.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: None

7. NONPROPRIETARY NAME:
Acyclovir Tablets

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

9. AMENDMENTS AND OTHER DATES:

Firm:

Submitted: December 10, 1996
Amendment: October 20, 1997 (Subject of this review)
FAX Amandment: March 4, 1998

FDA:

Acknowledgment: February 3, 1997
Bio Letter: May 20, 1997
Label Review: May 29, 1997
Chem Rev # 1 & FAX: June 12, 1997

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

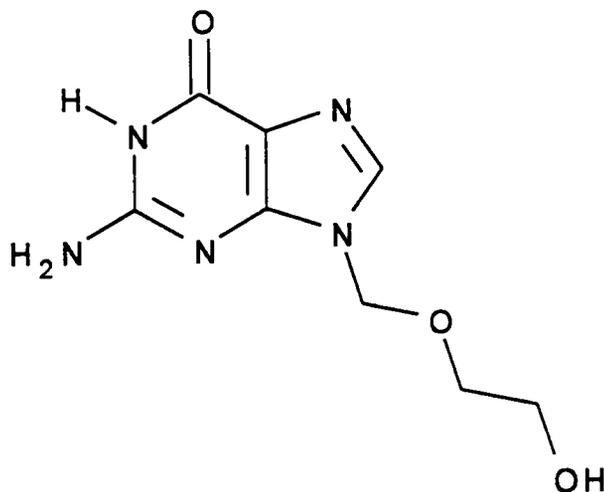
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet (Uncoated)

14. POTENCIES
400 mg & 800 mg

15. CHEMICAL NAME AND STRUCTURE:

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



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

16. RECORDS AND REPORTS: N/A

17. COMMENTS

- a. The chemistry, manufacturing and controls procedures are satisfactory.
- b. The label review is satisfactory for approval - 11/5/97.
- c. The bio review is satisfactory.
- d. The EIR is acceptable - 4/28/97.
- e. Methods validation satisfactory 1/14/98.

18. CONCLUSIONS AND RECOMMENDATIONS

This application can be approved.

19. REVIEWER:

Donald Shostak

DATE COMPLETED:

November 11, 1997
 (Revised 3/5/98 FAX amend)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75021

BIOEQUIVALENCE REVIEW(S)

1.1
Sho HAKO

ANDA 75-021

Copley Pharmaceutical, Inc.
Attention: William E. Brochu, Ph.D.
Canton Commerce Center
25 John Road
Canton, MA 02021
|||||

MAY 20 1997

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 interim 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 as the dissolution medium with apparatus 2 (paddle) at 50 rpm for the 400 and 800 mg tablets. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of the drug 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,



 Nicholas Fleischer, Ph.D.
 Director, Division of Bioequivalence
 Office of Generic Drugs
 Center for Drug Evaluation and Research

MAY 16 1997

Acyclovir

400 mg and 800 mg Tablets

ANDA #75-021

Reviewer: Z.Z. Wahba

File #75021sw.d96

Copley Pharmaceutical, Inc.

Canton, MA

Submission Date:

December 10, 1996

**REVIEW OF TWO IN-VIVO BIOEQUIVALENCE STUDIES,
IN VITRO DISSOLUTION TESTING DATA
AND WAIVER REQUEST**

I. OBJECTIVE:

Review the following:

1. Copley's in vivo bioequivalence study under fasting and non-fasting conditions comparing its drug product Acyclovir Tablets, 800 mg to the reference drug product Glaxo Wellcome's Zovirax® Tablets, 800 mg.
2. Dissolution data for the 400 mg and 800 mg strengths of the test and reference drug products.
3. Waiver request for the 400 mg strength Tablets.

II. INTRODUCTION:

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 genitalia 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® (Glaxo-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. BIOEQUIVALENCE STUDY UNDER FASTING CONDITION
Clinical Study #P95-072

A. Sponsor:

Copley Pharmaceutical, Inc.
25 John Road
Canton Commerce Center
Canton, MA 02021

Study Site:
Clinical Facility

Clinical Study Dates:

Period I: April 14, 1996
Period II: April 21, 1996

B. Study design:

Single dose, randomized, two-way crossover study under fasting conditions.

C. Subjects:

Forty-eight (48) healthy male subjects were recruited for study. Forty-six (46) subjects completed the clinical portion of the study (subjects # 1-34, 36 and 38-48). Subjects #35 and #37 dropped prior to Period II dosing for personal reasons. The subjects were within 18 to 38 years of age, and

their body weights were within \pm 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:

Only medically and physically healthy subjects with clinically normal ranges of laboratory tests (blood chemistry, hematology, urinalysis) were enrolled in the study.

Subject Exclusion Criteria:

- A history of cardiovascular, pulmonary, renal, gastrointestinal, hepatic, endocrine, neurological or hematological disease.
- A history of drug or alcohol addiction or abuse.
- A history of allergic responses to the class of drug being tested.
- Subjects who have been on an abnormal diet during the four weeks preceding the study.
- Blood donation within the past 14 days prior to the study.
- Use of any investigational drug within 30 days preceding entry into the study.
- Use of tobacco products.

Subject Restrictions:

- No subject took any medications, including OTC products for at least one week prior to the beginning of the study and until completion of the study.
- No alcoholic, xanthine and caffeine containing foods and beverages were allowed, beginning with 48 hours prior to dosing and until completion of the study.

D. Food and Fluid Intake:

Subjects fasted overnight for at least 10 hours before dosing and 4 hours after dosing. The drug products were administered with 240 mL tap water. Water was not permitted for 1 hour before and 1 hour after the dose, but was allowed at all other times. The subjects received their medication according to randomized dosing schedule. Standard meals were provided at appropriate times thereafter (at 4 and 9 hours after drug administration).

E. Treatment Plan:

Test product: 1 X 800 mg Acyclovir Tablet (Copley), Lot #301Z01, Batch size: tablets, assay potency: 100.3%, content uniformity: 99.1%, manufacturing date: 02/98.

Reference product: 1 X 800 mg Zovirax® Tablet (Glaxo-

Wellcome), Lot #4Z2480, assay potency: 101.2%, content uniformity: 100.1%, expiration date: 01/97.

Washout period: 7 days.

A single 800 mg dose was given in each period of the study.

F. Blood Sampling:

Blood samples were collected in vacutainers, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, 14 and 16 hours post-dosing. The plasma samples were separated, collected and stored frozen at -22°C until analysis.

G. Assay Methodology:

H. In Vivo BE Study and Statistical Analysis:

Forty-eight (48) healthy male subjects were recruited for study. Forty-six (46) subjects completed the clinical portion of the study (subjects # 1-34, 36 and 38-48). Subjects #35 and #37 dropped prior to Period II dosing for personal reasons. The pharmacokinetic parameters of acyclovir were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters for the plasma acyclovir concentrations, as well as the following parameters, AUCT, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

Table #6
Mean Plasma Concentrations (ng/mL)
of Acyclovir in 46 Subjects Following a Single Oral
Dose of 800 mg Acyclovir Under Fasting Conditions
(Test Lot #301Z01, Reference Lot #4Z2480)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	
0.25	47.76	56.36	46.32	52.65	1.03
0.5	288.45	184.69	264.10	153.86	1.09
0.75	505.42	246.65	458.63	210.08	1.10
1	614.44	264.52	571.11	230.23	1.08
1.25	680.98	285.61	622.69	214.62	1.09
1.5	718.87	300.28	666.84	229.90	1.08
1.75	712.98	287.51	690.46	261.55	1.03
2	697.02	276.47	688.04	291.85	1.01
2.5	639.54	255.95	633.61	298.64	1.01
3	564.33	244.50	556.33	256.90	1.01
4	426.54	196.96	418.52	200.65	1.02
6	243.06	111.83	241.02	108.76	1.01
8	149.01	62.07	146.99	62.96	1.01
10	97.77	39.11	94.18	38.62	1.04
12	66.07	23.76	63.86	24.57	1.03
14	47.22	16.65	46.00	18.01	1.03
16	37.20	13.47	33.17	17.42	1.12

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table #7
Mean Pharmacokinetic Parameters (Arithmetic)
in 46 Subjects Following a Single Oral Dose of
800 mg Acyclovir Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	4001.26	1337.66	3872.89	1408.70	1.03
AUCT	3779.37	1318.36	3663.80	1377.68	1.03
C _{MAX}	826.46	280.71	797.96	263.34	1.04
K _E	0.18	0.04	0.18	0.04	0.99
*LAUCI	3782.87	0.34	3614.22	0.38	1.05
*LAUCT	3554.10	0.36	3398.45	0.40	1.05
*LC _{MAX}	777.54	0.36	747.71	0.39	1.04
THALF	4.04	1.26	3.97	1.17	1.02
T _{MAX}	1.64	0.79	1.64	0.73	1.00

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
 * The values represent the geometric means (antilog of the means of the logs).

Table #8
LSMeans And The 90% Confidence Intervals
(Under Fasting Conditions)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
*LAUCI	3773.53	3602.79	1.05	95.42	114.97
*LAUCT	3543.65	3386.93	1.05	94.54	115.79
*LCMAX	774.82	745.42	1.04	93.60	115.43

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

Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

* The values represent the LSMEANS (antilog of the means of the logs).

1. The mean plasma acyclovir levels reached a maximum level of concentration around 1.50-1.75 hours (Table #6 and Figures #1 and 2).
2. The 90% confidence intervals for the LSMeans log-transformed AUCT, AUCI and CMAX were within the acceptable range of 80-125% (Table #8). The T/R mean ratios (RLSM12) for the log-transformed AUCT, AUCI and CMAX were within the acceptable range of 0.8-1.25% (Table #8).

There were no significant period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCT, AUCI and CMAX. However, there was a significant sequence effect (p less than 0.05) for the log-transformed pharmacokinetic parameters AUCT, AUCI and CMAX.

I. **Adverse Events:**

The adverse reactions are reported on page #1636, Vol. C1.5, section 'Final Report'. The following are the adverse events summary for study subjects under fasting conditions.

Parameter	Test Treatment (# of Subjects)	Ref. Treatment (# of Subjects)
Coughing	1	--
Dizziness	2	1
Dysphonia (hoarse voice)	1	--
Edema (Swollen Right Arm)	1	--
Headache	1	4
Hot Flushes	1	--
Pallor (Pale)	1	2
Pharyngitis	1	1
Purpura (Hematoma)	2	1
Rhinitis (Runny Nose)	3	--
Sweating	1	--
Syncope (Fainted)	--	1
Tremor (Hands Shaking)	--	1

None of the adverse events was considered serious or resulted in terminating any subject from study participation.

IV. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS
(clinical study project #P95-073)

A. Sponsor:

Copley Pharmaceutical, Inc.
25 John Road
Canton Commerce Center
Canton, MA 02021

Study Site:
Clinical Facility

Clinical Study Dates:

Period I: April 13-14, 1996

Period II: April 20-21, 1996

Period III: April 27-28, 1996

B. Study design:

Randomized, three-way crossover, single dose study, under fasting and non-fasting conditions.

C. Subjects:

Eighteen (18) subjects were recruited for this study. Sixteen (16) subjects completed the entire clinical portion of the study. Subjects #7 and #15 dropped prior to check-in for Period II for personal reasons. The subjects were 18 to 32 years of age, and their body weights were within $\pm 10\%$ of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Exclusion Criteria:

Same as in Protocol #P95-072 under fasting conditions

Subject Restrictions:

Same as in Protocol #P95-072 under fasting conditions

D. Treatment Plan:

Test Product:

Treatment A: 1 X 800 mg Acyclovir Tablet (Copley), Lot #301Z01, Batch size: tablets, assay potency: 100.3%, content uniformity: 99.1%, manufacturing date: 02/98, under fasting conditions.

Treatment B: 1 X 800 mg Acyclovir Tablet (Copley), Lot #301Z01, Batch size: tablets, assay potency: 100.3%,

content uniformity: 99.1%, manufacturing date: 02/98, under non-fasting conditions.

Reference Product:

Treatment C: 1 X 800 mg Zovirax® Tablet (Glaxo-Wellcome), Lot #4Z2480, assay potency: 101.2%, content uniformity: 100.1%, expiration date: 01/97, expiration date: 06/01/97, under non-fasting conditions.

Washout period: 7 days between doses.

A single 800 mg dose was given in each period of the study.

E. Drug, Food and Fluid Intake:

Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 4 hours after drug administration. Subjects who were fed standard recommended breakfast prior to dosing (treatments B and C) only fasted for 9.5 hours. Treatments B and C differed from treatment A in that the subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 8 fluid ounces (240 mL) of room temperature tap water according to randomized dosing schedule. Water was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times. Standard meals were provided at appropriate times thereafter (at 4 and 10 hours after dosing).

F. Blood Sampling:

Blood samples were collected in vacutainers, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, 14 and 16 hours post-dosing. The plasma samples were separated, collected and stored frozen at -22°C until analysis.

G. Assay Methodology:

Same as in Protocol #P95-72 (under fasting conditions).

H. In Vivo BE Study and Statistical Analysis
(Under Non-Fasting Conditions)

Eighteen (18) subjects were recruited for this study. Sixteen (16) subjects completed the entire clinical portion of the study. Subjects #7 and #15 dropped prior to check-in for Period II for personal reasons. Samples from 16 subjects were assayed for acyclovir. Therefore, the data set used for statistical and pharmacokinetic analyses contains data from subjects #1-6, 8-14 and 16-17.

Deviations from the protocol: (pages #1632-1633, vol. C1.5)

There were six deviations from the protocol instructions of non-prescription medications (to treat cases such as, headache, runny nose, rash on arms) within 7 days of Period I dosing. The clinical investigators reported that the medication should have been completely eliminated from the body prior to Period I dosing and should not compromise the outcome or validity of the study.

The pharmacokinetic parameters of acyclovir were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters of the level of plasma concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the tables below:

Table #11
Mean Plasma Concentrations of
Acyclovir (ng/mL) in 16 Subjects
Following 800 mg Oral Doses of Acyclovir
Under Non-Fasting Conditions
(Test Lot #301Z01, Reference Lot #4Z2480)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	73.07	71.29	4.01	11.45	2.09	8.38	18.24
0.5	301.55	161.04	51.22	59.36	74.59	95.80	5.89
0.75	478.81	209.48	227.28	178.40	234.32	178.93	2.11
1	583.19	240.91	509.51	290.61	443.39	260.04	1.14
1.25	636.19	262.52	776.38	326.16	624.55	288.59	0.82
1.5	669.19	276.81	936.38	296.06	789.63	329.69	0.71
1.75	659.56	272.77	990.88	289.90	835.00	318.57	0.67
2	645.44	290.19	983.31	270.55	878.56	309.94	0.66
2.5	586.13	250.33	924.69	329.91	874.25	254.94	0.63
3	513.63	256.50	839.13	329.71	849.56	285.62	0.61
4	380.13	188.28	656.50	247.21	761.13	306.03	0.58
6	235.93	109.04	360.75	132.35	422.75	163.70	0.65
8	149.81	63.53	211.88	74.20	239.81	98.66	0.71
10	97.87	36.73	132.69	42.93	148.22	55.16	0.74
12	67.34	21.99	88.46	27.59	101.59	37.31	0.76
14	47.42	15.00	62.16	19.30	68.58	24.97	0.76
16	38.69	10.61	48.11	17.81	53.94	18.54	0.80

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0		
0.25	34.90	1.91
0.5	4.04	0.69
0.75	2.04	0.97
1	1.32	1.15
1.25	1.02	1.24
1.5	0.85	1.19
1.75	0.79	1.19

2	0.73	1.12
2.5	0.67	1.06
3	0.60	0.99
4	0.50	0.86
6	0.56	0.85
8	0.62	0.88
10	0.66	0.90
12	0.66	0.87
14	0.69	0.91
16	0.72	0.89

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table #12
Mean Pharmacokinetic Parameters
in 16 Subjects Following a Single Oral Dose of
800 mg Acyclovir Under Non-Fasting Conditions

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	3855.88	1353.94	5375.38	1358.13	5633.13	1573.22	0.72
AUCT	3576.44	1336.34	5079.00	1312.04	5312.81	1509.22	0.70
C _{MAX}	762.13	292.63	1143.44	265.08	1053.31	222.57	0.67
KE	0.16	0.05	0.18	0.04	0.18	0.03	0.91
*LAUCI	3615.12	0.38	5229.47	0.24	5427.46	0.29	0.69
*LAUCT	3322.74	0.41	4937.07	0.24	5113.14	0.29	0.67
*LC _{MAX}	701.18	0.45	1117.07	0.22	1031.86	0.21	0.63
THALF	4.88	2.16	4.11	1.14	4.05	0.91	1.19
T _{MAX}	1.53	0.60	1.80	0.68	2.31	1.05	0.85

(CONTINUED)

PARAMETER	RMEAN13	RMEAN23
AUCI	0.68	0.95
AUCT	0.67	0.96
C _{MAX}	0.72	1.09
KE	0.91	1.00
*LAUCI	0.67	0.96
*LAUCT	0.65	0.97
*LC _{MAX}	0.68	1.08
THALF	1.20	1.01
T _{MAX}	0.66	0.78

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

- Under non-fasting conditions, the mean plasma acyclovir levels reached the maximum around 1.75-2.0 hours (Table #11 and Figures #3 and #4).
- Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUCT, AUCi, and C_{max}, were all within the acceptable range of 0.8 to

1.2 (Table #12).

I. Adverse Events:

The adverse reactions are reported on page #513, Vol. C1.3, section 'Final Report'. The following are the adverse events summary for study subjects under non-fasting conditions.

Parameter	Treat A (# of Subjects)	Treat B (# of Subjects)	Treat C (# of Subjects)
Abdominal Pain	--	1	1
Coughing	--	1	--
Headache	3	--	1
Pharyngitis	1	--	1
Purpura (Hematoma)	--	1	1
Rhinitis (Runny Nose)	1	--	--

None of the adverse events were considered serious or resulted in terminating any subject from study participation.

V. FORMULATION COMPARISON

Table #13 shows the composition of the test products, 400 mg and 800 mg Acyclovir Tablets. The 400 mg and 800 mg strengths are exactly proportional in active and inactive ingredients.

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

**Table #13
Composition of Copley's Acyclovir Tablets**

Ingredient	400 mg tablet		800 mg tablet	
	mg/Tablet	W/W%	mg/Tablet	W/W%
Acyclovir, USP	*424.00 mg (400.00)	83.13	*848.00 mg (800.00)	83.13
Microcrystalline cellulose NF				

FD&C Blue #2 Lake				
Providone USP				
Sodium Starch Glycolate, NF				
Magnesium Stearate, NF				
** Purified Water, USP				
Total Theoretical Weight	510.00	99.97	1020.00	99.97

* Includes a 6% excess to compensate for the water content of active.

** Used as a manufacturing aide during granulation. Final product is dried to moisture limit of

VI. IN VITRO DISSOLUTION TESTING

Method: USP 23 apparatus 2 (paddle) at 50 rpm
 Medium: 900 mL of Deionized water
 Sampling Time: 15, 30, 45 and 60 minutes.
 Test Product: Copley's Acyclovir Tablets
 800 mg, lot #301Z01
 400 mg, lot #327Z01

Reference Product: Glaxo Wellcome's Zovirax® Tablets
 800 mg, lot #4Z2480
 400 mg, lot #5R2592

Number of Units: 12 Tablets

The dissolution testing results are shown in Table #14.

Table IV. In Vitro Dissolution Testing	
Drug (Generic Name): Acyclovir Tablets	
Dose Strength: 400 mg and 800 mg	
ANDA No.: 75-021	
Firm: Copley Pharmaceutical, Inc.	
Submission Date: December 10, 1996	
File Name: 75021sw.d96	
I. Conditions for Dissolution Testing:	
USP 23 Basket: Paddle: X RPM: 50	
No. Units Tested: 12	
Medium: 900 mL of Deionized water	
Specifications: NLT in 30 minutes	
Reference Drug: Zovirax®	
Assay Methodology:	
II. Results of In Vitro Dissolution Testing:	

Sampling Times (Minutes)	Test Product Lot #301Z01 Strength(mg) 800			Reference Product Lot #4Z2480 Strength(mg) 800		
	Mean %	Range	%CV	Mean %	Range	%CV
10	52.1		16.1	83.9		9.7
20	78.3		10.3	90.4		3.8
30	86.6		5.9	92.7		2.0
45	90.6		4.7	93.7		1.6
Sampling Times (Minutes)	Test Product Lot #327Z01 Strength(mg) 400			Reference Product Lot #2R2592 Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
10	61.5		15.4	77.4		4.0
20	78.3		5.2	83.2		2.4
30	83.3		4.7	85.9		2.8
45	86.4		4.4	87.8		2.7

1. The dissolution data for the test and reference listed products are acceptable.
2. There is no USP dissolution methodology for acyclovir. The firm conducted the dissolution testing according to the FDA dissolution methodology.

VII. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Copley's Acyclovir Tablet 800 mg is bioequivalent to the reference product, Glaxo Wellcome's Zovirax® Tablets 800 mg. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%.
2. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Copley's Acyclovir Tablet 800 mg is bioequivalent to the reference product, Glaxo Wellcome's Zovirax® Tablets 800 mg. The ratios of the test mean to the reference mean for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.
3. The formulations of the 400 mg and 800 mg test products are proportional in active and inactive ingredients.

4. The dissolution testing and data have met the FDA dissolution requirements.

VIII. RECOMMENDATION

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, conducted by Copley Pharmaceutical, Inc. on its Acyclovir 800 mg Tablet, lot #301Z01, comparing it to the reference product Glaxo Wellcome's Zovirax® Tablets 800 mg, lot #4Z2480, have been found to be acceptable to the Division of Bioequivalence. The two studies demonstrate that under fasting and non-fasting conditions, Copley's Acyclovir 800 mg Tablets are bioequivalent to Glaxo Wellcome's Zovirax® Tablets 800 mg.
2. The dissolution testing conducted by the firm on its Acyclovir 800 mg Tablet (lot #301Z01) and 400 mg (lot #327Z01) has been found acceptable. The formulation for the 400 mg strength is proportionally similar to the 800 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 400 mg tablet of the test product is granted. The Division of Bioequivalence deems Copley's Acyclovir 400 mg Tablet to be bioequivalent to the reference product, Glaxo Wellcome's Zovirax® Tablets 400 mg.
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 as the dissolution medium with apparatus 2 (paddle) at 50 rpm for the 400 and 800 mg tablets. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

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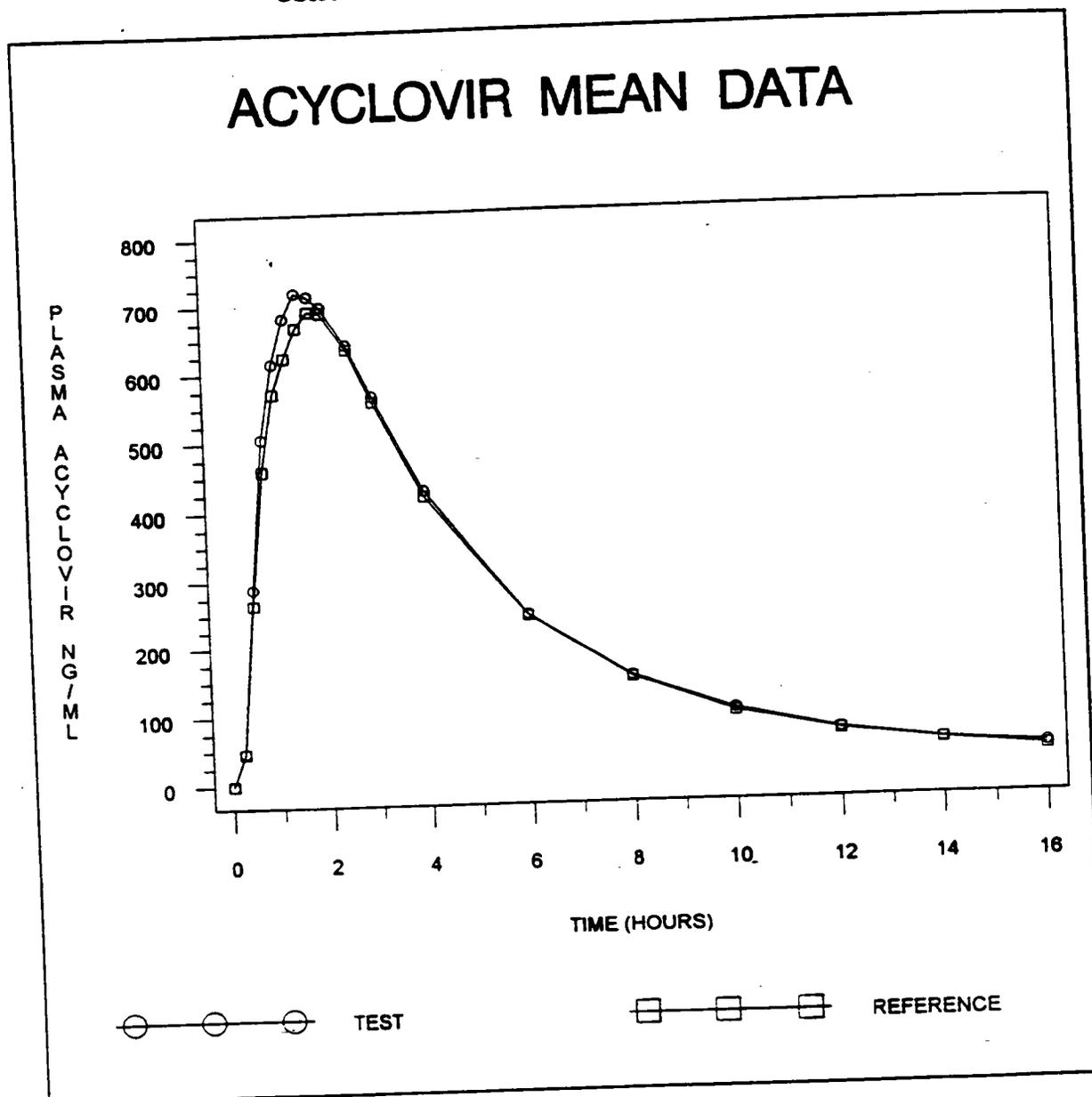
fw Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

Date: _____

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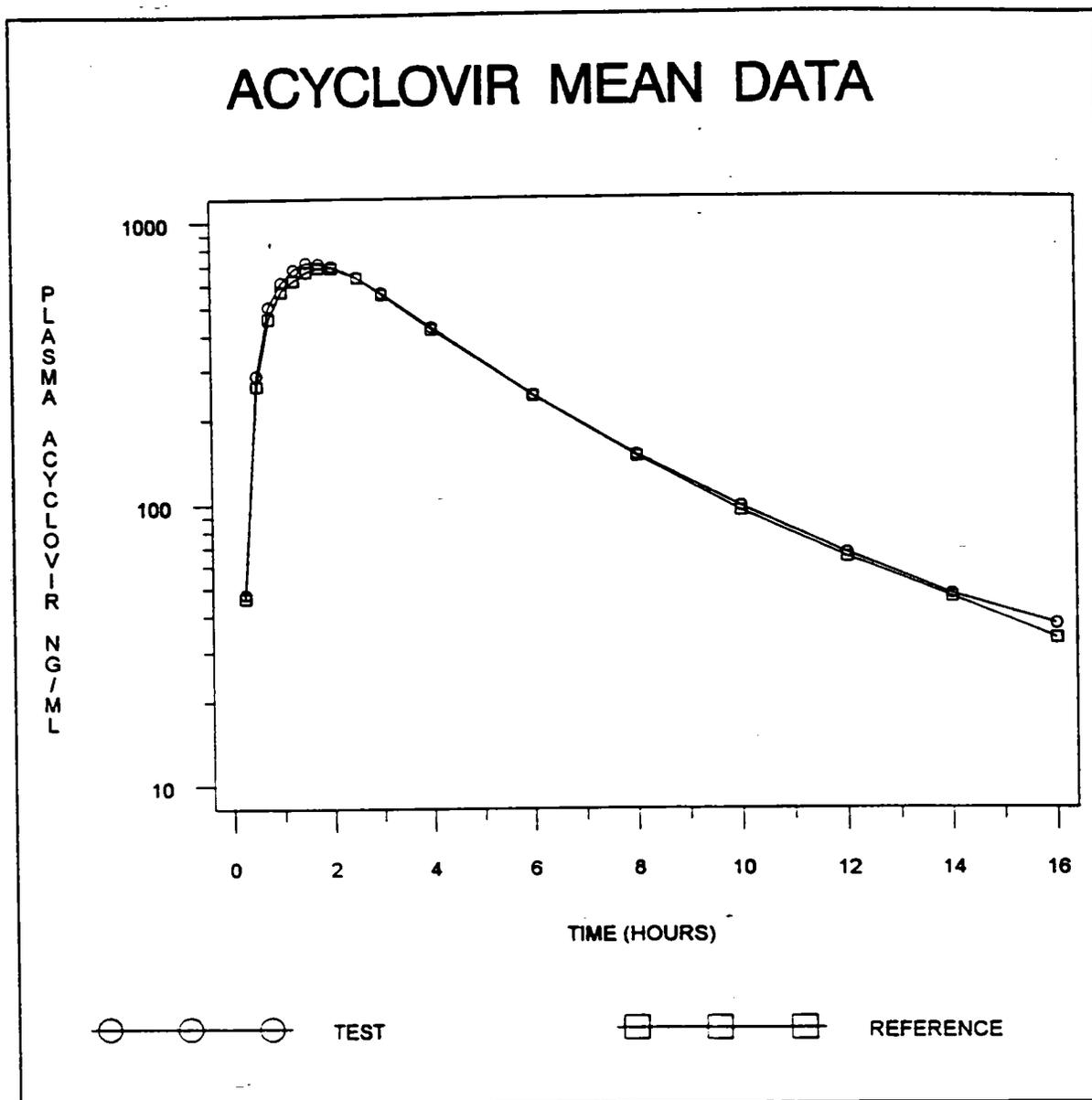
ACYCLOVIR 800 MG TABLET FASTING STUDY
COPLEY P95-072

Figure #1 Linear Plot of Mean Plasma Acyclovir Concentrations vs Time



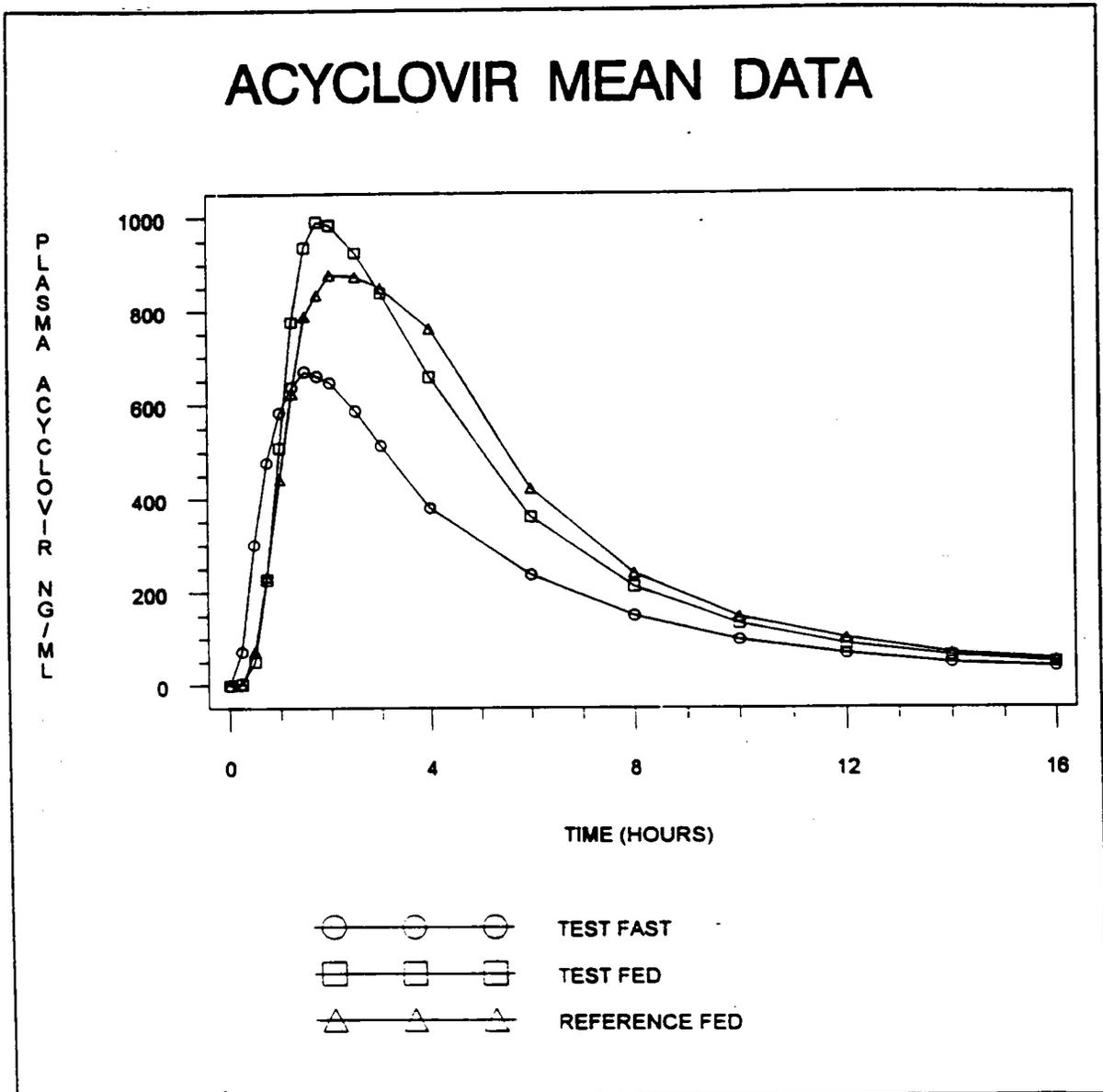
ACYCLOVIR 800 MG TABLET FASTING STUDY
COPLEY P95-072

Figure #2 Semi-logarithmic Plot of Mean Plasma
Acyclovir Concentrations vs Time



ACYCLOVIR 800 MG TABLET FOOD STUDY
COPLEY P95-073

Figure #3 Linear Plot of Mean Plasma Acyclovir Concentrations vs Time



ACYCLOVIR 800 MG TABLET FOOD STUDY
COPLEY P95-073

Figure #4 Semi-logarithmic Plot of Mean Plasma Acyclovir Concentrations vs Time

