CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-891

Name: Acyclovir Tablets, 400 mg and 800 mg

Sponsor: Apothecon, Inc.

Approval Date: October 31, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-891

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter	
Labeling	X
Labeling Reviews	X
Medical Review(s)	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review(s)	
Microbiology Reviews	
Administrative Documents	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-891

APPROVAL LETTER

ANDA 74-891

OCT 31 1997

Apothecon, Inc.
Attention: Walter G. Jump, Pharm.D.
P.O. Box 4500
Princeton, NJ 08543-4500

Dear Sir:

This is in reference to your abbreviated new drug application dated April 19, 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 September 25, November 20, 1996; and January 31, June 30, August 22, and September 12, 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, 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,

D. L. Sporn 10/30/97

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 74-891
Division File
Field Copy
HFD-600/Reading File
HFD-610/JPhillips
HFD-210/BPoole
HFD-92

Endorsements:

HFD-643/SRosencrance/7/22/97 see attached sheet for additional signatures
HFD-647/SBasaran/7/23/97
HFD-613/AVezza/10/9/97 10/9/97
HFD-613/CHoppes (final only) 10/9/97
HFD-617/TAmes/10/9/97
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F/T by smr/10/3/97 10/30/97

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Sincerely yours,

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APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-891

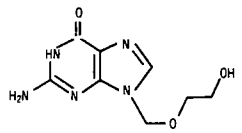
LABELING

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

ACYCLOVIR CAPSULES & TABLETS

DESCRIPTION

Acyclovir is an antiviral drug.The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxy-ethoxy)methyl]-6*H*-purin-6-one; it has the following structural formula:



$C_8H_{11}N_5O_3$

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. The pKa's of acyclovir are 2.27 and 9.25.

Each capsule for oral administration contains 200 mg of acyclovir. In addition, each capsule contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, and sodium starch glycolate. The capsule shell consists of gelatin, FD&C Blue No. 2 and titanium dioxide and is printed with iron oxide black ink.

Each tablet for oral administration contains 400 mg or 800 mg of acyclovir. In addition, each tablets contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide anhydrous, and sodium starch glycolate.

VIROLOGY

Mechanism of Antiviral Action

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV). In cell culture, acyclovir's highest antiviral activity 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 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.

Resistance of HSV to antiviral nucleoside analogues occurs by the same mechanism 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 to 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 bioavilability	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	200 mg	400 mg	800 mg
C_{max}^{SS}	0.83 mcg/mL	1.21 mcg/mL	1.61 mcg/mL
C_{trough}^{SS}	0.46 mcg/mL	0.63 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/m^2 and 600 mg/m^2 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 (6 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, placebo-controlled study of immunocompetent patients with localized cutaneous zoster infection, 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.

In a similar double-blind, placebo-controlled study, 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).

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 capsules and tablets are 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.**

Carcinogenesis, Mutagenesis, Impairment of Fertility

The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **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 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 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, weanling 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 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 the 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 postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the 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 aspermatogensis 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 3 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 occurence 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 up to 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when it is 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 5 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 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%) 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 5 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 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 tubulas 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, 5 times daily for 7 to 10 days.

Genital Herpes
Treatment of Initial Genital Herpes: 200 mg every 4 hours, 5 times daily for 10 days.
Chronic Suppressive Therapy for Recurrent Disease: 400 mg 2 times daily for up to 12 months, followed by re-evaluation. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 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, 5 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 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.
Adults and children over 40 kg: 800 mg 4 times daily for 5 days.
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 or symptoms.
Intravenous acyclovir is indicated for the treatment of varicella zoster infections in immunocompromised patients.

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 Regimen	Creatinine Clearance ($mL/min/1.73m^2$)	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 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 4 acyclovir 200 mg capsules (n=24).

HOW SUPPLIED
Acyclovir Tablets and Capsules are available as:

Acyclovir Tablets			
400 mg	Unit Dose Packs of 100	NDC 59772-4165-1	Each 12 mm, round, beveled-edge, unscored tablet is white, off-white and debossed with **AP 4165.**
	bottles of 100	NDC 59772-4165-2	
800 mg	Unit Dose Packs of 100	NDC 59772-4166-1	Each 21.5 mm x 9.5 mm capsule-shaped, beveled-edge unscored tablet is white, off-white and debossed with **AP 4166.**
	bottles of 100	NDC 59772-4166-2	
	bottles of 500	NDC 59772-4166-3	
Acyclovir Capsules			
200 mg	Unit Dose Packs of 100	NDC 59772-4168-1	Each size 1 capsule with blue cap and white body is printed in black ink with **AP 4168.**
	bottles of 100	NDC 59772-4168-2	
	bottles of 500	NDC 59772-4168-3	

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

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by Siegfried Pharma AG/LTD, Zofingen, Switzerland CH-4800 for
Apothecon®
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA

Acy74891, issued September 1997

Store at 15° to 25° C (59° to 77° F) and protect from light and moisture.
Dispense in a tight, light-resistant container.

Exp. Date
Control No.

100 tablets NDC 59772-4166-2

ACYCLOVIR TABLETS

Each tablet contains
800 mg

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

For indications, dosage, precautions, etc., see accompanying package insert.
Manufactured by Siegfried Pharma AG/LTD, Zofingen, Switzerland, CH-4800 for
APOTHECON® A Bristol-Myers Squibb Company,
Princeton, NJ 08540 USA 416620-01

3 59772 41662 6

Store at 15° to 25° C (59° to 77° F) and protect from light and moisture.
Dispense in a tight, light-resistant container.

Exp. Date
Control No.

500 tablets NDC 59772-4166-3

ACYCLOVIR TABLETS

Each tablet contains
800 mg

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

For indications, dosage, precautions, etc., see accompanying package insert.
Manufactured by Siegfried Pharma AG/LTD, Zofingen, Switzerland, CH-4800 for
APOTHECON® A Bristol-Myers Squibb Company,
Princeton, NJ 08540 USA 416630-01

3 59772 41663 3

Store at 15° to 25° C (59° to 77° F) and protect from light and moisture.
Dispense in a tight, light-resistant container.

Exp. Date
Control No.

100 tablets NDC 59772-4165-2

ACYCLOVIR TABLETS

Each tablet contains
400 mg

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

For indications, dosage, precautions, etc., see accompanying package insert.
Manufactured by Siegfried Pharma AG/LTD, Zofingen, Switzerland, CH-4800 for
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Princeton, NJ 08540 USA 416520-01

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74891

APPROVED OCT 31 1997

Exp. Date
Control No.

100 tablets NDC 59772-4165-1
(10 blisterpacks of 10 tablets each)

UNIT DOSE PACK
ACYCLOVIR TABLETS
Each tablet contains
400 mg

Store at 15° to 25° C (59° to 77° F) and protect from light and moisture. Dispense in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

This unit dose packaging is intended for institutional inpatient use. If dispensed for outpatient use, an appropriate safety closure should be provided.
For indications, dosage, precautions, etc., see accompanying package insert.

Manufactured by
Siegfried Pharma AG/LTD,
Zofingen, Switzerland,
CH-4800 for

APOTHECON®
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA
416510-01

3 59772 41651 0

NDC 59772-4165-1
ACYCLOVIR TABLET
400 mg
LOT

EXP

Manufactured by Siegfried Pharma AG/Ltd, Zofingen, Switzerland, CH-4800 for Apotheco® Princeton, NJ 08540 USA

Exp. Date
Control No.

APPROVED
OCT 31 1997

100 tablets NDC 59772-4166-1

(20 blisterpacks of 5 tablets each)

UNIT DOSE PACK

ACYCLOVIR TABLETS

Each tablet contains

800 mg

Store at 15° to 25° C (59° to 77° F) and protect from light and moisture. Dispense in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

This unit dose packaging is intended for institutional inpatient use. If dispensed for outpatient use, an appropriate safety closure should be provided.
For indications, dosage, precautions, etc., see accompanying package insert.

Manufactured by
Siegfried Pharma AG/LTD,
Zofingen, Switzerland,
CH-4800 for

APOTHECON®
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-891

LABELING REVIEWS

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

Date of Review: August 15, 1996

Date of Submission: May 30, 1996

Primary Reviewer: Jacqueline White, Pharm.D.

ANDA Number: 74-891 Review Cycle: First [Draft]

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

Manufacturer's Name (If different than applicant): Siegfried Pharma AG; Zofingen, Switzerland

Proprietary Name: None

Established Name: Acyclovir Tablets, 400 mg and 800 mg

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

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

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER: 400 mg - 100s
800 mg - 100s and 500s

a. We encourage you to differentiate between your two drug products strengths by using boxing and/or contrasting colors.

b. Revise the "Storage statement" to read:

... protect from light and moisture.

c. Revise the "Dispense in" statement to read:

> Dispense in a tight, light-resistant container.

d. Please note 21 CFR 201.1(h)(2) states that "the appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacture". We note that Apothecon appears on the label without qualification. Since Apothecon is the packer or distributor of this drug product, include one of the qualifying statements found in 21 CFR 201.1(h)(5) or (6). In addition include the statement "Made in Switzerland". In lieu of this statement, you may include the name and place of business of the manufacturer.

2. UNIT DOSE BLISTER:

Satisfactory in draft.

3. CARTON: Unit dose 100s

See comments under CONTAINER.

4. INSERT:

a. General Comments

i. When abbreviating micrograms we encourage the use of "mcg" rather than "μg". Please revise your insert labeling accordingly.

ii. Throughout your labeling print *"in vitro"* and *"in vivo"* in italic print.

b. DESCRIPTION

i. Include the molecular formula of acyclovir, $C_8H_{11}N_5O_3$.

ii. Revise your inactive ingredient's list to include all the components of your capsule shell [i.e., gelatin ~~and the~~, coloring ~~dye~~]. pigments, and dyes, anti-microbial

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

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

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

Delete the first sentence of the third paragraph, "[redacted]".

d. PRECAUTIONS

Pediatric Use

... in pediatric patients less ...

e. DOSAGE AND ADMINISTRATION

Delete all references to the oral suspension.

f. HOW SUPPLIED

Please refer to comment 1(d) under CONTAINER.

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

We note your insert labeling for this application, ANDA 74-889 (acyclovir capsules) is shared with ANDA 74-891 (acyclovir tablets). If both applications are not approved at the same time further revisions may be required prior to approval to include information pertaining to the approved dosage form only.

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	

Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x,for unit dose		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**

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

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

FOR THE RECORD:

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

2. Dispensing recommendations:

   USP: Not USP [However, USP packaging and storage for acyclovir is "Preserve in tight containers].
   NDA: Well-closed conainer as defined in the U.S.P. [Container]
   ANDA:Tight container as defined in the U.S.P.

   Storage recommendations:

   NDA: Store at 15° to 25°C(59° to 77°F) and protect from moisture. [Insert]
   Store at 15° to 25°C(59° to 77°F).[Container]
   ANDA: Store at 15° to 25°C (59° to 77°F) and protect form light and moisture. [Insert]
   Store at 15° to 25°C (59° to 77°F) and protect form moisture. [Container]
   See comment under CONTAINER & CARTON.

3. Patents/Exclusivity

   RLD patent expires 4/22/97. Apothecon's patent and certification and exclusivity statement is accurate.

4. Components/Composition

   The list of inactive ingredients in the DESCRIPTION section are consistent with the firm's components and composition statement [Vol. 1.9, p. 3167].

5. Container/Closure

   100s - HDPE - CR
   500s - HDPE - NCR
   [Vol. 1.13, p. 4279]

6. The firm's tablet imprints described in the HOW SUPPLIED section is consistent with the firm's finished dosage form tablet description. [Vol. B1.13, p.4354 & p. 4365]

7. The applicant indicates that Manufacturing functions will be performed at Siegfried Pharma AG; Zofingen, Switzerland [Vol. 1.10, p. 3288]

8. The following information is from a previous review/reviewer FTR.

   a. The insert mentions no food effect -

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

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

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

Primary Reviewer — Date 10-9-96

Secondary Reviewer — Date 10/10/96

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

cc: ANDA 74-891
Division File

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

ANDA Number: 74-891

Date of Submission: January 31, 1997

Applicant's Name: Apothecon, Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. CONTAINER: 400 mg - 100s
   800 mg - 100s and 500s

   Are the container labels you plan to use in marketing the same size, color and clarity as those submitted? If not, please submit.

2. UNIT DOSE BLISTER:

   Revise "Apothecon" to read "Manufactured for Apothecon ..." as seen on your container labels and insert labeling. Note the qualifying phrase may be abbreviated. We refer you to 21 CFR 201.1(h)(2) for further guidance.

3. CARTON: 400 mg and 800 mg - Unit dose 100s

   a. See comment under CONTAINER.

   b. We note you have printed the statement "For indications, dosage, ... insert" on the front and side panels. We encourage you to delete this statement from the main panel.

4. INSERT:

   a. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

      Upon further review, we request you to revise the third paragraph to read as follows:

      > A single oral dose bioavailability study in 23 normal volunteers showed that acyclovir capsules 200 mg are bioequivalent to 200 mg acyclovir in aqueous solution; and in a separate study in 20 volunteers, it was shown

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

ii. We acknowledge your comment regarding a food effect. Our Office is aware of this issue.

b. PRECAUTIONS (Information for Patients)

Chickenpox

The text of this sub-subsection does not require bold print. Therefore, delete the bolding from this entire sub-subsection except the title, "*Chickenpox*".

c. ADVERSE REACTIONS (Observed During Clinical Practice: *Nervous*)

Due to changes in the insert labeling of the reference listed drug Zovirax® (Glaxo Welcome Inc.: revised May 1996 and approved January 8, 1997) revise this subsection to read as follows:

...paresthesia, seizure, somnolence...

d. HOW SUPPLIED

Acyclovir Tablets and Capsules are not listed in the USP. Therefore, delete "USP" following the established name of your drug products.

Revise your labels and labeling as described above, then submit in final print.

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

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x,for unit dose		
Are there any other safety concerns?		x	
LABELING			

Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? *See comment under Unit dose blister.	*		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients of the innovator differ from this ANDA].	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?*See FTR.		x*	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. *See FTR below & in the file folder	x*		
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review based package insert for Zovirax® (Glaxo Wellcome Company), revised 5/96; approved 1/8/97.

2. The patent for Zovirax® expired on 4/22/97. There are no exclusivities pending.

3. Storage recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]
   NDA: Store at 15° to 25°C(59° to 77°F) and protect from moisture. [Insert]
   Store at 15° to 25°C(59° to 77°F).[Container]
   ANDA: Store at 15° to 25°C (59° to 77°F) and protect form light and moisture. [Insert]
   Store at 15° to 25°C (59° to 77°F) and protect form moisture. [Container]

4. Dispensing recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]
   NDA: Well-closed container as defined in the U.S.P. [Container]
   ANDA:Tight, light-resistant container

5. Components/Composition

The list of inactive ingredients in the DESCRIPTION section are consistent with the firm's components and composition statement [Vol. 2.1, p. 18 & 1.9, p. 3167].

6. The firm's tablet imprints described in the HOW SUPPLIED section is consistent with the firm's finished dosage form tablet description. [Vol. B1.13, p.4354 & p. 4365]

7. Container/Closure

100s - HDPE - CR
500s - HDPE - NCR
[Vol. 1.13, p. 4279]

8. The applicant indicates that Manufacturing functions will be performed at Siegfried Pharma AG; Zofingen, Switzerland [Vol. 1.10, p. 3288]

9. Package/market size-

Zovirax® by Glaxo Wellcome, for oral use is available as:

200 mg capsule - 100s & unit dose 100s
400 mg tablet - 100s
800 mg tablets - 100s & unit dose 100s
200 mg/5 mL suspension - Bottle of 1 pint (473 mL)
This ANDA is for a 200 mg capsule packaged in 100s and 1000s.

ANDA:

400 mg - 100s & unit dose 100s
800 mg - 100s, 500s & unit dose 100s

10. Bioequivalence/Pharmacokinetic data

-Bio. acceptable letter: date 1/15/97 [Vol. 2.1]
-A waiver was granted for the 400 mg tablet.
-Both fasting & fed studies were done.
-Fasting study: results from bio. review of 10/28/96
    -No significant differences were found between AUC and Cmax.
    -The ANDA & RLD t1/2 were comparable to each other but differs from the insert labeling [ANDA t1/2-5.22hr, RLD t1/2-6.03 hr, insert t1/2-2.5 to 3.3 hr]
-Fed study: results from bio. review of 10/28/96
    -There were significant differences found for AUC and Cmax.
    -Cmax, Tmax and AUC increased while the t1/2 remained about the same. NOTE: This differs from the insert labeling which reports that the influence of food on

the absorption was not apparent.
See FTR from previous review below.
[Vol. B1.1]

11. The following information is from a previous review/reviewer FTR.

    a. The insert mentions no food effect -

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

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

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

Date of Review: 5/13/97

Date of Submission: 1/31/97

Jacqueline White, Pharm.D. — 5-16-97
Primary Reviewer — Date

Secondary Reviewer — Date

Team Leader, Labeling Review Branch — Date 5/14/97

cc: ANDA 74-891
Division File
njg/5/16/97/x:\new\...\74891na2.1
HFD-613/JWhite/CHoppes/JGrace
review

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

ANDA Number: 74-891

Date of Submission: June 30, 1997

Applicant's Name: Apothecon, Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. CONTAINER: 400 mg - 100s
   800 mg - 100s and 500s

   Satisfactory

2. UNIT DOSE BLISTER: 400 mg and 800 mg

   Increase the prominence of the established name and strength, (i.e., upper case/bold print).

3. CARTON: 400 mg and 800 mg - Unit dose 100s

   Satisfactory

4. INSERT:

   General Comment

   Revise your insert labeling to be in accord with the enclosed copy of the insert labeling of the reference listed drug Zovirax® (Glaxo Wellcome Inc.; revised; March 1997 and approved May 29, 1997).

Revise your labels and labeling as described above, then submit in final print.

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

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

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

Enclosure: Insert labeling of the reference listed drug.

APPEARS THIS WAY
ON ORIGINAL

Copy of Reference Listed Drug labeling removed.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x,for unit dose		
Are there any other safety concerns?		x	
LABELING			

Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? *See comment under Unit dose blister.	*		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients of the innovator differ from this ANDA].	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?*See FTR.		x*	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. *See FTR below & in the file folder	x*		
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review based package insert for Zovirax® (Glaxo Wellcome Company), revised; March 1997 and approved May 29, 1997).

2. The patent for Zovirax® expired on 4/22/97. There are no exclusivities pending.

3. Storage recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]
   NDA: Store at 15° to 25°C(59° to 77°F) and protect from moisture. [Insert]
   Store at 15° to 25°C(59° to 77°F).[Container]
   ANDA: Store at 15° to 25°C (59° to 77°F) and protect form light and moisture. [Insert]
   Store at 15° to 25°C (59° to 77°F) and protect form moisture. [Container]

4. Dispensing recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]
   NDA: Well-closed container as defined in the U.S.P. [Container]
   ANDA:Tight, light-resistant container

5. Components/Composition

The list of inactive ingredients in the DESCRIPTION section are consistent with the firm's components and composition statement [Vol. 2.1, p. 18 & 1.9, p. 3167].

6. The firm's tablet imprints described in the HOW SUPPLIED section is consistent with the firm's finished dosage form tablet description. [Vol. B1.13, p.4354 & p. 4365]

7. Container/Closure

100s - HDPE - CR
500s - HDPE - NCR
[Vol. 1.13, p. 4279]

8. The applicant indicates that Manufacturing functions will be performed at Siegfried Pharma AG; Zofingen, Switzerland [Vol. 1.10, p. 3288]

9. Package/market size-

Zovirax® by Glaxo Wellcome, for oral use is available as:

200 mg capsule - 100s & unit dose 100s
400 mg tablet - 100s
800 mg tablets - 100s & unit dose 100s
200 mg/5 mL suspension - Bottle of 1 pint (473 mL)
This ANDA is for a 200 mg capsule packaged in 100s and 1000s.

ANDA:

400 mg - 100s & unit dose 100s
800 mg - 100s, 500s & unit dose 100s

10. Bioequivalence/Pharmacokinetic data

-Bio. acceptable letter: date 1/15/97 [Vol. 2.1]
-A waiver was granted for the 400 mg tablet.
-Both fasting & fed studies were done.
-Fasting study: results from bio. review of 10/28/96
    -No significant differences were found between AUC and Cmax.
    -The ANDA & RLD t1/2 were comparable to each other but differs from the insert labeling [ANDA t1/2-5.22hr, RLD t1/2-6.03 hr, insert t1/2-2.5 to 3.3 hr]
-Fed study: results from bio. review of 10/28/96
    -There were significant differences found for AUC and Cmax.
    -Cmax, Tmax and AUC increased while the t1/2 remained about the same. NOTE: This differs from the insert labeling which reports that the influence of food on the absorption was not apparent.

See FTR from previous review below.
[Vol. B1.1]

11. Please see firm's response regarding FPL, in their letter dated 6/30/97.

12. The following information is from a previous review/reviewer FTR.

    a. The insert mentions no food effect -

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

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

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

Date of Review: 7/30/97

Date of Submission: 6/30/97

Jacqueline White, Pharm.D. — Primary Reviewer — Date: 8-11-97

Secondary Reviewer — Date

Team Leader, Labeling Review Branch — for John Grace — Date: 8/14/97

cc: ANDA 74-891
Division File
njg/8/11/97/x:\new\...\74891na3.l
HFD-613/JWhite/CHoppes/JGrace
review

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

ANDA Number: 74-891

Date of Submission: August 22, 1997

Applicant's Name: Apothecon, Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. UNIT DOSE BLISTERS: 400 mg and 800 mg

   Satisfactory.

2. INSERT:

   a. DESCRIPTION

      Revise this section to read as follows:

      ... an antiviral drug. The chemical name of acyclovir ... 2.27 and 9.25.

      Each capsule for oral administration contains 200 mg acyclovir. In addition, each capsule contains the following inactive ingredients: magnesium stearate, ...

      Each tablet for oral administration contains 400 mg or 800 mg of acyclovir. In addition, each tablet contains the following inactive ingredients: magnesium stearate, ...

   b. CLINICAL PHARMACOLOGY

      i. Pharmacokinetics

         Revise "health" to read "healthy" in the first sentence of the first paragraph.

      ii. Special Population (*Pediatrics*)

         Revise "— hours" to read "2.6 hours".

c. PRECAUTIONS (Pregnancy)

Delete ~~_____~~

d. ADVERSE REACTIONS (Chickenpox)

Revise "events" to read "event".

e. DOSAGE AND ADMINISTRATION

i. Treatment of Chickenpox: *(Adults and children over 40 kg)*

Add the following as the second paragraph:

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

ii. Bioequivalence of Dosage Forms:

Revise to read, "Acyclovir suspension was shown to be bioequivalent to acyclovir capsules (n=20) and one acyclovir 800 mg tablet ...".

Revise your insert labeling as described above, then submit in final print.

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

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

_____

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x,for unit dose		
Are there any other safety concerns?		x	
LABELING			

Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients of the innovator differ from this ANDA].	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	

Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?*See FTR.		x*	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review based package insert for Zovirax® (Glaxo Wellcome Company), revised; March 1997 and approved May 29, 1997).

2. The patent for Zovirax® expired on 4/22/97. There are no exclusivities pending.

3. Storage recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]
   NDA: Store at 15° to 25°C(59° to 77°F) and protect from moisture. [Insert]
   Store at 15° to 25°C(59° to 77°F).[Container]
   ANDA: Store at 15° to 25°C (59° to 77°F) and protect form light and moisture. [Insert]
   Store at 15° to 25°C (59° to 77°F) and protect form moisture. [Container]

4. Dispensing recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]
   NDA: Well-closed container as defined in the U.S.P. [Container]
   ANDA:Tight, light-resistant container

5. Components/Composition

   The list of inactive ingredients in the DESCRIPTION section are consistent with the firm's components and composition statement [Vol. 2.1, p. 18 & 1.9, p. 3167].

6. The firm's tablet imprints described in the HOW SUPPLIED section is consistent with the firm's finished dosage form tablet description. [Vol. B1.13, p.4354 & p. 4365]

7. Container/Closure

100s - HDPE - CR
500s - HDPE - NCR
[Vol. 1.13, p. 4279]

8. The applicant indicates that Manufacturing functions will be performed at Siegfried Pharma AG; Zofingen, Switzerland [Vol. 1.10, p. 3288]

9. Package/market size-

Zovirax® by Glaxo Wellcome, for oral use is available as:

200 mg capsule - 100s & unit dose 100s
400 mg tablet - 100s
800 mg tablets - 100s & unit dose 100s
200 mg/5 mL suspension - Bottle of 1 pint (473 mL)
This ANDA is for a 200 mg capsule packaged in 100s and 1000s.

ANDA:

400 mg - 100s & unit dose 100s
800 mg - 100s, 500s & unit dose 100s

10. Bioequivalence/Pharmacokinetic data

-Bio. acceptable letter: date 1/15/97 [Vol. 2.1]
-A waiver was granted for the 400 mg tablet.
-Both fasting & fed studies were done.
-Fasting study: results from bio. review of 10/28/96
    -No significant differences were found between AUC and Cmax.
    -The ANDA & RLD t1/2 were comparable to each other but differs from the insert labeling [ANDA t1/2-5.22hr, RLD t1/2-6.03 hr, insert t1/2-2.5 to 3.3 hr]
-Fed study: results from bio. review of 10/28/96
    -There were significant differences found for AUC and Cmax.
    -Cmax, Tmax and AUC increased while the t1/2 remained about the same. NOTE: This differs from the insert labeling which reports that the influence of food on the absorption was not apparent.
    See FTR from previous review below.
    [Vol. B1.1]

11. Please see firm's response regarding FPL, in their letter dated 6/30/97.

12. The following information is from a previous review/reviewer FTR.

    a. The insert mentions no food effect -

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

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

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

Date of Review: 9/4/97

Date of Submission: 8/22/97

Primary Reviewer
Jacqueline White, Pharm.D.

9-9-97
Date

Team Leader

9/9/97
Date

cc: ANDA 74-891
Division File
njg/9/9/97/x:\new\...\74891na.1
HFD-613/JWhite/CHoppes
review

APPROVAL SUMMARY

(See NOTE under FOR THE RECORD)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-891** Date of Submission: **September 12, 1997**

Applicant's Name: **Apothecon, Inc.**

Established Name: **Acyclovir Tablets, 400 mg and 800 mg**

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 400 mg - 100s and 800 mg - 100s and 500s
Satisfactory as of June 30, 1997 submission.
(for labels submitted in January 31, 1997 amendment)

Unit Dose Blister Label:
Satisfactory as of August 22, 1997 submission.

Unit Dose Carton Label: 400 mg and 800 mg - 100s
Satisfactory as of June 30, 1997 submission.

Professional Package Insert Labeling:
Satisfactory as of September 12, 1997 submission.

Revisions needed post-approval: UD blister label - encourage the firm to further distinguish the 400 mg from the 800 mg by boxing, color, or some other means - INSERT - D & A, chickenpox, Adults & Children - relocate sentence "Intravenous acyclovir..." to appear as its own paragraph after "...for 5 days."

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 20-089

NDA Drug Name: Zovirax® (acyclovir) Tablets

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: 5/29/97 (S-011)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: labels on file

Basis of Approval for the Carton Labeling: labeling on file

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? YES - FOR THE UNIT DOSE Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths? See FTR	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
	Yes	No	N.A.
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients of the innovator differ from this ANDA]	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done? See FTR	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

Note: Both the capsule and the tablet dosage forms are referenced in the HOW SUPPLIED section of the insert submitted. The applications for these dosage forms (tablets and capsules) will need to be approved together in this insert labeling.

The FTR issues below are from the previous review.

1. Labeling review based on package insert for Zovirax® (Glaxo Wellcome Company), revised; March 1997 and approved May 29, 1997).

2. The patent for Zovirax® expired on 4/22/97. There are no exclusivities pending.

3. Storage recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder - 1996]
   NDA: Store at 15° to 25°C (59° to 77°F) and protect from moisture. [Insert]
   Store at 15° to 25°C (59° to 77°F). [Container]
   ANDA: Store at 15° to 25°C (59° to 77°F) and protect form light and moisture. [Insert]
   Store at 15° to 25°C (59° to 77°F) and protect form moisture. [Container]

4. Dispensing recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder - 1996]
   NDA: Well-closed container as defined in the U.S.P. [Container]
   ANDA: Tight, light-resistant container

5. Components/Composition

   The list of inactive ingredients in the DESCRIPTION section are consistent with the firm's components and composition statement [Vol. 2.1, p. 18 & 1.9, p. 3167].

6. The firm's tablet imprints described in the HOW SUPPLIED section are consistent with the firm's finished dosage form tablet descriptions. [Vol. B 1.13, p.4354 & p. 4365]

7. Container/Closure

100s - HDPE - CR
500s - HDPE - NCR
[Vol. 1.13, p. 4279]

8. The applicant indicates that manufacturing functions will be performed at Siegfried Pharma AG; Zofingen, Switzerland [Vol. 1.10, p. 3288]

9. Package/market size-

Zovirax® by Glaxo Wellcome, for oral use is available as:

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

ANDA:

400 mg - 100s & unit dose 100s
800 mg - 100s, 500s & unit dose 100s

10. Bioequivalence/Pharmacokinetic data

-Bio. acceptable letter: date 1/15/97 [Vol. 2.1]
-A waiver was granted for the 400 mg tablet.
-Both fasting & fed studies were done.
-Fasting study: results from bio. review of 10/28/96
    -No significant differences were found between AUC and C_{max}.
    -The ANDA & RLD $t_{1/2}$ were comparable to each other but differs from the insert labeling [ANDA $t_{1/2}$ - 5.22 hr, RLD $t_{1/2}$ - 6.03 hr, insert $t_{1/2}$ - 2.5 to 3.3 hr]
-Fed study: results from bio. review of 10/28/96
    -There were significant differences found for AUC and C_{max}.
    -C_{max}, T_{max} and AUC increased while the $t_{1/2}$ remained about the same. NOTE: This differs from the insert labeling which reports that the influence of food on the absorption was not apparent.
    See FTR from previous review below.
    [Vol. B 1.1]

11. The following information is from a previous review/reviewer FTR.

a. The insert mentions no food effect -

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

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

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

Date of Review: 9/24/97 Date of Submission: 9/12/97

Primary Reviewer: Adolph Vezza Date:

A. Vezza 9/29/97

Team Leader: Charlie Hoppes Date:

Charlie Hoppes 9/29/97

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cc: ANDA 74-891
Division File
njg/9/26/97/X:\NEW\FIRMSAM\APOTHECO\LTRS&REV\74891.APL
HFD-613/AVezza/CHoppes
review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-891

CHEMISTRY REVIEWS

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

---

1. **CHEMIST'S REVIEW NO.** 1

2. **ANDA#** 74-891

3. **NAME AND ADDRESS OF APPLICANT**
Apothecon® Inc.
A Bristol-Myers Squibb Company
P.O. Box 4500
Princeton, NY 08543-4500

4. **LEGAL BASIS FOR ANDA SUBMISSION**
The application is based on the reference listed drug **Zovirax®** manufactured by Burroughs Wellcome (NDA 20-089). Apothecon certifies that they will not infringe U.S. Patent No. 4,199,574 owned by Burroughs Wellcome. This patent, which covers acyclovir product, composition and method of use, expires on 4/22/97. The firm also certifies that the manufacturing process used by the acyclovir raw material suppliers (————————) will not infringe U.S. Patent No. 4,544,634 also owned by Burroughs Wellcome.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Acyclovir Tablets

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

9. **AMENDMENTS AND OTHER DATES**
Firm:
Original Submission: 4/22/96
Amendment: 5/30/96

FDA:
Refusal to File: 5/20/96
Acceptance to File: 6/13/96

10. **PHARMACOLOGICAL CATEGORY**
Antiviral

11. **HOW DISPENSED**
Rx

12. **RELATED IND/NDA/DMFs**

ANDA 20-089 - Burroughs Wellcome (RLD - Zovirax®)

DMF [redacted]
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

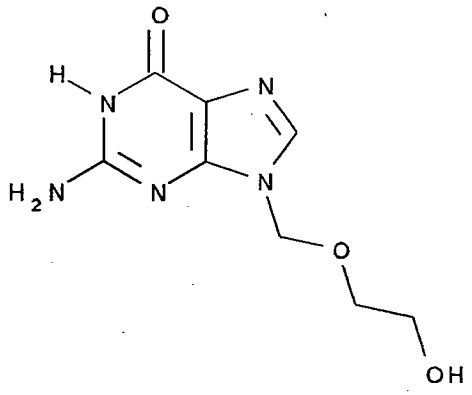
13. **DOSAGE FORM/ROUTE OF ADMINISTRATION**

Tablets/Oral

14. **STRENGTHS**

400 mg
800 mg

15. **CHEMICAL NAME AND STRUCTURE**



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

$C_8H_{11}N_5O_3$
Molecular Weight: 225.21

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**
The application contains various CMC deficiencies (see review comments for details). Issues with respect to the dissolution specification need to be resolved by the Division of Bioequivalence. The methods validation package will be held until this issue is resolved by Bio. DMFs for the active ingredient are satisfactory. The EER remains pending.

18. **CONCLUSIONS/RECOMMENDATIONS**
Not-approvable/MAJOR

19. **REVIEWER** Susan Rosencrance 12/20/96 **DATE COMPLETED** 11/19/96

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CHEMISTRY REVIEW #1

cc: AADA 74-891
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Division File
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Endorsements:
HFD-643/SRosencrance/11/19/96 S M Rosencrance 12/20/96
HFD-647/JSimmons/12/2/96 J S Simmons 12.20.96
X:\NEW\FIRMSAM\APOTHECO\LTRS&REV\74891NA1.F
F/T by smr/12/20/96

NOT APPROVABLE: MAJOR

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

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1. **CHEMIST'S REVIEW NO.** 2

2. **ANDA#** 74-891

3. **NAME AND ADDRESS OF APPLICANT**
Apothecon® Inc.
A Bristol-Myers Squibb Company
P.O. Box 4500
Princeton, NY 08543-4500

4. **LEGAL BASIS FOR ANDA SUBMISSION**
The application is based on the reference listed drug **Zovirax®** manufactured by Glaxo Wellcome (NDA 20-089). Apothecon certifies that they will not infringe U.S. Patent No. 4,199,574 owned by Glaxo Wellcome. This patent, which covers acyclovir product, composition and method of use, expired on 4/22/97. The firm also certifies that the manufacturing process used by the acyclovir raw material suppliers (————————) will not infringe U.S. Patent No. 4,544,634 also owned by Glaxo Wellcome.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Acyclovir Tablets

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

9. **AMENDMENTS AND OTHER DATES**
Firm:
Original Submission: 4/19/96
Amendment: 5/30/96
Amendment: 1/31/97

FDA:
Refusal to File: 5/20/96
Acceptance to File: 6/13/96
Deficiency Letter: 12/31/96

10. **PHARMACOLOGICAL CATEGORY**
Antiviral

11. **HOW DISPENSED**
Rx

12. RELATED IND/NDA/DMFs

ANDA 20-089 - Burroughs Wellcome (RLD - Zovirax®)

DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
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DMF
DMF
DMF
DMF
DMF
DMF

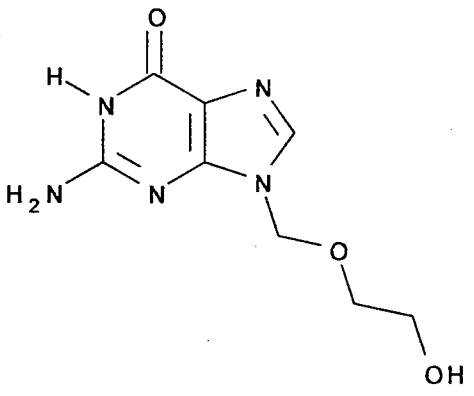
13. DOSAGE FORM/ROUTE OF ADMINISTRATION

Tablets/Oral

14. STRENGTHS

400 mg
800 mg

15. CHEMICAL NAME AND STRUCTURE



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

$C_8H_{11}N_5O_3$
Molecular Weight: 225.21

16. RECORDS AND REPORTS
N/A

17. COMMENTS
While most CMC deficiencies were resolved with the firm's 1/31/97 amendment, a few issues remain with respect to the release/stability requirements and the stability commitment (see review comments for details). An acceptable EER was received, but the methods validation remains pending.

18. CONCLUSIONS/RECOMMENDATIONS
Not-approvable/~~MINOR~~ FACSIMILE

19. REVIEWER S M Rosencrance 5/30/97 DATE COMPLETED
Susan Rosencrance 4/23/97

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CHEMISTRY REVIEW #2

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Please provide updated stability data in your next amendment.

2. Please note that the validation of your analytical methods has not yet been completed by our laboratories.

Sincerely yours,

6/4/97

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

cc: AADA 74-891
DUP File
Division File
HFD-600/Reading File
Field Copy

Endorsements:

~~HFD-640/PHolcombe~~/
HFD-643/SRosencrance/4/23/97; revised 5/7/97 5/30/97
HFD-647/SBasaran/5/6/97 5/30/97
HFD-617/TAmes/5/29/97 6/2/97
~~HFD-613/JWhite~~/
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F/T by vlj/5/29/97

NOT APPROVABLE: ~~MINOR~~
FACSIMILE

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

---

1. **CHEMIST'S REVIEW NO.** 3

2. **ANDA#** 74-891

3. **NAME AND ADDRESS OF APPLICANT**
   Apothecon® Inc.
   A Bristol-Myers Squibb Company
   P.O. Box 4500
   Princeton, NY 08543-4500

4. **LEGAL BASIS FOR ANDA SUBMISSION**
   The application is based on the reference listed drug **Zovirax®** manufactured by Glaxo Wellcome (NDA 20-089). Apothecon certifies that they will not infringe U.S. Patent No. 4,199,574 owned by Glaxo Wellcome. This patent, which covers acyclovir product, composition and method of use, expired on 4/22/97. The firm also certifies that the manufacturing process used by the acyclovir raw material suppliers (————————————) will not infringe U.S. Patent No. 4,544,634 also owned by Glaxo Wellcome.

5. **SUPPLEMENT(s)**
   N/A

6. **PROPRIETARY NAME**
   N/A

7. **NONPROPRIETARY NAME**
   Acyclovir Tablets

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

9. **AMENDMENTS AND OTHER DATES**
   Firm:
   Original Submission: 4/19/96
   Amendment: 5/30/96
   Amendment: 1/31/97
   Facsimile Amendment: 6/30/97

   FDA:
   Refusal to File: 5/20/96
   Acceptance to File: 6/13/96
   Deficiency Letter: 12/31/96
   Deficiency Letter (facsimile): 6/6/97

10. **PHARMACOLOGICAL CATEGORY**
Antiviral

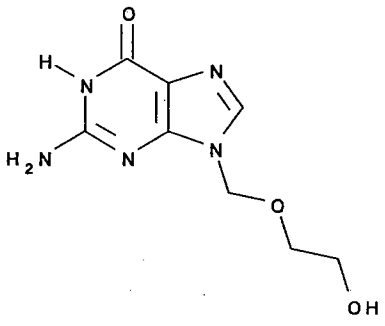
11. **HOW DISPENSED**
Rx

12. **RELATED IND/NDA/DMFs**
ANDA 20-089 - Burroughs Wellcome (RLD - Zovirax®)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. **DOSAGE FORM/ROUTE OF ADMINISTRATION**
Tablets/Oral

14. **STRENGTHS**
400 mg
800 mg

15. **CHEMICAL NAME AND STRUCTURE**



9-[(2-Hydroxyethoxy)methyl]guanine.
$C_8H_{11}N_5O_3$
Molecular Weight: 225.21

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**
All remaining CMC deficiencies were resolved with the firm's 6/30/97 fax amendment. The only issues remaining include labeling and methods validation.

Methods validation acceptable - 7/31/97

Labeling acceptable - 9/29/97

18. **CONCLUSIONS/RECOMMENDATIONS**
Recommend approval

19. **REVIEWER** S M Rosencrance 10/3/97
Susan Rosencrance

DATE COMPLETED
7/21/97

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CHEMISTRY REVIEW #3

cc: AADA 74-891
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Endorsements:

HFD-643/SRosencrance/7/21/97 S M Rosencrance 10/3/97
HFD-647/SBasaran/7/23/97 U. V. Venkataraw 10/6/97
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F/T by smr/10/3/97
APPROVAL

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ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA: 74-891

DRUG PRODUCT: Acyclovir Tablets

FIRM: Apothecon, Inc.

DOSAGE FORM: Tablets **STRENGTHS:** 400 and 800 mgs

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification provided on pages 3306 & 3315 (original submission). EER found acceptable 3/12/97.

BIO STUDY: Bio study (800 mg) and waiver request (400 mg) were found acceptable by the Division of Bioequivalence on 4/22/97.

METHOD VALIDATION: Methods found suitable by the District on 7/31/97.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): The 6 month accelerated data and the 12 month room temperature data support the proposed 24 month expiration date for the product. Containers used in the studies are identical to the proposed market containers. Additional room temperature stability studies (12-month) were done in the bulk containers used in shipping product to the contract packager.

LABELING: Found acceptable by A.Vezza on 9/29/97

STERILIZATION VALIDATION (IF APPLICABLE): Not Applicable

SIZE OF BIO BATCH: The bio batch (9508B003) consisted of ——— tablets and was manufactured with active ingredient from ———.

SIZE OF STABILITY BATCHES: Approval is sought for multiple strengths (400 & 800 mgs) and multiple raw material sources (——— ———). The firm has manufactured multiple stability batches of the proper size in accordance with P&P Guide 22-90 (see chemistry review for details).

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The maximum production batch size is ——— tablets for the 800 mg strength and ——— tablets for the 400 mg strength. A ——— is used. The manufacturing process described in the executed batch records is the same as that described in the blank production batch record.

CHEMIST: Susan Rosencrance **DATE:** 10/3/97

TEAM LEADER: U.V. Venkataram **DATE:** 10/6/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-891

BIOEQUIVALENCE REVIEWS

OCT 28 1996

Acyclovir Tablets, 400 & 800 mg
ANDA # 74-891
Reviewer: Hoainhon Nguyen
WP # 74891sdw.496

Apothecon Inc.
Princeton, NJ
Submission Date:
April 19, 1996
September 23, 1996

Review of Bioequivalence Studies, Dissolution Data and Waiver Request

I. Background:

Acyclovir is a synthetic purine nucleoside analog derived from guanine, used in the treatment of initial episodes, the management of recurrent episodes of genital herpes in certain patients and the acute treatment of herpes zoster (shingles) and chickenpox (varicella). The inhibitory activity of acyclovir for herpes simplex types 1(HSV-1) and 2(HSV-2), varicella-zoster virus(VZV) and Epstein-Barr virus(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 converts acyclovir into acyclovir monophosphate which is further converted into diphosphate and triphosphate by a number of cellular enzymes. Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. A maximum solubility of acyclovir in water is 2.5 mg/ml at 37^{0}C. Dosage regimen for treatment of initial genital herpes is 200 mg every 4 hours.

Acyclovir oral absorption is slow, variable, and incomplete, with absolute bioavailability estimated 15-30%. Reported values for CMAX and TMAX in healthy subjects after a 200 mg capsule were 0.3$\pm$0.1 mg/l and 1.5-2.5 hours, respectively. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg in a study with steady-state peak and trough concentrations of acyclovir being 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.

Following oral administration, the mean half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. Acyclovir is

predominantly eliminated by glomerular filtration and tubular secretion, with approximately 45-79% of a dose recovered unchanged in the urine and about 15% as an inactive metabolite, 9-carboxymethoxymethyl-guanine. Acyclovir may decrease the renal clearance of other drugs, such as methotrexate, that are eliminated by active tubular secretion.

The influence of food on the absorption of acyclovir was not apparent.

Adverse effects associated with acyclovir include nausea and/or vomiting, diarrhea, dizziness, anorexia, fatigue, edema, skin rash, and headache.

Acyclovir is available commercially as Zovirax^{R} 200 mg capsules, 800 and 400 mg tablets, and oral suspension 200 mg/5 ml, manufactured by Burroughs-Wellcome.

The firm has submitted one fasting and one non-fasting, single-dose bioequivalence study comparing its Acyclovir Tablets, 800 mg, with Burroughs-Wellcome's Zovirax^{R} tablets, 800 mg. Comparative dissolution data for the test and reference products, 800 mg as well as 400 mg, were also submitted in support of a request for waiver of in-vivo bioequivalence requirements for the 400 mg strength.

II. Bioequivalence Studies:

A. Fasting Study: Study No. 9517201B

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Apothecon's acyclovir tablets, 800 mg, and Burroughs-Wellcome's Zovirax^{R} tablets, 800 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at ——————————. between October 14, 1995 and October 22, 1995. The principal investigator was ——————————, M.D.. Plasma samples were assayed by——— analytical laboratory, ——————————, under

the supervision of ———————, between November 6, 1995 and November 28, 1995.

Demographics:

Thirty-seven normal, healthy, male volunteers between 18-45 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 134-197 lbs and 65-84 in., respectively. There were 18 caucasians and 19 blacks.

Inclusion criteria:

Subjects especially did not have any history of: chronic infectious disease, heart disease, pulmonary obstructive disease, hepatic or renal disease, bronchial asthma, or hypertension, gastrointestinal disease or malabsorption within the last year, psychiatric disorders, allergy and/or sensitivity to acyclovir, use of pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes within 30 days prior to initial study dosing, or drug or alcohol addiction.

Restrictions:

They were free of all prescription medications at least 14 days and any over-the-counter 7 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed for 48 hours prior to initial study dosing until their release from confinement in each period. The subjects fasted for approximately 10 hours prior to and 4 hours after each drug administration. The washout duration between the two phases was one week. Duration of confinement was approximately 12 hours pre-dose to 24 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 800 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Apothecon's Acyclovir Tablets, 800 mg, lot # 9508B003 (Batch size of ——— units, potency of 101.4%).

Reference product: Burroughs-Wellcome's Zovirax^{R} Tablets, 800 mg, lot # 5M1530 (Potency of 100.4%).

Blood samples were collected predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 19 and 24 hours following drug administration. Blood samples were heparinized centrifuged and the plasma was separated and immediately stored at -20^{0}C until shipping to the analytical laboratory.

Assay Methodology:

Stability:

Stability of frozen samples was demonstrated **in a pre-study validation study** using frozen control samples which were prepared, stored at -15^{0}C, and analyzed at 0, 3, 14 and 210 days. It appears that there was no degradation trend occuring within the studied period for the controls of 0.150 and 3.50 mcg/ml.

Stability of processed samples at 4^{0}C for 5 days and of five freeze-thaw cycles was confirmed.

Stability studies are acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL].

CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Thirty-six of thirty-seven enrolled volunteers completed the clinical portion of the study. Subject # 27 was withdrawn from the study after Period 1 because of positive drug screen. The statistical analysis was performed using balanced 36 data sets.

There was no significant difference (alpha=0.05) between treatments for AUC (0-T), AUC (0-Infinity), CMAX, lnAUC(0-T), lnAUC(0-Infinity) and lnCMAX. The results are summarized in the tables below:

Table I

Acyclovir Comparative Pharmacokinetic Parameters

Dose = 800 mg; n = 36

Parameters	Apothecon's Mean (CV)	Zovirax® Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) mcg.hr/ml	4.554*	4.414*	[0.94;1.13]	1.03
AUC (0-Inf) mcg.hr/ml	5.093*	4.647*	[0.99;1.21]	1.10
CMAX(mcg/ml)	0.9366*	0.9176*	[0.94;1.11]	1.02
TMAX (hrs)	1.74(39)	1.72(42)		
KEL (1/hrs)	0.161(37)	0.152(41)		
T1/2 (hrs)	5.22(56)	6.03(72)		

*Geometric LS Means

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Table II
Comparative Mean Plasma Levels of Acyclovir
mcg/ml(CV)
Dose = 800 mg; n = 36

Hour	Apothecon's	Zovirax®
0	0.002(592)	0
0.25	0.054(129)	0.039(139)
0.5	0.367(48)	0.342(57)
1.0	0.769(43)	0.733(40)
1.50	0.856(38)	0.798(34)
2.0	0.841(36)	0.843(36)
2.5	0.787(39)	0.797(49)
3.0	0.698(41)	0.710(61)
4.0	0.545(49)	0.553(65)
5.0	0.406(49)	0.425(73)
6.0	0.315(45)	0.320(69)
8.0	0.195(45)	0.212(72)
10.0	0.135(48)	0.142(65)
12.0	0.091(44)	0.093(65)
15.0	0.051(75)	0.051(91)
19.0	0.018(167)	0.021(156)
24.0	0.015(180)	0.014(191)
AUC(0-T)mcg.hr/ml	4.823(36)	4.881(52)
AUC(0-Inf)mcg.hr/ml	5.016(31)	4.943(35)
CMAX	0.984(33)	0.982(41)

Adverse Effects:

None of the adverse reactions reported was serious. There were eight and five subjects who reported adverse effects during the treatment of the test and reference products, respectively. The reactions judged probably or possibly related to the treatments were headache, tiredness, nausea and dizziness.

B. Non-Fasting Study: Study No. 9517204B

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Apothecon's acyclovir tablets, 800 mg, and Burroughs-Wellcome's Zovirax^{R} tablets, 800 mg, in a fasting/non-fasting single dose, three-treatment, three-period crossover study design.

Study Investigators and Facilities:

The study was conducted at ———————— between September 30. 1995 and October 15, 1995. The principal investigator was ———————— M.D.. Plasma samples were assayed by——— analytical laboratory,———————— under the supervision of ————————, between November 29, 1995 and December 8, 1995.

Demographics:

Twenty-four normal, healthy, male volunteers between 19-45 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three-treatment, three-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 141-191 lbs and 65-74 in., respectively. There were 8 caucasians and 16 blacks.

Inclusion criteria:

Same as in the Fasting Study Protocol above.

Restrictions:

They were free of all prescription medications at least 14 days and any over-the-counter 7 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were

allowed for 48 hours prior to initial study dosing until their release from confinement in each period. The subjects fasted for approximately 10 hours prior to and 4 hours after each drug administration during the fasting leg of the study. During the non-fasting legs, they were served a standardized breakfast at 0.33 hours prior to dosing following an overnight 10-hour fast. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 rasher of Canadian bacon, hashed browned potatoes, 180 ml of orange juice and 240 ml whole milk. The washout duration between the phases was one week. Duration of confinement was approximately 12 hours pre-dose to 24 hours post-dose.

Treatments and Sampling:

The three treatments consisted of a single 800 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Apothecon's Acyclovir Tablets, 800 mg, lot # 9508B003 (Batch size of ——— units, potency of 101.4%), given under fasting conditions (**Treatment A**), or under non-fasting conditions (**Treatment B**).

Reference product: Burroughs-Wellcome's Zovirax^{R} Tablets, 800 mg, lot # 5M1530 (Potency of 100.4%) given under non-fasting conditions (**Treatment C**).

Blood samples were collected predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 19 and 24 hours following drug administration. Blood samples were heparinized centrifuged and the plasma was separated and immediately stored at -20^{0}C until shipping to the analytical laboratory.

Assay Methodology:

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW

Pharmacokinetic Results and Statistical Analyses:

Same as in Fasting Study Protocol above. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test; however, only T/R ratios of AUCs and CMAX were considered in determining the bioequivalency of the test product under non-fasting conditions.

Results:

All twenty-four enrolled volunteers completed the clinical portion of the study. The statistical analysis was performed using 24 data sets.

There was significant differences (alpha=0.05) between treatments for CMAX, lnCMAX, AUC(0-T), AUC(0-Inf), lnAUC(0-T) and lnAUC(0-Infinity) (all with p = 0.0001). The results are summarized in the tables below:

Table III

Acyclovir Comparative Pharmacokinetic Parameters

Dose = 800 mg; n = 24

Parameters	Apothecon's Mean (CV) Fasting	Apothecon's Mean (CV) Non-Fasting	Zovirax® Mean(CV) Non-Fasting	90% C.I.	Ratio T/R Non-Fasting
AUC (0-T) mcg.hr/ml	4.241*	6.845*	6.796*	[0.91;1.11]	1.01
AUC (0-Inf) mcg.hr/ml	4.704*	7.376*	7.104*	[0.95;1.14]	1.04
CMAX(mcg/ml)	0.8932*	1.228*	1.266*	[0.90;1.05]	0.97
TMAX (hrs)	1.52(57)	2.42(34)	2.58(44)		
KEL (1/hrs)	0.130(45)	0.143(32)	0.142(37)		
T1/2 (hrs)	7.41(74)	5.55(45)	6.16(77)		

*Geometric LS Means

APPEARS THIS WAY
ON ORIGINAL

Table IV
Comparative Mean Plasma Levels of Acyclovir
mcg/ml(CV)
Dose = 800 mg; n = 24

Hour	Apothecon's Fasting	Apothecon's Non-Fasting	Zovirax® Non-Fasting
0	0	0	0
0.25	0.081(96)	0.003(469)	0.002(490)
0.5	0.416(36)	0.071(175)	0.091(186)
1.0	0.821(31)	0.482(62)	0.454(94)
1.50	0.850(39)	0.904(36)	0.824(46)
2.0	0.790(47)	1.049(37)	1.028(33)
2.5	0.694(54)	1.123(32)	1.067(28)
3.0	0.598(57)	1.099(30)	1.062(28)
4.0	0.439(59)	0.924(33)	0.916(34)
5.0	0.376(59)	0.674(34)	0.732(37)
6.0	0.269(51)	0.534(30)	0.548(32)
8.0	0.177(50)	0.330(32)	0.340(36)
10.0	0.126(42)	0.217(28)	0.220(34)
12.0	0.091(43)	0.152(28)	0.153(33)
15.0	0.058(61)	0.097(30)	0.094(30)
19.0	0.024(146)	0.045(78)	0.048(72)
24.0	0.017(182)	0.020(161)	0.017(185)
AUC(0-T)mcg.hr/ml	4.521(42)	7.042(23)	6.972(23)
AUC(0-Inf)mcg.hr/ml	4.635(26)	7.487(26)	7.400(22)
CMAX	0.944(35)	1.265(24)	1.292(20)

Adverse Effects:

None of the adverse reactions reported was serious. There were one, two and six subjects who reported adverse effects during the test (fasted), test (fed) and reference (fed) treatments, respectively. The reactions judged probably or possibly related to the treatments were all headache.

III. Dissolution Testing:

Drug (Generic Name): Acyclovir Tablets Firm: Apothecon
Dose Strength: 800 mg, 400 mg ANDA # 74-891
Submission Date: April 19, 1996

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket __ Paddle X RPM 50 No. Units Tested: 12
Medium: Water Volume: 900 ml
Reference Drug: (Manuf.) Zovirax®; Burroughs-Wellcome
Assay Methodology: HPLC

II. Results of In-Vitro Dissolution Testing:

Sampling Times (min)	Test Product Lot # 9508B003 Strength (mg) 800 Mean % Dissolved	Range	(S.D.)	Reference Product Lot # 5M1530 Strength (mg) 800 Mean % Dissolved	Range	(S.D)
5	56.67		(13.4)	62.84		(9.95)
10	90.13		(4.42)	87.65		(4.57)
15	95.03		(1.35)	88.78		(3.46)
20	97.18		(1.25)	91.49		(2.95)
30	98.83		(1.49)	93.74		(2.49)
45	99.35		(1.18)	95.75		(2.81)
60	99.06		(1.09)	97.02		(2.21)

Sampling Times (min)	Test Product Lot # 9509B006 Strength (mg) 400 Mean % Dissolved	Range	(S.D.)	Reference Product Lot # 5M1432 Strength (mg) 400 Mean % Dissolved	Range	(S.D)
5	35.47		(8.93)	80.72		(4.23)
10	71.38		(7.24)	91.13		(2.70)
15	92.36		(4.05)	95.21		(2.07)
20	96.29		(2.40)	96.27		(1.77)
30	99.61		(2.21)	97.68		(1.65)
45	100.6		(1.82)	97.94		(1.75)
60	101.9		(2.21)	98.13		(1.19)

Specification:
NLT ___ % in 30min

IV. Comments:

1. The single-dose, fasting and non-fasting bioequivalence studies conducted by Apothecon on the test product, Acyclovir Tablets, 800 mg, lot # 9508B003, comparing it with the reference product, Zovirax^{R} Tablets, 800 mg, lot # 5M1530, demonstrate that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) under fasting and non-fasting conditions.

2. Food appeared to significantly increase AUCs (by approximately 60%), CMAX (by approximately 37%) and TMAX (by approximately 60%). This finding differs from that of Zovirax's manufacturer Burrough-Wellcome: "In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent."

3. Dissolution testing for the test and reference products at the 400-mg and 800-mg strengths is acceptable.

4. Comparative formulations given for 400 mg and 800 mg show that the 400-mg strength is proportionally similar to the 800 mg. (See formulations attached)

V. Recommendations:

1. The single-dose, fasting and non-fasting bioequivalence studies conducted by Apothecon on the test product, Acyclovir Tablets, 800 mg, lot # 9508B003, comparing it with the reference product, Zovirax^{R} Tablets, 800 mg, lot # 5M1530, have been found **acceptable** by the Division of Bioequivalence. The studies demonstrate that the test product is bioequivalent to the reference product under fasting and non-fasting conditions.

2. The in-vitro dissolution testing conducted by Apothecon on its Acyclovir Tablets, 800 mg and 400 mg, has been found **acceptable.**

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^{0}C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

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

3. The firm has demonstrated that the formulation of its Acyclovir Tablets, 400 mg, is proportionally similar to the 800mg strength that underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 400 mg tablets is granted. The firm's Acyclovir Tablets, 400 mg, are therefore deemed bioequivalent to Zovirax[R] Tablets, 400 mg, respectively, manufactured by Burroughs-Wellcome.

10-3-96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 10/3/96

Concur: Date: 10/28/96

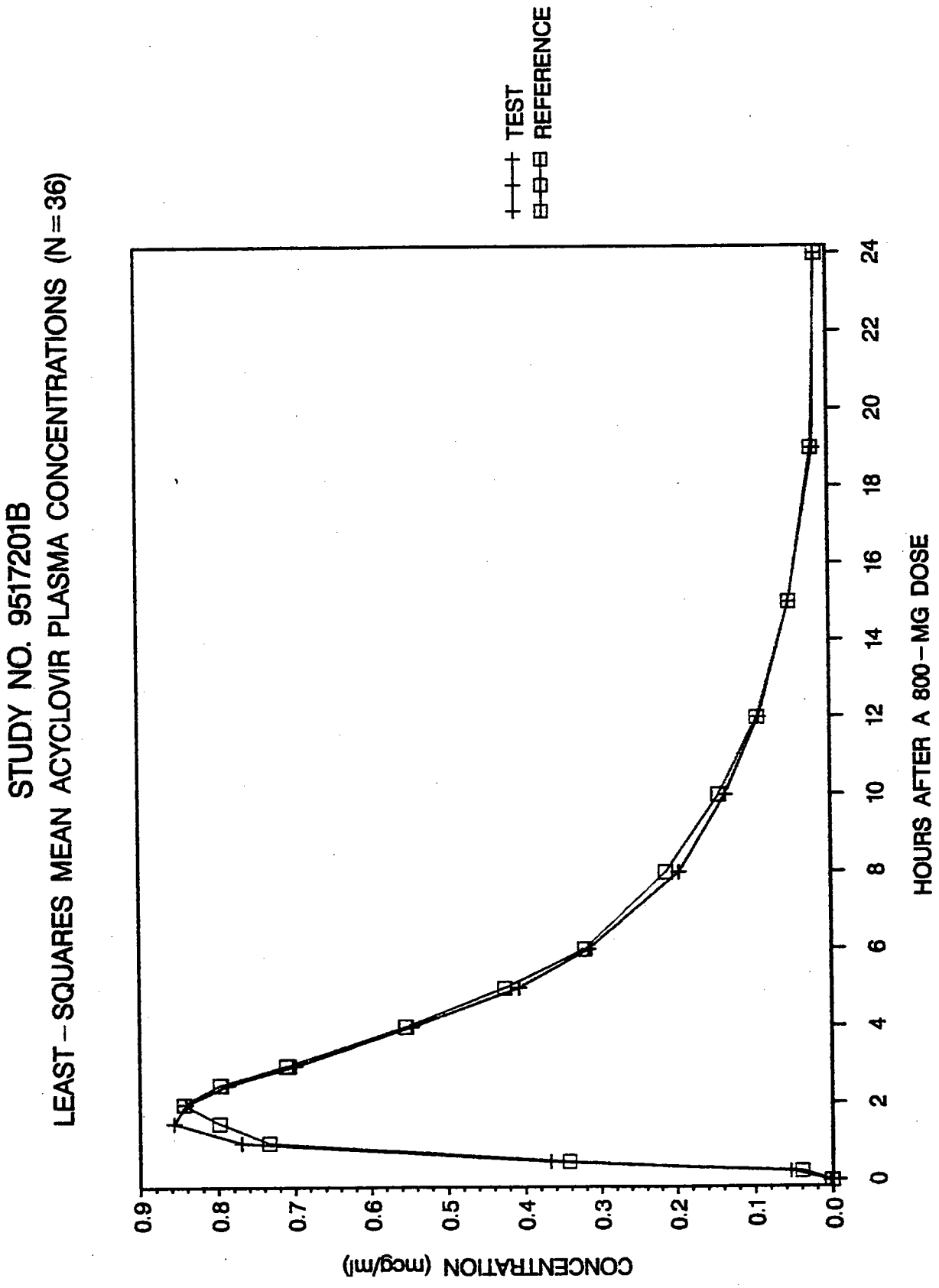
for Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-891 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

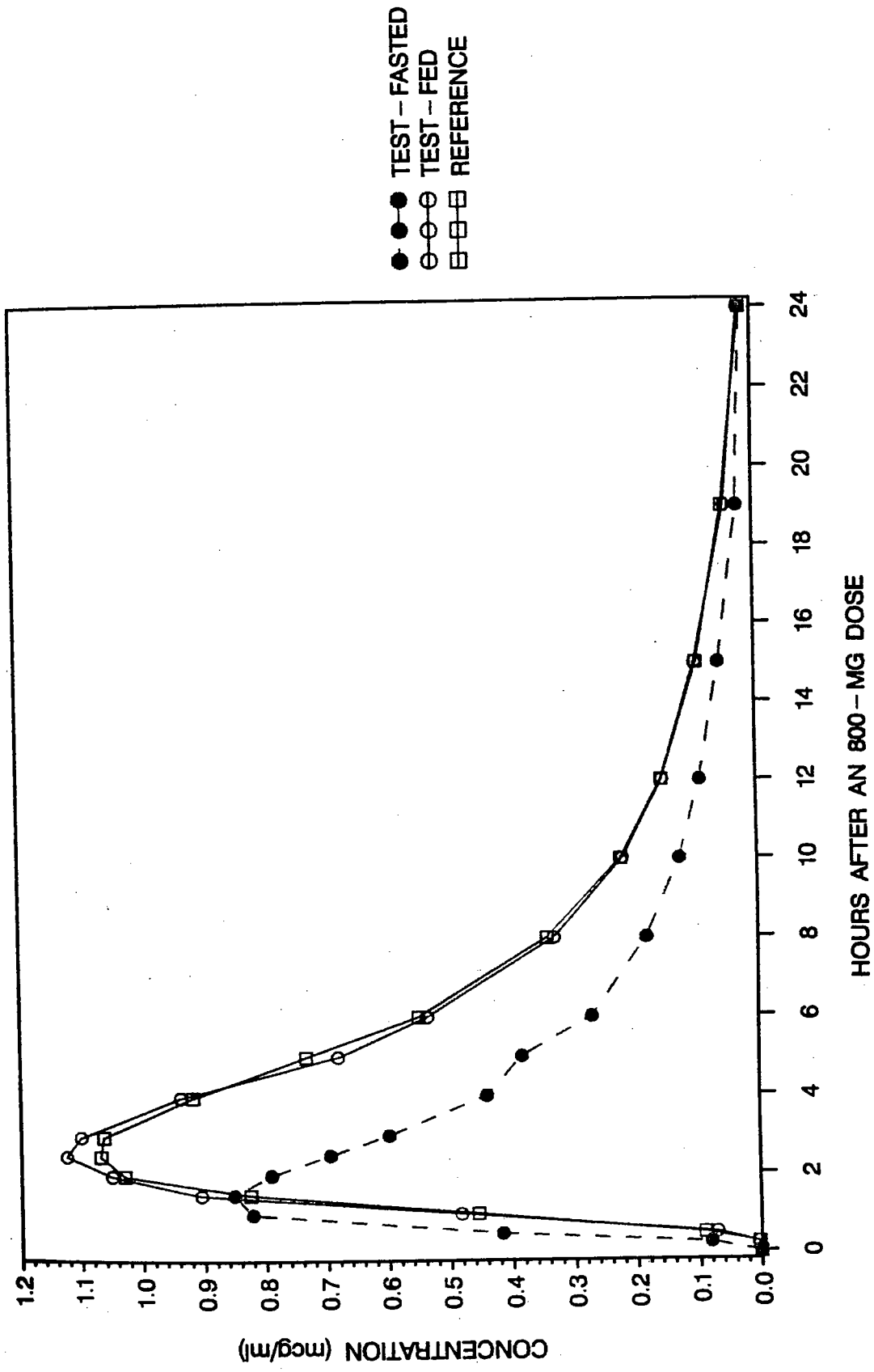
Hnguyen/09-25-96/WP #74891sdw.496

Attachments: 3 pages

WP # 74891sdw.496 Attachment 1 of 3



WP # 74891 sdw. 496 Attachment 2 of 3



WP# 74891 sdw. 496 Attachment 3 of 3

VI. Bioavailability/Bioequivalence

B. Request for Biowaiver for 400 mg Tablets

1. Introduction

In accordance with 21 CFR 320.22 (d)(2) we request a waiver of bioequivalence for our 400 mg acyclovir tablet as this drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to our acyclovir 800 mg tablet which has demonstrated bioequivalence to Zovirax® 800 mg tablets in both fasting and food effect biostudies. Presented below, and also presented in Section VII of this filing, is a tabular representation of our acyclovir tablet formulations. Following this page is the data supporting the *in vitro* equivalence of these products.

Acyclovir Tablets

Ingredient	800 mg	400 mg	Composition	Demonstration Tablet Batch Size
Compressed Tablet	(mg/tab)	(mg/tab)	%	
Acyclovir	800.00	400.00	69.57	
Sodium Starch Glycolate, NF				
Microcrystalline Cellulose, NF ——				
Microcrystalline Cellulose, NF ——				
Povidone, USP				
Silicon Dioxide Anhydrous				
Magnesium Stearate, NF				
—— †				
Total††	1150.00	575.00	100.00	

† [ ]

†† Please note that the —— is not utilized in the calculation of the percent composition or mg per tablet calculations.

APR 22 1997

Acyclovir Tablets
AADA #74-891: 400 mg & 800 mg
Reviewer: Hoainhon Nguyen
WP #74891a.n96

Apothecon
Princeton, NJ
Submission Date:
November ~~6~~ 20, 1996

Review of an Amendment: Changes in Dissolution Specifications

The firm has submitted the current amendment in response to the Division of Bioequivalence's following comment included in the letter issued October 31, 1996 concerning the dissolution requirements for Acyclovir Tablets, 400 mg and 800 mg:

"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 XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> *Not less than — % of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes".*

The firm questioned the above FDA-recommended dissolution procedure and specifications because:

(i) They are significantly different from the firm's proposed specifications of NLT —% dissolved in 30 minutes.

(ii) They also differ significantly from the proposed USP method of NLT 80% (Q) in 45 minutes (Pharmacopeal Forum 22, No. 4, p. 2493).

Comments and Recommendations:

1. The FDA-recommended specification should rather be read "NLT — % dissolved in 30 minutes".

2. The dissolution data submitted by the firm indicated that the test product met the dissolution requirements.

3. The FDA-recommended dissolution procedure and specification are being used as **the interim requirements** until official USP dissolution procedure and specification for the drug product are published. The USP dissolution requirements then will be considered the final regulatory specification. The firm should be advised to follow the method and specifications that FDA recommends for the interim period.

The firm should be informed of the division comments and recommendations.

Hoaihon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 4/22/97

Concur: Date: 4/22/97
Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

cc: AADA #74-891(original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/03-20-97/WP#74891a.n96/Revised 04-21-97
Attachment: None

Office BioSynth

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-891 SPONSOR: APOTHECON
DRUG & DOSAGE FORM: Acyclovir Tablets
STRENGTH (s): 400 & 800 mg

TYPE OF STUDY: (SD) (SDF) MULT OTHER
STUDY: IES (2) ☒Acceptable (Both on 800 mg)

DISSOLUTION: ☒Acceptable

WAIVER: ☒Acceptable for 400 mg

REVIEWER: H. Nguyen BRANCH: I
INITIAL: HN DATE: 10/9/97

BRANCH CHIEF: a/b for Y.C. Hsu BRANCH: I
INITIAL: DATE: 10/10/97

Acting DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: M. Saltiel DATE: 10/19/97

Fasting: AUCI, N=26
AUCT N = 36
CMAX N = 36
Fed Study: AUCT (N=24), AUCI (N=19), CMAX N=2

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: DATE:

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-891

ADMINISTRATIVE DOCUMENTS

ANDA/AADA OFFICE LEVEL APPROVAL ROUTING SUMMARY

ANDA # 74-891
AADA #
ig Acyclovir Tablets
sage Form Tablets
crength 400, 800 mg
Applicant Apotheon, Inc
Proposed Action (AP) TA

REVIEWER:		RECEIPT	ACTION
1.	Project Manager M. Anderson Review Support Branch	Date 10/7/97 Initials MA	Date 10/9/97 Initials MA

Original Rec'd date 4/22/96 6/3/96
Date Acceptable for Filing 6/13/96
Open Amendment Date(s) 9/25, 11/20/96; 1/31, 6/30, 9/12/97
Chemistry Reviewer Rosencrance F/22
Supervisor Venkataarum
Bio Reviewer Nguyen
Supervisor Huang
Date of Office Level Bio Review [redacted] 10/19/97
Pending Legal Case Yes ____ No ✓
Comments:

EER Status Acceptable on EES 10/10/97
OAI Status Yes ____ No ✓
Patent Certification ____
Citizen Petition Yes ____ No ____ If YES attach Email from Project Manager to Petition Coordinator of pending approval

2.	Director of Chem. I or II Office of Generic Drugs	Date 10/9/97 Initials	Date 10/29/97 Initials

Comments: Chemistry is satisfactory.

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

Comments: There are multiple ANDAs approved for this drug product. 10/30/97

4.	P. Rickman Supv., Reg. Support Branch	Date 10/30/97 Initials	Date 10/30/97 Initials

Contains certification required by the GDEA if sub after 6/1/92
Yes ✓ No ____ //// Determination of involvement? Yes ____ No ✓
Paragraph 4 Certification ____ Yes ✓ No
Comments:
Patent '574 expired 4/22/97 - No exclusivity issues
Office Level Bio 10/19/97

5.	J. Phillips Director Division of LPS Office of Generic Drugs	TTA-16 months (1-2)	Date 10/30/97 Initials	Date Initials

Comments:
[illegible]ptable EES dated 4/7/97 (printed 10/30/97). No O.A.I. alerts noted. Bioequivalency studies (pivotal and fed) for 800 mg strength reviewed and found acceptable on 10/28/96. In-vitro dissolution studies also found acceptable. Waiver granted on 400 mg strength due to compositional proportionality to the 800 mg strength. Office-level bio endorsed 10/19/97 (R. Patnaik). Dissolution specs. revised (corrected) and bio letter-out dated 4/30/97. CMC found acceptable on 10/3/97 - Chemistry Rev #3. Methods validation acceptable 7/31/97. FPL acceptable on 9/29/97. This applications shares a common package insert with Rem's ANDA 74-889 for capsules.
—MPR—>

6. G.Johnston — J Phillips for — Date 10/30 Initials — Date 10/30 Initials
Deputy Director
Office of Generic Drugs
Patent Cert - P_4 - Yes___ No X
Petition status _____
Pend. Legal Actions - Yes___ No X
Comments:

Satisfactory for approval.

7. D. Sporn — Date 10/30/97 Initials — Date 10/30/97 Initials
Director
Office of Generic Drugs

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

8. Project Manager T. Ames — Date 10/31/97 Initials for Tim — Date 10/31/97 Initials for Tim

Company Notified
8:15 Time notified of approval via telephone
8:20 Time notified of approval via facismile

LETTER SIGNED: D. Sporn 10/30/97
(Name and Date)

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

DLPS Review (continued):

That ANDA is also ready for approval at this time. There are no controlled correspondence or Citizens Petition issues pending on this drug product. There are no current patent or exclusivity issues for this drug product.

Recommend: Approve.

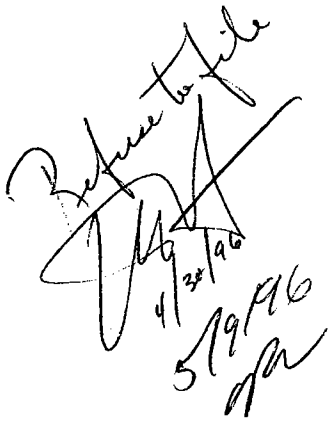
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-891

CORRESPONDENCE

APOTHECON
P.O. Box 4500 Princeton, NJ 08543-4500
609 897-2470 Fax: 609 897-6005



Walter G. Jump, Pharm.D.
Senior Director
Medical and Regulatory
Operations

April 19, 1996

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: Acyclovir Tablets
Original ANDA Filing

Dear Mr. Sporn:

Pursuant to 21 CFR 314.92, Apothecon®, Inc. respectfully submits this application for Acyclovir Tablets 800 mg and 400 mg.

The product will be produced at one manufacturing site, our contract manufacturer, Siegfried Pharma AG, Zofingen, Switzerland. Bulk tablets will be sent to our facilities in the United States for commercial packaging into bottles with the unit dose blister packaging occurring at Siegfried Pharma AG, Zofingen, Switzerland. Product release and control of this product will be performed at our Evansville, Indiana site.

This filing contains information on the indication, labeling, bioequivalency to Zovirax® Tablets, drug substance, inactive components, formula, method of manufacture, packaging components, drug product specifications, analytical methods, in-process specifications, and marketed product stability of our product, Acyclovir Tablets. Data diskettes containing the concentration and parameter data are attached to the cover of the first volume of each study; that is, the disk for the fasting study precedes Volume 2 and the disk for the food effect study precedes Volume 8.

This filing also certifies that:

- the development and submission for this filing was not provided by any person or persons currently debarred by the FDA;
- all nonclinical laboratory work was performed according to GLPs;
- all manufacturing work was performed according to cGMPs;
- all bioavailability testing and bioequivalency analysis was performed according to FDA regulations;
- no patents or exclusivity time periods will be violated by Apothecon.

A complete Table of Contents is included in the first volume of this application and in each volume. Four copies of draft labeling appear, bound, in the review copy of this application. According to FDA guidelines, we are submitting one review copy, one archival copy, one bioequivalency review copy, and one copy to each regional district office which oversees the manufacturing, packaging, and testing sites. A listing of the offices that received a copy of this application is included in the "Basis for Submission" section of this filing. Each copy has a complete Table of Contents in the first volume.

I trust that you will find this application complete and that we will receive a prompt review and approval from the Agency. Should comments or questions arise during the review of this application, please do not hesitate to call or FAX your comments (telephone 609-897-2470 or FAX 609-897-6005). We will provide timely responses.

Sincerely,

Walter G. Jump, Pharm.D.
Director
Development, Medical & Regulatory Operations

ANDA 74-891

Apothecon, Inc.
A Bristol-Myers Squibb Co.
Attention: Walter G. Jump, Pharm.D.
P.O. Box 4500
Princeton, NJ 08543-4500

MAY 20 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated April 19, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Tablets, 400 mg and 800 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to provide a signed, dated letter of authorization from the drug master file (DMF) holder, ———————————————————, that allows ———————————— to act as agent in granting the Agency reference to the DMF for ————————. As an alternative, you may provide authorization from the holder of the DMF for ———————————————————— ———————————, allowing the Agency to access their DMF in support of your application. Please provide authorization from the DMF holder.

You have failed to provide English translations of all documents not in English. Examples include, but are not limited to, Certificates of Analysis from the manufacturers of inactive ingredients. Please review your application and provide translations of all pages not in English [314.50(g)(2)].

You have failed to provide a certification of compliance with current Good Manufacturing Practices (cGMP) for the applicant, Apothecon. Please provide this certification.

You are required to completely package your exhibit batches in the 100-tablet and 500-tablet containers proposed for marketing. Partial packaging, packaging in bulk containers, or a packaging configuration for which you are not seeking approval is not acceptable unless a protocol has been submitted and approved prior to the submission of the application. If, for example, you intend to market your proposed drug product in bulk containers, you must provide draft labeling and a side-by-side comparison of your bulk labels as well. Please refer to the letters to industry from the Director, Office of Generic Drugs, dated November 8, 1991, and August 4, 1993. We also refer you to the Office of Generic Drugs' Policy and Procedure Guide #41-95, dated February 8, 1995.

You have failed to provide three-month accelerated stability data for your 400 mg or 800 mg tablet packaged in the unit-dose blister package or the 500-tablet bottle using the ——— active ingredient. Please provide this data.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, you have failed to provide three **separately bound** copies of your Methods of Validation. Please submit three copies in separate binders.

Also, while we note that you provide copies of your proposed labeling with those of the reference listed drug, you have failed to include a comparison of your proposed labeling with the approved labeling for the reference listed drug with all differences **annotated and explained** [314.94(a)(8)(iv)].

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Project Manager
(301) 594-0315

Sincerely yours,

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

ANDA 74-891
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman,Chief, RSB 5/17/96 date
HFD-615/WRussell, CSO 5/14/96 date 5.17.96
HFD-647/JSimmons, Sup.Chem. 5/17/96 date
File\x:\new\firmsam\Apotheco\ltrs&rev\74891rtf.f
F/T File hrw 5-14-96
ANDA Refuse to File!

APOTHECON
P.O. Box 4500 Princeton, NJ 08543-4500
609 897-2470 Fax: 609 897-6005

505(j)(2)(A) acceptable for filing 6/5/96

6/10/96

Walter G. Jump, Pharm.D.
Senior Director
Medical and Regulatory
Operations

RECEIVED

JUN 03 1996

GENERIC DRUGS

May 30, 1996

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AC AMENDMENT
DR. Lukel

Re: Acyclovir Tablets
AADA 74-891
Refusal to File Letter of May 20, 1996

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, Apothecon®, Inc. respectfully submits this amendment to our AADA for Acyclovir Tablets 400 and 800 mg, submitted on April 19, 1996 for which a Refusal to File Letter was sent on May 20, 1996 and recieved on May 30, 1996.

We are disappointed that the Agency chose not to telephone our company concerning the issues noted in the Agency's May 1996 letter. We believe that the majority if not all the issues could have been resolved within 10 business days and without the Agency issuing the May 1996 letter.

This letter constitutes our response to the May 1996 letter. We have re-iterated the Agency's comments in italic Courier type followed by our response in plain Geneva type to aid the Agency in review of our response.

If there are any concerns or comments concerning our responses we would appreciate a telephone call so that we can efficiently address all remaining Agency concerns and obtain a prompt and efficient FDA review of our application.

I can be reached by telephone or FAX at the following numbers: 609-897-2470 (telephone), 609-897-6005 (FAX).

Sincerely,

Walter G. Jump, Pharm.D.
Senior Director, Medical and Regulatory Operations

ANDA 74-891

Apothecon, Inc.
A Bristol-Myers Squibb Co.
Attention: Walter G. Jump, Pharm.D.
P.O. Box 450
Princeton, NJ 08543-4500

JUN 13 1996

Dear Sir:

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

Reference is also made to our "Refuse to File" letter dated May 20, 1996, and your amendment dated May 30, 1996.

NAME OF DRUG: Acyclovir Tablets, 400 mg and 800 mg

DATE OF APPLICATION: April 19, 1996

DATE OF RECEIPT: April 22, 1996

DATE ACCEPTABLE FOR FILING: June 3, 1996

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

However, while we note you have provided a side-by-side comparison of your bulk label with a label of the reference listed drug, to be in compliance with 314.50(e)(2)(ii), you must provide four copies of all draft labeling in the archival copy of the application. Please provide three additional draft copies of the proposed bulk container labeling.

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

Should you have questions concerning this application, contact:

Timothy Ames
Project Manager
(301) 594-0305

Sincerely yours,

6/13/96

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

ANDA 74-891
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB 6/13/96 date
HFD-615/WRussell, CSO_____date
HFD-647/JSimmons, Sup. Chem_____date
File\x:\new\firmsam\Apothco\ltrs&rev\74891ac.f
F/T hrw 6-10-96
ANDA Acknowledgement Letter!

APOTHECON
P.O. Box 4500 Princeton, NJ 08543-4500
609 897-2470 Fax: 609 897-6005

BIOAVAILABILITY NEW CORRESP
NC/BIO

Walter G. Jump, Pharm.D.
Senior Director
Medical and Regulatory
Operations

September 25, 1996

Keith Chan, Ph.D.
Bioequivalence Review/Bioequivalence Division
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place , Room 150
Rockville, MD 20855-2773

RECEIVED
SEP 27
GENERIC DRUGS

RE: Acyclovir Tablets
AADA 74-891
TELEPHONE AMENDMENT

Dear Dr. Chan:

Reference is made to our pending application for Acyclovir Tablets, AADA 74-891, the Dr. Saundra Middleton's call of Friday, September 20, 1996, our FAX of September 22, 1996 and Dr. Middleton's call on Tuesday September 24, 1996 concerning the missing table: Table A3: Acyclovir Control Sample Summary.

Dr. Middleton requested that we designate this communication as a BIODIVISION TELEPHONE AMENDMENT when we provided hard copies of our September 22, 1996 FAX. This submission complies with is request.

We would like to thank the Agency for contacting our company by telephone for this information. We hope that our response has been timely and sufficient

If there are any other questions or concerns please contact us as we are ready to provide the Agency with complete and prompt responses.

Sincerely,

Walter G. Jump, Pharm.D.

Enc. Table A3: Acyclovir Control Sample Summary, Food Effect Biostudy

ANDA 74-891

Apothecon, Inc.
A Bristol-Myers Squibb Co.
Attention: Walter G. Jump, Pharm.D.
P.O. BOX 450
Princeton NJ 08543-4500

OCT 31 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 specification:

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

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

Sincerely yours,

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

cc: ANDA 74-891, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File

Letter Out, Bio Acceptable

Endorsements:

H. Nguyen 10/29/96
for Y.C. Huang 10/30/96
M. Anderson 10/30/96

DRAFTED: STM 10/29/96 X:\WPFILE\BIO\FINAL\N74891.APP

APPEARS THIS WAY ON ORIGINAL

APOTHECON

P.O. Box 4500 Princeton, NJ 08543-4500
609 897-2470 Fax: 609 897-6005

Walter G. Jump, Pharm.D.
Senior Director
Medical and Regulatory
Operations

November 20, 1996

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: Acyclovir Tablets
AADA 74-891
Bioequivalence Letter of 10/31/1996

Dear Dr. Patnaik:

Pursuant to 21 CFR 314.96, Apothecon®, Inc. respectfully submits this amendment to our AADA 74-891 for Acyclovir Tablets 400 mg and 800 mg, submitted in April 1996 for which a Bioequivalence Letter was sent by the Agency dated October 31, 1996.

The Division of Bioequivalence has recommended a change in specification while continuing to utilize our proposed method.

This letter constitutes our response to the October 31, 1996 letter. We have re-iterated the Agency's comments in italic Courier type followed by our response in plain Geneva type to aid the Agency in review of our response.

If there are any concerns or comments concerning our responses we would appreciate a telephone call so that we can efficiently address all remaining Agency concerns and obtain a prompt and efficient FDA review of our application.

I can be reached by telephone or FAX at the following numbers: 609-897-2470 (telephone), 609-897-6005 (FAX).

Sincerely,

Walter G. Jump, Pharm.D.
Senior Director, Medical and Regulatory Operations

Apothecon Response to Agency's Bioequivalence letter...

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 specification:

NTL — % of the labeled amount of acyclovir in the dosage form dissolved in 30 minutes.

Apothecon Response:
Apothecon currently utilizes the above conditions in its dissolution testing program. Therefore only the specifications proposed will be addressed for this product. The current FDA recommendation for specifications is significantly different from our proposed specifications in that it would prohibit any dissolution value to be below — %. The use of a Q value would allow excursions below the specification proposed by the FDA. The FDA proposal is inconsistant with the USP proposed monograph of NLT 80% (Q) in 45 minutes. We view our proposal of NLT —% (Q) in 30 minutes to be rational and a compromise between the FDA's and the USP's position. As we are testing the drug product in our stability program under the conditions and methods proposed by the FDA, we propose to wait for USP resolution of the differences prior to adopting a final regulatory specification.

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-891

Apothecon, Inc.
A Bristol-Myers Squibb Co.
Attention: Walter G. Jump, Pharm.D.
P.O. Box 4500
Princeton, NJ 08543-4500

DEC 31 1996

Dear Dr. Jump:

This is in reference to your abbreviated new drug application dated April 19, 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 amendment dated May 30, 1996.

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

A. Chemistry Deficiencies:

Components & Composition:

1. [redacted]

2. [redacted]

Raw Materials (Active & Inactive):

3. [redacted]

4. [redacted]

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

12/31/1996 FDA LETTER

B. Labeling Deficiencies (DRAFT):

1. CONTAINER: 400 mg - 100s
800 mg - 100s and 500s

a. We encourage you to differentiate between your two drug products strengths by using boxing and/or contrasting colors.

b. Revise the "Storage statement" to read:

... protect from light and moisture.

c. Revise the "Dispense in" statement to read:

Dispense in a tight, light-resistant container.

d. Please note 21 CFR 201.1(h)(2) states that "the appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacture". We note that Apothecon appears on the label without qualification. Since Apothecon is the packer or distributor of this drug product, include one of the qualifying statements found in 21 CFR 201.1(h)(5) or (6). In addition include the statement "Made in Switzerland". In lieu of this statement, you may include the name and place of business of the manufacturer.

2. UNIT DOSE BLISTER:

Satisfactory in draft.

3. CARTON: Unit dose 100s

See comments under CONTAINER.

4. INSERT:

a. General Comments

i. When abbreviating micrograms we encourage the use of "mcg" rather than "μg". Please revise your insert labeling accordingly.

ii. Throughout your labeling print *"in vitro"* and *"in vivo"* in italic print.

b. DESCRIPTION

i. Include the molecular formula of acyclovir, $C_8H_{11}N_5O_3$.

ii. Revise your inactive ingredient's list to include all the components of your capsule shell [i.e., gelatin, coloring agents and dyes, antimicrobials].

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

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

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

Delete the first sentence of the third paragraph, "[redacted]".

d. PRECAUTIONS

Pediatric Use

... in pediatric patients less ...

e. DOSAGE AND ADMINISTRATION

Delete all references to the oral suspension.

f. HOW SUPPLIED

Please refer to comment 1(d) under CONTAINER.

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

We note your insert labeling for this application, ANDA 74-889 (acyclovir capsules) is shared with ANDA 74-891 (acyclovir tablets). If both applications are not approved at the same time further revisions may be required prior to approval to include information pertaining to the approved dosage form only.

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

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

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

Please provide updated stability data in your next amendment.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You have been notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

12/31/96

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

cc: ANDA 74-891
DUP/Division File
HFD-600/RF
Field Copy

Endorsements:
HFD-643/SRosencrance/11/19/96 SM Rosencrance 12/20/96
HFD-647/JSimmons/12/2/96 J Simmons 12.20.96
HFD-617/TAmes/12/14/96
HFD-613/JWhite/12/6/96 12/24/96 J White Read 12/30/96
X:\NEW\FIRMSAM\APOTHECO\LTRS&REV\74891NA1.F
F/T by smr/12/20/96
NOT APPROVABLE: MAJOR

APPEARS THIS WAY
ON ORIGINAL

APOTHECON
P.O. Box 4500 Princeton, NJ 08543-4500
609 897-2470 Fax: 609 897-6005

Walter G. Jump, Pharm.D.
Senior Director
Medical and Regulatory
Operations

NDA ORIG AMENDMENT
Ac

January 31, 1997

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: ANDA 74-891, Acyclovir Tablets
FDA Letter of December 31, 1996
MAJOR AMENDMENT

Dear Mr. Sporn:

This is in reference to our abbreviated new drug application dated April 19, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Acyclovir Tablets, 400 and 800 mg, and to the Agency's letter of December 31, 1996.

The Agency letter of December 31, 1996 indicated that the Agency had comments and concerns that prevented you from approving our application. We have responded to all Agency comments in this amendment. For ease of review we have included the Agency comments in italics and our response in plain type.

We would like to thank the Agency for the new policy of FAXing copies of the letters to applicants. This has allowed us to start the process of obtaining the requested information sooner and providing a quick response to your letters.

RECEIVED
FEB 06 1997
GENERIC DRUGS

We would like to suggest that the Agency consider not citing as deficiencies changes that occur in the USP/NF compendia after the submission of an application. As we cannot foresee such official compendia changes until they are official we believe that a statement such as; "Please acknowledge in your response to this letter that the USP/NF has had recent compendial changes in the following areas concerning your pending application : (list changes). We require certification that you will meet these changes in the future.". Such a statement would acknowledge that the application did conform to the USP/NF requirements at the time of the demonstration batch while assuring that the application would conform to the most current USP/NF compendia.

If you have any additional comments or questions, please feel free to contact me by telephone or FAX.

Sincerely,

Walter G. Jump, Pharm.D.
Senior Director, Medical & Regulatory

1.1

ANDA 74-891

Apothecon, Inc.
A Bristol-Myers Squibb Co.
Attention: Walter G. Jump, Pharm.D.
P.O. Box 4500
Princeton, NJ 08543-4500

APR 30 1997

Dear Sir:

This is in reference to our correspondence of October 31, 1996, stating the dissolution testing requirements for Acyclovir Tablets, 400 mg and 800 mg.

Reference is also made to your amendment dated November 20, 1996.

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

2. The following FDA recommended 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 at 37°C using USP 23 apparatus II (Paddle) at 50 rpm. The test product should meet the following specification:

   > Not less than — % (Q) 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,

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

cc: ANDA 74-891, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
H. Nguyen

Letter Out, Bio Acceptable

Endorsements:

L. Sanchez 4/29/97

DRAFTED: STM 4/29/97 X:\WPFILE\BIO\FINAL\74891BIO.FAP

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE AMENDMENT JUN 6 1997

ANDA/~~AADA~~: 74-891

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 ([redacted])

TO: APPLICANT Apotheçon, Inc PHONE 609 897-2470
ATTN: Walter Jump FAX 609-897-5515

FROM: Tim Ames, PROJECT MANAGER (301-827-5849)

Dear Sir/~~Madam~~:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 4/19/96, submitted pursuant to Section 505(j)/~~507~~ of the Federal Food, Drug, and Cosmetic Act for Acyclovir Tablets 400mg + 800 mg

Reference is also made to your amendment(s) dated 1/31/97.

Attached are 5 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

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of trade secret and/or

confidential commercial

information from

6/6/1997 FDA FAX

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Please provide updated stability data in your next amendment.

2. Please note that the validation of your analytical methods has not yet been completed by our laboratories.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 74-891

Date of Submission: January 31, 1997

Applicant's Name: Apothecon, Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. CONTAINER: 400 mg - 100s
   800 mg - 100s and 500s

   Are the container labels you plan to use in marketing the same size, color and clarity as those submitted? If not, please submit.

2. UNIT DOSE BLISTER:

   Revise "Apothecon" to read "Manufactured for Apothecon ..." as seen on your container labels and insert labeling. Note the qualifying phrase may be abbreviated. We refer you to 21 CFR 201.1(h)(2) for further guidance.

3. CARTON: 400 mg and 800 mg - Unit dose 100s

   a. See comment under CONTAINER.

   b. We note you have printed the statement "For indications, dosage, ... insert" on the front and side panels. We encourage you to delete this statement from the main panel.

4. INSERT:

   a. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

      Upon further review, we request you to revise the third paragraph to read as follows:

      > A single oral dose bioavailability study in 23 normal volunteers showed that acyclovir capsules 200 mg are bioequivalent to 200 mg acyclovir in aqueous solution; and in a separate study in 20 volunteers, it was shown

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

ii. We acknowledge your comment regarding a food effect. Our Office is aware of this issue.

b. PRECAUTIONS (Information for Patients)

Chickenpox

The text of this sub-subsection does not require bold print. Therefore, delete the bolding from this entire sub-subsection except the title, "*Chickenpox*".

c. ADVERSE REACTIONS (Observed During Clinical Practice: *Nervous*)

Due to changes in the insert labeling of the reference listed drug Zovirax® (Glaxo Welcome Inc.: revised May 1996 and approved January 8, 1997) revise this subsection to read as follows:

...paresthesia, seizure, somnolence...

d. HOW SUPPLIED

Acyclovir Tablets and Capsules are not listed in the USP. Therefore, delete "USP" following the established name of your drug products.

Revise your labels and labeling as described above, then submit in final print.

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

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

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

APPEARS THIS WAY
ON ORIGINAL

APOTHECON
P.O. Box 4500 Princeton, NJ 08543-4500 609 897-2000

7/17/97
FA noted
① To Chemistry Reviewer
② Then to Labeling Reviewer
for review,

June 30, 1997

FACSIMILE AMENDMENT

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP

Re: Acyclovir Tablets
AADA 74-891
FAX Deficiency Letter of June 6, 1997

Dear Mr. Sporn:

Reference is made to the FAXed deficiency letter received from the Agency on June 6, 1997, our amendments of January 31, 1997 and May 30, 1996, and our original submission of April 19, 1996.

In accordance with the instructions contained on the FAX and the verbal instructions of Mr. Mark Anderson we are FAXing a copy of our response and sending a copy by express mail (to facilitate the review of the labeling components). We believe we have addressed all the Agency's comments and look forward to the approval of our application.

For Agency convenience we have repeated the comments received in Courier italics and our response is in Helvetica type font.

If you have any comments or additional concerns, I can be reached by telephone or FAX at the following numbers: 609-897-2470 (telephone), 609-897-5515 (FAX).

Sincerely,

Walter G. Jump, Pharm.D.
Senior Director, Medical and Regulatory Operations

RECEIVED
JUL 0 2 1997
GENERIC DRUGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-600)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

Apodhecon 74891

DATE: 8-14-97

TO: Dr. W. Jump

FROM: [signature]

PHONE: 609 897 2490

PHONE: (301) 594-

FAX: 609 897 5515

FAX: (301) 594-0180

TOTAL NUMBER OF PAGES: _____
(Excluding cover sheet)

SPECIAL INSTRUCTIONS:

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

ANDA Number: 74-891

Date of Submission: June 30, 1997

Applicant's Name: Apothecon, Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. CONTAINER: 400 mg - 100s
   800 mg - 100s and 500s

   Satisfactory

2. UNIT DOSE BLISTER: 400 mg and 800 mg

   Increase the prominence of the established name and strength, (i.e., upper case/bold print).

3. CARTON: 400 mg and 800 mg - Unit dose 100s

   Satisfactory

4. INSERT:

   General Comment

   Revise your insert labeling to be in accord with the enclosed copy of the insert labeling of the reference listed drug Zovirax® (Glaxo Wellcome Inc.; revised; March 1997 and approved May 29, 1997).

Revise your labels and labeling as described above, then submit in final print.

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

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

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

Enclosure: Insert labeling of the reference listed drug.

APPEARS THIS WAY
ON ORIGINAL

APOTHECON

P.O. Box 4500 Princeton, NJ 08543-4500 609 897-2000

August 22, 1997

FACSIMILE AMENDMENT

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: Acyclovir Tablets
AADA 74-891
FAX Deficiency Letter of August 14, 1997

Dear Mr. Sporn:

Reference is made to the FAXed deficiency letter received from the Agency on August 14, 1997, our amendments of January 31, 1997, May 30, 1996, and June 16, 1997 and our original submission of April 19, 1996.

In accordance with the instructions, we are FAXing a copy of our response and sending a copy by express mail (to facilitate the review of the final printed labeling components). We believe we have addressed all the Agency's comments and look forward to the approval of our application.

For Agency convenience we have repeated the comments received in Courier italics and our response is in Helvetica type font.

If you have any comments or additional concerns, I can be reached by telephone or FAX at the following numbers: 609-897-2470 (telephone), 609-897-5515 (FAX).

Sincerely,

Walter G. Jump, Pharm.D.
Senior Director, Medical and Regulatory Operations

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-600)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

ANDA 74891

DATE: August 1997

TO: W. Jump, Pharm.D.

FROM: J. White, Pharm.D. Labeling Review Branch

PHONE: 609 897 2470

PHONE: (301) 594-5839

FAX: 609 897-5515

FAX: (301) 594-0180

TOTAL NUMBER OF PAGES: _____
(Excluding cover sheet)

SPECIAL INSTRUCTIONS:

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

ANDA Number: 74-891

Date of Submission: August 22, 1997

Applicant's Name: Apothecon, Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. UNIT DOSE BLISTERS: 400 mg and 800 mg

   Satisfactory.

2. INSERT:

   a. DESCRIPTION

      Revise this section to read as follows:

      ... an antiviral drug. The chemical name of acyclovir ... 2.27 and 9.25.

      Each capsule for oral administration contains 200 mg acyclovir. In addition, each capsule contains the following inactive ingredients: magnesium stearate, ...

      Each tablet for oral administration contains 400 mg or 800 mg of acyclovir. In addition, each tablet contains the following inactive ingredients: magnesium stearate, ...

   b. CLINICAL PHARMACOLOGY

      i. Pharmacokinetics

         Revise "health" to read "healthy" in the first sentence of the first paragraph.

      ii. Special Population (*Pediatrics*)

         Revise "— hours" to read "2.6 hours".

c. PRECAUTIONS (Pregnancy)

Delete

d. ADVERSE REACTIONS (Chickenpox)

Revise "events" to read "event".

e. DOSAGE AND ADMINISTRATION

i. Treatment of Chickenpox: *(Adults and children over 40 kg)*

Add the following as the second paragraph:

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

ii. Bioequivalence of Dosage Forms:

Revise to read, "Acyclovir suspension was shown to be bioequivalent to acyclovir capsules (n=20) and one acyclovir 800 mg tablet ...".

Revise your insert labeling as described above, then submit in final print.

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

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

Charlie Phillips for

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

APOTHECON

P.O. Box 4500 Princeton, NJ 08543-4500 609 897-2000

labeling satisfactory for approval label review drafted 9/24/97 abegs

September 12, 1997

FACSIMILE AMENDMENT

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

AMENDMENT
FA

Re: Acyclovir Tablets
AADA 74-891
FAX Deficiency Letter of September 11, 1997

Dear Mr. Sporn:

Reference is made to the FAXed deficiency letter received from the Agency on September 11, 1997, our amendments of August 22, 1997, January 31, 1997, May 30, 1996, and June 16, 1997 and our original submission of April 19, 1996.

In accordance with the instructions, we are FAXing a copy of our response and sending a copy by express mail (to facilitate the review of the final printed labeling components). We believe we have addressed all the Agency's comments and look forward to the approval of our application.

For Agency convenience we have repeated the comments received in Courier italics and our response is in Helvetica type font.

If you have any comments or additional concerns, I can be reached by telephone or FAX at the following numbers: 609-897-2470 (telephone), 609-897-5515 (FAX).

Sincerely,

Walter G. Jump, Pharm.D.
Senior Director, Medical and Regulatory Operations

RECEIVED
SEP 15 1997