CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-889

Name: Acyclovir Capsules, 200 mg

Sponsor: Apothecon, Inc.

Approval Date: October 31, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-889

CONTENTS

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-889

APPROVAL LETTER

ANDA 74-889

OCT 31 1997

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

Dear Dr. Jump:

This is in reference to your abbreviated new drug application dated April 18, 1996, and found acceptable for filing on May 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Acyclovir Capsules, 200 mg.

Reference is also made to your amendments dated November 6, 1996, February 4, June 6, September 9 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 Capsules 200 mg to be bioequivalent and therefore, therapeutically equivalent to those of the listed drug (Zovirax® Capsules 200 mg of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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 74-889
Division File
Field Copy
HFD-610/JPhillips
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HFD-330

Endorsements:

HFD-647/LTang/10-6-97 10-20-97

HFD-647/UVenkataram/10-7-97 U.V. Venkataram 10/21/97

HFD-613/AVezza/10-16-97 A Vezza 10/27/97

HFD-613/CHoppes/ Cllappes 10/28/97

HFD-647/TAmes/10-17-97 10/24/97

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10/28/97

TYPE OF LETTER: APPROVAL

Jerry Phillips 10/30/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-889

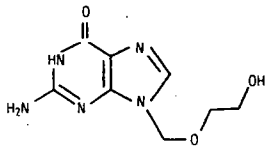
APPROVED LABELING

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^{SS}_{max}	0.83 mcg/mL	1.21 mcg/mL	1.61 mcg/mL
C^{SS}_{trough}	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 vancella-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.

OCT · 3 | 1997

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.

ENLARGED BY FOI STAFF TO 115%

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

Nursing Mothers
Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir 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 tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

Acute Treatment of Herpes Zoster
800 mg every 4 hours orally, 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

NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA	NDC 59772-4168-1 Acyclovir Capsule 200 mg LOT EXP Manufactured by Siegfried Pharma for Apothecon® Princeton, NJ 08540 USA
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Exp. Date
Control No.

100 capsules NDC 59772-4168-1

(10 blisterpacks of 10 capsules each)

UNIT DOSE PACK

ACYCLOVIR CAPSULES

Each capsule contains

200 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

416810-01

3 59772 41681 7

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 OCT 31 1997
Control No.

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

500 capsules NDC 59772-4168-3

ACYCLOVIR CAPSULES

Each capsule contains
200 mg

CAUTION: Federal law prohibits dispensing without prescription.

APPROVED

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 416830-01

3 59772 41683 1

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. OCT 31 1997

APOTHECON®
A BRISTOL-MYERS SQUIBB COMPANY

100 capsules NDC 59772-4168-2

ACYCLOVIR CAPSULES

Each capsule contains
200 mg

CAUTION: Federal law prohibits dispensing without prescription.

APPROVED

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 416820-01

3 59772 41682 4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-889

LABELING REVIEWS

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

Date of Review: August 13, 1996

Date of Submission: May 30, 1996

Primary Reviewer: Jacqueline White, Pharm.D.

Secondary Reviewer: Chan Park, Ph.D.

ANDA Number: 74-889 Review Cycle: First

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 Capsules 200 mg

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

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

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER: 100s and 500s

a. Revise the "Dispensing statement" to read:

Dispense in a tight, light-resistant container.

b. Revise the "Storage statement" to read:

... protect from light and moisture.

c. 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, dyes and coloring agents]. also, use FD&C Blue NO.2 rather than "_____".

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, "_____".

d. PRECAUTIONS

Pediatric Use

... in pediatric patients less ...

e. DOSAGE AND ADMINISTRATION

Delete all references to the oral suspension.

h. HOW SUPPLIED

Please refer to comment 1(c) 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 of an application.

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.

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

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

NOTE TO THE CHEMIST

1. Do you concur with our labeling comment under DESCRIPTION, 4(b)(ii)?

concur 11/18/96

2. The NDA's most current insert labeling storage statement indicates that the drug product should be protected from moisture, with no mention to protect from light. However, the NDA's carton labeling had printed on it protect from light and moisture. Acyclovir capsules are not listed in the USP, only acyclovir, with packaging and storage recommendations to preserve in tight containers.

   a. We have asked the firm to include protect from light on their container labels. Do you concur?

concur 11/18/96

b. Is the firm's unit dose "BLISTER" packaging sufficient to protect this drug product from light? See chem def. letter - dtd 11/18/96

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: Tight, light resistant container
   ANDA:Tight container [See comment under CONTAINER].

   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) and protect from light and moisture. [Container & Carton]

   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 from moisture [container label and carton labeling].

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 should be revised to include all components of the capsule shell. [See comment under DESCRIPTION & NOTE TO THE CHEMIST & Vol. 1.10, p.3281]. The other inactive ingredients are consistent with the firm's components statement [Vol. 1.10, p. 3200].

5. Container/Closure

100s - HDPE - CR
500s - HDPE - NCR
[Vol. 1.12, p. 3761]

6. The firm's capsule imprints described in the HOW SUPPLIED section is consistent with the firm's finished dosage form capsule description. [Vol. B1.10, p.3279]

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.

Reviewer — Date: 10/10/96

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

cc: ANDA 74-889
Division File
HFD-613/JWhite/AVezza (no cc)
njg/9/23/96/x:\new\...\Apothecon...\74889na1.l
review

Updated by Review of 8/28/97.

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

ANDA Number: 74-889

Date of Submission: February 4, 1997

Applicant's Name: Apothecon, Inc.

Established Name: Acyclovir Capsules 200 mg

Labeling Deficiencies:

1. CONTAINER: 200 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: 200 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

NOTE TO THE CHEMIST

The firm has revised their list of inactive ingredients in the DESCRIPTION section. Do you concur?

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? [For tablets and capsules]	x*		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			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)		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. [See comment under DESCRIPTION].	x		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [pending]			
Insert labeling references a food effect or a no-effect? If so, was a food study done?*See FTR	*		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. *See FTR in 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. [See FTR].			

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. Dispensing recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]
   NDA: Tight, light resistant container
   ANDA:Tight, light resistant container

4. 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) and protect from light and moisture. [Container & Carton]

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 light from moisture [container label and carton labeling].

5. Components/Composition

The firm's list of inactive ingredients in the DESCRIPTION section was revised, [as requested] to include all components of the capsule shell.
[Vol. 1.10, p.3281].
Their revised list of inactive ingredients is consistent with their components and composition statement. [Vol. 2.1, p. 23]

6. Container/Closure

100s - HDPE - CR
500s - HDPE - NCR
[Vol. 1.12, p. 3761]

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

8. The firm's capsule imprints described in the HOW SUPPLIED section is consistent with the firm's finished dosage form capsule description.
[Vol. 2.1, p. 45A;Appendix 11; Vol. B1.10, p.3279]

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:

200 mg - 100s, 500s & unit dose 100s

10. Bioequivalence/Pharmacokinetic data

-Bio. INCOMPLETE letter: date 10/15/97 [Vol. 1.1]
-Both fasting & fed studies were done.
-Fasting study: results from bio. review of 9/26/96
-The ANDA & RLD t1/2 were comparable to each & to the