

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75101

Trade Name Acyclovir Capsules 200mg

Generic Name Acyclovir Capsules 200mg

Sponsor Chelsea Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75101

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75101

APPROVAL LETTER

ANDA 75-101

APR 15 1998

Chelsea Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
P.O. Box 15686
8606 Reading Road
Cincinnati, OH 46215-0686

Dear Sir:

This is in reference to your abbreviated new drug application dated March 28, 1997, 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 20, December 3, 1997, and March 5, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Capsules, 200 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Capsules, 200 mg, of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

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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,

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

Sporn
4-15-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75101

FINAL PRINTED LABELING

CHELSEA LABORATORIES, INC.
ACYCLOVIR CAPSULES, USP 200 mg

Acyclovir Capsules, 200 mg
ANDA# 75-101
1000 count label
GMID 50013975

NDC 0536-5725-10 Prod. No. 005-7255

Rugby®

**Acyclovir
Capsules
200 mg**

**CAUTION: Federal Law Prohibits
Dispensing Without Prescription.**

1000 CAPSULES

**MANUFACTURED FOR RUGBY LABORATORIES, INC.
NORCROSS, GEORGIA 30071**

Acyclovir USP
200 mg
Each capsule contains
Acyclovir USP 200 mg, plus
inert ingredients. See package insert
for full prescribing information.
Store at 20° to 25°C (68° to 77°F).
Protect from light and moisture.
Dispense in original light-resistant container.
See package insert for USP & NME
compliance information.

KEEP OUT OF REACH OF CHILDREN

Manufactured by
CHELSEA LABORATORIES, INC.
Cincinnati, OH 45215

50013975
50013975

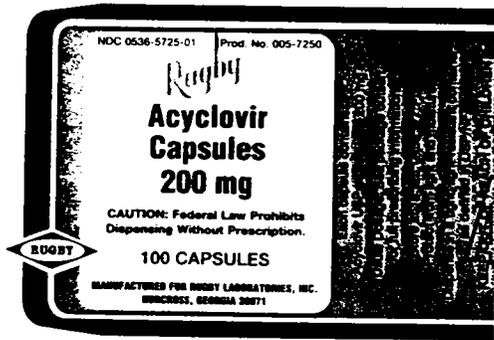


50013975

000031

CHelsea LABORATORIES, INC.
ACYCLOVIR CAPSULES, USP 200 mg

Acyclovir Capsules, 200 mg
ANDA# 75-101
100 count label
GMID 50013973



Manufactured by
CHelsea LABORATORIES, INC.
Cincinnati, OH 45215



000029

CHELSEA LABORATORIES, INC.
ACYCLOVIR CAPSULES, USP 200 mg

Acyclovir Capsules, 200 mg
ANDA# 75-101
500 count label
GMID 50013974

NDC 0536-5725-05 Prod. No. 005-7252

Rugby

**Acyclovir Capsules
200 mg**

CAUTION: Federal Law Prohibits
Dispensing Without Prescription.

500 CAPSULES

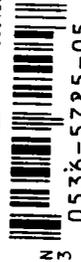
MANUFACTURED FOR RUGBY LABORATORIES, INC.
DORCHES, GEORGIA 30071

Each capsule contains
Acyclovir, USP 200 mg.
The dosage for this product
is determined by the physician.
Do not use if the seal is broken.
Keep out of reach of children.

KEEP OUT OF REACH OF CHILDREN

Manufactured by
CHELSEA LABORATORIES, INC.
Cincinnati, OH 45215

50013974
50013974



N 3 0536-5725-05 7



50013974

000030

APR 15 1999

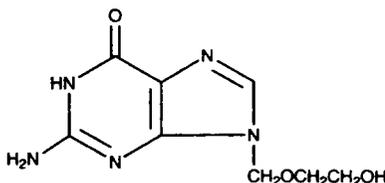
APPROVED

50014600

ACYCLOVIR
CAPSULES

DESCRIPTION: Acyclovir Capsules, an antiviral drug, are formulated for oral administration. Each capsule, for oral administration, contains 200 mg of acyclovir. In addition, each capsule contains the following inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, and sodium lauryl sulfate. The capsule shell contains: gelatin, FD&C Blue No. 1, and titanium dioxide. The imprinting ink contains: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, pharmaceutical glaze, propylene glycol, and synthetic black iron oxide.

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



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

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

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

Antiviral Activities: The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL.

Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/mL.

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

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

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

Table 1: Acyclovir Pharmacokinetic Characteristics (Range)

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

* Bioavailability decreases with increasing dose.

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

Table 2: Acyclovir Peak and Trough Concentrations at Steady State

| Parameter | 200 mg | 400 mg | 800 mg |
|--------------|-------------|-------------|-------------|
| C_{max} | 0.83 mcg/mL | 1.21 mcg/mL | 1.61 mcg/mL |
| C_{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 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

600 mg/m² in pediatric patients ages 7 months to 7 years was 2.6 hours (range 1.59 to 3.74 hours).

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

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

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

In a study of patients who received Acyclovir 400 mg twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the patients showed that 71% to 87% were recurrence-free in each quarter.

Herpes Zoster Infections: In a double-blind, placebo-controlled study of immunocompetent patients with localized cutaneous zoster infection, Acyclovir (800 mg five times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.

In a similar double-blind, placebo-controlled study, Acyclovir (800 mg five times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).

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

Adults greater than 50 years of age showed greater benefit.

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

INDICATIONS AND USAGE:

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

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

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

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

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

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

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

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

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

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study, they were 8 to 15 times human levels. At higher doses (50 mg/kg/day, s.c.) in rats and rabbits (11 to 22 and 16 to 31 times human levels, respectively) implantation efficacy, but not litter size, was decreased. In a rat peri- and post-natal study at 50 mg/kg/day, s.c., there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

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

Pregnancy: Teratogenic Effects: Pregnancy Category B. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16* and 106, and 11 and 22 times, respectively, human levels. In a non-standard test, rats were given three s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. In this test, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.

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

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when indicated.

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

Pediatric Use: Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS:

Herpes Simplex: Short-Term Administration: The most frequent adverse events reported during clinical trials of treatment of genital herpes with Acyclovir 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200-mg capsules) two times daily for 1 year in 586 patients treated with Acyclovir were nausea (4.8%) and diarrhea (2.4%). The 589 control patients receiving intermittent treatment of recurrences with Acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), and headache (2.2%).

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

Chickenpox: The most frequent adverse event reported during three clinical trials of treatment of chickenpox with oral Acyclovir at doses of 10 to 20 mg/kg four times daily for 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

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

Antiviral Activities: The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC₅₀), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC₅₀ 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 IC₅₀ 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 IC₅₀ 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 mechanisms as resistance to VZV. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

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

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| Parameter | Range |
|------------------------------|---------------|
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| Average oral bioavailability | 10% to 20%* |

* Bioavailability decreases with increasing dose.

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

Table 2: Acyclovir Peak and Trough Concentrations at Steady State

| Parameter | 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 may be administered with or without food. The only known urinary metabolite is 9-[(carboxymethoxy)methyl]guanine.

Special Populations: Adults with Impaired Renal Function: The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Pediatrics: In general, the pharmacokinetics of acyclovir in pediatric patients is similar to that of adults. Mean half-life after oral doses of 300 mg/m² and

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

Adults greater than 50 years of age showed greater benefit.

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

INDICATIONS AND USAGE:

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

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

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

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

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

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

and 100 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16, and 106, and 11 and 22 times, respectively, human levels. In a non-standard test, rats were given three s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. In this test, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.

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

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when indicated.

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

Pediatric Use: Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS:

Herpes Simplex: Short-Term Administration: The most frequent adverse events reported during clinical trials of treatment of genital herpes with Acyclovir 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200-mg capsules) two times daily for 1 year in 586 patients treated with Acyclovir were nausea (4.8%) and diarrhea (2.4%). The 589 control patients receiving intermittent treatment of recurrences with Acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), and headache (2.2%).

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

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

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral Acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis
Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy
Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE: Patients have ingested intentional overdoses of up to 100 capsules (20 g) of Acyclovir, with no unexpected adverse effects. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION:

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

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

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

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

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

Treatment of Chickenpox: Children (2 years of age and older): 20 mg/kg per dose orally four times daily (80 mg/kg/day) for 5 days.

Children over 40 kg should receive the adult dose for chickenpox.

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

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

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

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

Table 3: Dosage Modification for Renal Impairment

| Normal Dosage Regimen | Creatinine Clearance (mL/min/1.73 m ²) | Adjusted Dosage Regimen | |
|-----------------------|--|-------------------------|-------------------------|
| | | Dose (mg) | Dosing Interval |
| 200 mg every 4 hours | > 10 | 200 | every 4 hours |
| | 0 - 10 | 200 | 5x daily 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 four Acyclovir 200-mg capsules (n=24).

HOW SUPPLIED: Acyclovir Capsules are supplied as follows:

200 mg: White opaque/light blue opaque capsules, imprinted Rugby and 5725, in bottles of 100 (NDC 0536-5725-01), 500 (NDC 0536-572505) and 1000 (NDC 0536-5725-10).

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

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Chelsea Laboratories, Inc.
Cincinnati, OH 45215

Rev. 9/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75101

CHEMISTRY REVIEW(S)

**OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW**

1. **CHEMIST'S REVIEW NO.** 3
2. **ANDA#** 75-101
3. **NAME AND ADDRESS OF APPLICANT**
Chelsea Laboratories, Inc.
8606 Reading Road
Cincinnati, Ohio 45215-0686
4. **LEGAL BASIS FOR ANDA SUBMISSION**
The application is based on the reference listed drug **Zovirax[®] Capsules** manufactured by Glaxo Wellcome (NDA 18-828). A patent certification and exclusivity statement were provided.
5. **SUPPLEMENT(s)**
N/A
6. **PROPRIETARY NAME**
N/A
7. **NONPROPRIETARY NAME**
Acyclovir Capsules
8. **SUPPLEMENT(s) PROVIDE(s) FOR**
N/A
9. **AMENDMENTS AND OTHER DATES**
Firm:
Original Submission: 3/28/97
Amendment: 7/18/97
Fax Amendment: 10/10/97
Minor Amendment: 11/20/97
Minor Amendment: 12/3/97
Telephone Amendment: 3/5/98

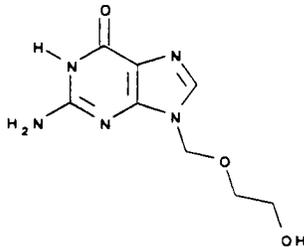
FDA:
Acceptance to File: 5/2/97
Chemistry/Labeling Deficiencies (Facsimile): 9/22/97
Bio Deficiencies: 10/9/97
Chemistry/Labeling Deficiencies (Minor): 11/12/97
10. **PHARMACOLOGICAL CATEGORY**
Antiviral
11. **HOW DISPENSED**
Rx

12. **RELATED IND/NDA/DMFs**
 NDA 18-828 - Glaxo Wellcome (RLD - Zovirax®)

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

14. **STRENGTH(s)**
 200 mg

15. **CHEMICAL NAME AND STRUCTURE**



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

C₁₁H₁₁N₅O₃
 Molecular Weight: 225.21

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

17. **COMMENTS**
 The application is now complete from a CMC standpoint. Other review components are also complete (labeling, bio, EER, methods validation).

18. **CONCLUSIONS/RECOMMENDATIONS**
 Approval of the application is recommended

- | | |
|------------------------------|------------------------------|
| 19. <u>REVIEWER</u> | <u>DATE COMPLETED</u> |
| Susan Rosencrance 3/16/98 | 12/31/97; revised 3/11/98 |

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75101

BIOEQUIVALENCE REVIEW(S)

Acyclovir
200 mg capsule
ANDA 75-101
Reviewer: Pradeep M. Sathe, Ph.D.
WP #75101o.n97

Chelsea Labs
Cincinnati, Ohio-45215
Submission Date:
November 20, 1997

REVIEW OF AN AMENDMENT

INTRODUCTION : Acyclovir is a synthetic purine nucleoside analog, 9-[(2-hydroxyethoxy)methyl]guanine, in which a linear side chain has been substituted for the cyclic sugar of the naturally occurring guanosine molecule. It is a white crystalline powder with a molecular weight of 225.21 Daltons with a maximum water solubility of 2.5 mg/ml at 37°C. Acyclovir is used as an anti-viral agent in the treatment of human herpes viruses, including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella zoster virus (VZV), Epstein Barr virus (EBV) and cytomegalovirus (CMV). In cell culture Acyclovir has highest anti-viral activity against HSV-1, followed by HSV-2, VZV, EBV and CMV in that order. The mechanism of action includes inhibition of DNA synthesis resulting in inhibition of viral replication. In order to inhibit DNA synthesis, Acyclovir must be phosphorylated first by viral thymidine kinase. The affinity of Acyclovir for herpes-virus encoded thymidine kinase is 200 times greater than for the mammalian enzyme, and phosphorylation of Acyclovir by mammalian enzyme proceeds at a negligible rate. After synthesis of Acyclovir monophosphate (acyclo-GMP) in viral infected cells, normal cellular enzymes catalyze the sequential synthesis of acyclo-GDP and acyclo-GTP. The amount of acyclo-GTP formed in a herpes virus infected cell is 40 to 100 times greater than in uninfected cells. Acyclo-GTP then selectively inhibits the viral DNA polymerase by competing with deoxoguanosine triphosphate and to a much lesser extent, the cellular polymerase. In addition acyclo-GTP is incorporated into the elongating viral DNA, where it causes termination of biosynthesis of the viral DNA strand.

The oral availability of the drug is about 15-30% and decreases with increasing doses. Protein binding is about 15%. The drug is primarily cleared by renal route by glomerular filtration and tubular secretion. The urinary excretion accounts for up to 75% of the drug clearance, while 15% of the drug is recovered as an inactive metabolite, 9-carboxy methoxy guanine. In patients with normal renal function, mean volume of distribution and half-life are about 0.69 liters/kg, and 2.4 hours respectively. The normal dosage regimen is 200 mg every four hours, five times daily for 10 days. The draft labeling states that "in the study in six volunteers, the influence of food on the absorption of Acyclovir was not apparent." The above information suggests the conduct of a food challenge study.

II.BACKGROUND: The firm had submitted three bio-studies and comparative dissolution on March 28, 1997. The application consisted of A] a single dose fasting bio-equivalence study (study p96-127), B] a single dose 'food challenge' bio-equivalence study, and C] Dissolution testing methodology and data comparing 200 mg test (Chelsea) and reference (Burroughs Wellcome's Zovirax^R) capsule formulations. The fasting study Cmax (n=32) failed the regulatory 80-125% acceptance criterion, primarily due to different results from one subject (#8). Subsequently, in another mini-fasting study involving 3 subjects (study p96-363), the firm repeated the subject (#8), for whom the study results had failed, along with two other co-participants (#22 and #36) from the first fasting study. The results of the new study indicated that this time subject #8 pharmacokinetic Cmax measures agree closely for the test and the reference formulations and were comparable to the other two subjects. Based on the first fasting study results (study p96-127), in a review dated October 5, 1997, the Division recommended non-acceptance of the bio-study results and bio-equivalence of the two formulations.

III.THE AMENDMENT: In the current amendment, the firm is seeking a reconsideration of the Division recommendation. The Division's comments and the firm's response are as follows:

Division Comment:

1. The results of study P97-127 indicate that 90% confidence intervals of the log transformed Cmax mean parameter (n=32) fails, being outside the regulatory limits of 80-125%.

Firm's Response:

It is important to note that the aberrant Cmax value in the initial study (P96-127) was exhibited by the reference drug product and not Chelsea's test drug product. Furthermore the following has been cited in the book entitled "Generics and Bioequivalence" (edited by A.J.Jackson, OGD/CDER/FDA).

“As with any other type of studies, there are always values that do not compare well with other results in the bioequivalence study. These curious values which cannot be attributed to missing concentrations in the profile or any extreme concentration in the profile are called outliers. There are many tests to identify outliers, but routine removal from the study is not valid because such outliers can indicate two important and real possible outcomes. One, the profile is a result of a product failure; or, two, this could be the realization of a subject-by-formulation interaction. The main point is that the observation could be very meaningful and should not be discarded unthinkingly.

The only legitimate way of removing a subject's results is to bring the subject back to the study center and repeat both formulations. It is far cheaper to have one subject return than to redo the whole study. If the results are different again we probably have a real subject-by-formulation interaction. Further study of this would be required by the agency. If the two repeated results are similar for the two formulations, then one of the formulations of the initial pair failed and can be identified by comparison with its respective repeat. If it was the reference product that failed, then the test formulation should not be penalized and the subject's results are removed. Usually no more than 5% of the subjects should be considered outliers before the quality of the study would be questioned. If the test formulation failed, then another study may be warranted although it may be wise to do more *in vitro* formulation development before any *in vivo* repeat. Results with and without these outliers should be submitted for review. It should be noted that an *a priori* test for outlier screening should be part of the study protocol and followed even if the study indicates bioequivalence”.

The purpose of the redosing study (P96-363) was to determine if there was a subject-by-formulation interaction that caused the reference drug product to exhibit low bioavailability in subject #8 relative to the test drug product. The results of the redosing study confirmed the lack of subject-by-formulation interaction since the test and reference drug products performed similarly. Thus the elimination of the data for subject #8 should be allowed from the database. The validity of the redosing study was shown by the data obtained for the other two subjects (“control”) namely subject #22 and #36, whose test/reference ratios were similar for the initial and redosing studies i.e. 0.77 vs 0.79 and 1.29 vs 0.97, respectively. Furthermore a comparison of the C_{max} values in the redosing study for the 3 subjects for both the test and reference drug products, based on the expected within subject CV of 0.27 observed in the initial study, showed all values to be within expectation except for the change of reference value for subject #8 from 193 ng/ml to 506 ng/ml from initial study to redosing study ($p < 0.02$).

Division Comment:

2. The (P96-363) study, indicated that subject #8 levels following the redosing of the test and reference products were more similar as opposed to (P96-127) study, where test treatment levels of #8 were considerably greater than the reference. However it is interesting to note that test and reference levels of all the repeated subjects in the (P96-363) study show less differences than those

seen for the (P96-127) study. It may be argued that, based on the large inter-subject variability, it would have been possible that some other subject would have shown more differences, had the (16-363) study been conducted redosing all 32 subjects. Also it could be argued that, since there is large inter-study variation in levels, the redosed subjects may possibly give different levels if dosed for the third time. In short, the reviewer is not convinced of the firm's claim about fasting study bioequivalence. Based on the provided information and failure of $\ln-C_{max}$ 90% confidence interval, the test product cannot be considered bioequivalent to the reference.

Firm's Response:

There are only 3 subjects in the redosing study. Subject #8 was expected to show less of a difference because of the aberrant C_{max} results for the reference drug product. Subject #22 showed a value of 0.77 and 0.79 in the initial and redosing studies, virtually identical. Subject #36 showed a ratio of 1.29 and 0.97 for the initial and redosing study, respectively, which are not very different, certainly within the statistical expectations. We believe that the data in the redosing study are not unusual in this regard.

The inter-study variability based on the 3 subjects does not seem to be very large. Even including the aberrant results in the initial study for the C_{max} for subject #8, the average results are 477 and 580 for initial and redosing studies, respectively. This is only about a 21% difference, which cannot be considered as a very large difference. Furthermore, this difference of 21% is attributed to primarily due to aberrant results of subject #8 for reference drug product observed in the initial (P96-127) study. Even if the studies showed a large difference in response, the ratios of the two products should not be significantly affected.

DIVISION COMMENTS TO FIRM'S RESPONSES:

Points 1-3 state the cons- and points 4-5 state the pros- for accepting the study results.

1. The possible causes for the failure of any bioequivalence study (assuming adequate subjects) involve differences in a. The mean pharmacokinetic measures, b. Intra-subject variabilities or c. Combination of both of the above. The mean C_{max} (test-ref) difference with $n=32$ was 57.93 ng/ml, while the same with $n=31$, i.e. without subject #8 results, was 41.98 ng/ml. The intra-subject %CV for C_{max} (29%-30%, for both $n=32$ and $n=31$) was found to be comparable and so was the inter-subject variability for C_{max} (CV, 38% for the test, 32% for the reference, for $n=31$ and 38% for the test and 33% for the reference, for $n=32$). It is therefore evident that for this study, the main cause for the failure of 80-125% bioequivalence criterion was the mean difference of (test-ref) C_{max} .
2. It is possible that the observed mean difference in the test C_{max} may be due to the overall faster absorption of the test product. The mean T_{max} , 1.52 hour for test and 1.64 hour for the reference, also points in this direction. The in-vitro drug releases reflect a similar behavior. The mean

dissolution of the test formulation at 10 min is 84.7% versus 74.8% for that of the reference formulation. It is possible that the drug release differences may be causing the observed differences in the drug input and absorption.

3. It could be argued that in the initial (P96-127) fasting study, subject #8's low Reference Cmax value may not be an outlier. If the test treatment Cmax of 785 ng/ml for subject #8, which is lower than 867 ng/ml, 845 ng/ml and 829 ng/ml for subjects #12, #17 and #28 respectively, is considered as coming from a single population, the reference treatment Cmax of 193 ng/ml for subject #8 which is lower than 225 ng/ml, for subject #9, could also be viewed as coming from a single population.

4. Based on the second P96-363 mini-study results, it could be argued that possibly, there may not be a subject-by-formulation interaction.

5. The most important argument in favour of the accepting the firm's request (which may outweigh the cons-) is that subject #8 Cmax aberration in the two studies (#P96-127 and #P96-363) has occurred with respect to the 'Reference' product and not the 'test' product. The question therefore can be posed as should a *test* formulation which is *consistent* with respect to the Cmax for the two studies be turned down based on the *inconsistent* Cmax of the *reference* formulation?

IV. RECOMMENDATIONS:

Based on the Comments 1-5 above which state the cons, (1-3) and pros (4-5), for accepting the study results, the following recommendations are made.

1. The fasting bioequivalence study (P96-127) conducted by Chelsea Labs. on its 200 mg Acyclovir capsule lot # R57720, comparing it to Zovirax^R 200 mg capsule, lot #5S1287 has been found acceptable by the Division of Bioequivalence. The studies (P96-127 and P96-363) together suggest that Chelsea Labs' Acyclovir 200 mg capsule may be deemed bioequivalent to the reference product, Zovirax^R 200 mg Acyclovir capsule manufactured by Burroughs Wellcome.

2. The food challenge bioequivalence study conducted by Chelsea Labs. on its 200 mg Acyclovir capsule, lot # R57720, comparing it to Zovirax^R 200 mg capsule, lot #5S1287 is found acceptable by the Division of Bioequivalence.

3. The dissolution testing conducted by Chelsea Labs. on its 200 mg Acyclovir capsule, lot # R57720, comparing it to Zovirax^R 200 mg capsule, lot #5S1287 is found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml deaerated water at 37°C using USP 23 apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

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

At the acceptance criteria, the firm should refer to the acceptance table in the USP 23.

4. From the bioequivalence point of view, the firm has met the requirements of the in-vivo bioequivalence and in-vitro dissolution and the application is acceptable.

U 2/17/98
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD Initialed by YCHuang
FT Initialed by YCHuang

2/17/98

Concur

Date: 2/17/98

Dale Conner, Pharm.D.

Director, Division of Bioequivalence

cc: ANDA #75-101 (Original, Duplicate), HFD-650 (Director), HFD-652 (Huang, Sathe), Drug File, Division File.

2.1

Acyclovir
200 mg capsule
ANDA 75-101
Reviewer: Pradeep M. Sathe, Ph.D.
WP #75101o.398

Chelsea Labs
Cincinnati, Ohio-45215
Submission Date:
March 5, 1998

REVIEW OF A MINOR AMENDMENT

The amendment consists of firm's dissolution data results related to the stability of the formulation. The application should therefore be forwarded to the concerned Chemistry Division for their opinion.

n //

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD Initialed by YCHuang
FT Initialed by YCHuang Y

3/20/98

Concu _____
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

Date: 3/20/98

cc: ANDA #75-101 (Original, Duplicate), HFD-650 (Director), HFD-652 (Huang, Sathe), Drug File, Division File.

101

ANDA 75-101

OCT - 9 1997

Chelsea Laboratories, Inc.
Attention: Ernest Lengle
8606 Reading Road
Cincinnati, OH 45215-0686

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on March 28, 1997, for Acyclovir Capsules, 200 mg.

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

COMMENTS ON THE TWO FASTING BIOEQUIVALENCE STUDIES:

1. The study results of study P96-127, indicate that the 90% confidence intervals of the log transformed C_{MAX} mean parameter (n = 32) fails, being outside the regulatory limits of 80-125%.
2. The study results for P96-363, indicated that subject #8 levels following the redosing of the test and reference products were similar to each other, as opposed to study P96-127, where test treatment levels of subject #8 were considerably greater than the reference. It is interesting to note, however, that the test and reference levels of all the repeated subjects in study P96-363 show less differences than those seen for study P96-127. It may be argued that, based on the large inter-subject variability, it would have been possible that some other subject would have shown more differences, had the study P96-363 been conducted by redosing all 32 subjects. It also could be argued that, since there is large inter-study variation in levels, the redosed subjects might possibly give still different levels if dosed for a third time. Based on the provided information and failure of the 90% confidence interval for the log transformed C_{MAX}, the test product cannot be considered bioequivalent to the reference.

We have no further questions on the fed study or the dissolution data, however, we wish to clarify and emphasize that the FDA recommended 'Q' is NLT dissolved in 30 minutes; and not NLT dissolved in 30 minutes as you proposed..

The fasting bioequivalence study has been found unacceptable by the Division of Bioequivalence. It fails to demonstrate bioequivalence between the two products.

Note: The application was submitted to the agency in an Electronic Submission format in addition to the Hard Copy. After comparing the two, the Division has found discrepancies in the provided Electronic Submission information. The fasting study P96-127, in the electronic format, did not include subject #8 data. The data, thus, consisted of 31 subjects. For the conducted bio-studies, and from the electronic format, only the pre-study and not during study validation information could be accessed. You provided 32 subject data and analysis as well as 31 subject data and analysis in the Hard Copy. The hard copy also had information about the pre- as well as during study validation. In the Division's opinion, the discrepancy between the two formats is of concern since it possibly may lead to incorrect data analysis, interpretations and conclusions.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

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