CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074738

Trade Name : ACYCLOVIR ORAL SUSPENSION

Generic Name: Acyclovir Oral Suspension

Sponsor : Alpharma

Approval Date: April 23, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074738

APPROVAL LETTER

ANDA 74-738

APR 23 1997

Alpharma, U.S. Pharmaceuticals Division
Attention: Vincent Andolina
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

This is in reference to your abbreviated new drug application dated August 31, 1995, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Acyclovir Oral Suspension, 200 mg/5 mL.

Reference is also made to your amendments dated March 25, 1996 and February 27, 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 Oral Suspension, 200 mg/5 mL, to be bioequivalent and, therefore therapeutically equivalent to the listed drug (Zovirax® Oral Suspension, 200 mg/5 mL, 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,

[redacted]/S/ 4/28/97

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074738

FINAL PRINTED LABELING

MAKED

Alpharma

ANDA #74-738

Acyclovir Oral Suspension 200 mg/5 mL

Final Printed Labeling

NDC 0472-0082-16

ACYCLOVIR
ORAL
SUSPENSION

ALPHARMA

200 mg/5 mL

00820297A1 VC102089

ONE PINT (473 mL)

N 3 04720 08216 3

NDC 0472-0082-16

ACYCLOVIR
ORAL SUSPENSION

ALPHARMA

200 mg/5 mL

Shake Well Before Using

EACH 5 mL (1 TEASPOONFUL) CONTAINS:
Acyclovir 200 mg and added as preservatives methylparaben 0.1% and propylparaben 0.02%.

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

Store between 15°-25°C (59°-77°F).

Dispense in a tight container as defined in the USP.

See label or bottom of container for lot number and expiration date.

CAUTION: Federal law prohibits dispensing without prescription.

ONE PINT (473 mL)

Manufactured by **Alpharma USPD Inc.**, Baltimore, MD 21244

Label One Pint 00820297A1

ACYCLOVIR
ORAL SUSPENSION

FORM NO. 0082
Rev. 2/97 VC1298

ACYCLOVIR ORAL SUSPENSION

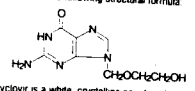
DESCRIPTION

Acyclovir is an antiviral drug. Acyclovir suspension is formulated for oral administration.

EACH TEASPOONFUL (5 mL) OF ACYCLOVIR ORAL SUSPENSION CONTAINS: 200 mg of acyclovir.

INACTIVE INGREDIENTS: Carboxymethylcellulose sodium, flavor, glycerin, methylparaben (0.1%), microcrystalline cellulose, propylparaben (0.02%), purified water and sorbitol.

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



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

CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV2 converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up, 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus-infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology: The quantitative relationship between the *in vitro* susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤2.2 mcg/mL and 50% of all isolates were sensitive to ≤0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

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Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TKor viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.3 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 mcg/mL (0.66 to 1.8 mcg/mL) and 0.55 mcg/mL (0.14 to 1.1 mcg/mL), respectively.

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

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 mcg/mL, 1.21 and 0.63 mcg/mL, and 1.61 and 0.83 mcg/mL for the 200, 400, and 800 mg dosage regimens, respectively.

In another study the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy)methyl]guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

INDICATIONS AND USAGE

Acyclovir Oral Suspension is indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir Oral Suspension is indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella).

Genital Herpes Infections:

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional, and psychosocial difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus, orally administered acyclovir is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies[23, 24, 25] have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention, or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous acyclovir.

Recurrent Episodes: Double-blind, placebo-controlled studies[16, 26-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

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

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with acyclovir. Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

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Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies[31, 32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections:
In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to acyclovir and 94 to placebo), acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33]

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to acyclovir and 43 to placebo), acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).[34]

Chickenpox:
In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented **within 24 hours** of the onset of a typical chickenpox rash, acyclovir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15, or 20 mg/kg depending on the age group. Treatment with acyclovir reduced the maximum number of lesions (336 vs. greater than 500; lesions beyond 500 were not counted). Treatment with acyclovir also shortened the mean time to 50% healing (7.1 days vs. 8.7 days), reduced the number of vesicular lesions by the second day of treatment (49 vs. 113), and decreased the proportion of patients with fever (temperature greater than 100°F) by the second day (19% vs. 57%). Treatment with acyclovir did not affect the antibody response to varicella-zoster virus measured 1 month and 1 year following the treatment.[35]

In two concurrent double-blind, placebo-controlled studies, a total of 883 normal patients, ages 2 to 18 years, were enrolled **within 24 hours** of the onset of a typical chickenpox rash, and acyclovir was administered at 20 mg/kg orally up to 800 mg 4 times daily for 5 days. In the larger study of 815 children ages 2 to 12 years, treatment with acyclovir reduced the median maximum number of lesions (277 vs. 386), reduced the median number of vesicular lesions by the second day of treatment (26 vs. 40), and reduced the proportion of patients with moderate to severe itching by the third day of treatment (15% vs. 34%).[36] In addition, in both studies (883 patients, ages 2 to 18 years), treatment with acyclovir also decreased the proportion of patients with fever (temperature greater than 100°F), anorexia, and lethargy by the second day of treatment, and decreased the mean number of residual lesions on Day 28.[36, 37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at 1 month following treatment in patients receiving acyclovir compared to patients receiving placebo.[38]

Diagnosis:
Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. While cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39]

Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

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

WARNINGS
Acyclovir Oral Suspension is intended for oral ingestion only.

PRECAUTIONS
General: Acyclovir has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY, Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

with moderate to severe [illegible] treatment (15% vs. 34%).[36] In addition, in both studies (883 patients, ages 2 to 18 years), treatment with acyclovir also decreased the proportion of patients with fever (temperature greater than 100°F), anorexia, and lethargy by the second day of treatment, and decreased the mean number of residual lesions on Day 28.[36, 37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at 1 month following treatment in patients receiving acyclovir compared to patients receiving placebo.[38]

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Caution should be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. Acyclovir Oral Suspension is for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/ gonadal toxicity and mutagenesis. long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of acyclovir per day for 6 months in humans did not show similar findings.[40] Chromosomal breaks were seen *in vitro* after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of acyclovir per day for 1 year in humans did not show any abnormalities in structure or number of chromosomes.[26]

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with acyclovir showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that treatment of chickenpox with acyclovir would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 5 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 5 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the

higher and lower dosing schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the 1-month study and were 24 to 48 times human levels in the 6-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for 1 month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for 1 year (6 to 12 times human levels).

PREGNANCY

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

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[43, 44] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

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

ADVERSE REACTIONS

Herpes Simplex: Short-Term Administration: The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered acyclovir were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%), and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year included asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster: The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%) and constipation (2.4%).

Chickenpox

the second year) also received continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year included asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster: The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%), and constipation (2.4%).

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

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

General: **fever, headache, pain, peripheral edema,** and rarely, **anaphylaxis**

Nervous: **confusion, dizziness, hallucinations, paresthesia, seizure, somnolence** (These symptoms may be marked, particularly in older adults.)

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

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Treatment of Initial Genital Herpes: 200 mg (one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg (two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

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

Acute Treatment of Herpes Zoster: 800 mg (four teaspoonfuls [20 mL] suspension) every 4 hours orally, 5 times daily for 7 to 10 days.

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

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

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

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

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m2)	Adjusted Dosage Dose (mg)	Dosage Regimen Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5 × 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, 5 × 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.[45, 46]

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.[47, 48]

HOW SUPPLIED

Acyclovir Oral Suspension (off-white, banana-flavored) containing 200 mg acyclovir in each teaspoonful (5 mL)–Bottle of 1 pint (473 mL).

Store between 15°-25°C (59°-77°F).

Dispense in a tight container as defined in the USP.

CAUTION: Federal law prohibits dispensing without prescription.

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Form No. 0082

Rev. 2/97
VC1298

Manufactured by
Alpharma USPD Inc.
Baltimore, MD 21244

CENTER FOR DRUG EVALUATION AND RESEARC

APPLICATION NUMBER 074738

CHEMISTRY REVIEW(S)

DJ

ANDA 74-738

Barre-National Inc.
Attention: Deborah Miran
333 Cassell Drive
Suite 3500
Baltimore MD 21224

Dear Madam::

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Oral Suspension, 200 mg/5mL.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should however be done in 900 mL of **0.1N HCl** at 37°C using apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

   Not less than (b)4 of the labeled amount of Acyclovir in the dosage form is dissolved in **45 minutes**.

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

Sincerely yours,

/S/

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

cc: ANDA 74-738, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
Letter Out, Bio Acceptable

Endorsements:

K. Dhariwal 4/24
S. Nerurkar 4/25/96
M. Anderson

DRAFTED: STM 04/24/96 X:\WPFILE\BIO\FINAL\N74738.APP

D, J

APR 16 1996

Acyclovir
200 mg/5 mL Oral Suspension
ANDA# 74-738
Reviewer: Kuldeep R. Dhariwal
File Name: 74738SD.395

Barre-National Inc.
333, Cassell Drive
Suite 3500
Baltimore, MD 21224
Submission Date:
August 31, 1995
March 25, 1996

Review of Fasting and Fed Bioequivalence Studies and Dissolution Data

The firm has submitted a single-dose *in vivo* bioequivalence study under fasting and fed conditions and dissolution data comparing its acyclovir oral suspension containing 200 mg acyclovir per 5 mL with Burroughs Wellcome's acyclovir oral suspension, 200 mg/5 mL (Zovirax®). Each dose consisted of oral suspension 400 mg/10 mL of either the test or reference product.

The firm had not submitted potency assay of reference listed drug with the application. The firm was called on March 19, 1996 (telecommunication between Jason Gross and Vincent Angelino of Barre-National) and was requested to submit the data. The firm submitted the requested information as amendment on March 25, 1996 which was received by Office of Generic Drugs on March 29, 1996 and given to this reviewer on April 9, 1996.

Introduction:

Acyclovir, 9-[(2-hydroxyethoxy)methyl]guanine is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 and 2, varicella-zoster virus, Epstein-Barr virus and cytomegalovirus. The inhibitory activity of acyclovir for these viruses is highly selective, involving preferential uptake into virus-infected cells and requiring a virus-specific thymidine kinase for conversion to the monophosphate. Subsequent conversion to the triphosphate results in irreversible binding to DNA polymerase and termination of DNA replication.

The absorption of acyclovir in humans after its oral administration is slow, variable, and incomplete. The absolute bioavailability from different studies involving both normals and patients is reported to be 15-30%. In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet and one 800 mg tablet 5 times daily, absorption decreased with increasing dose and the estimated

bioavailabilities were 20%, 15%, and 10% respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In another study, the influence of food on the absorption of acyclovir was not apparent.

The reference product is Zovirax® available as 200 mg capsule, 400 mg and 800 mg tablets, and as 200 mg per 5 mL suspension. It is marketed by Burroughs Wellcome.

Bioavailability of Acyclovir Oral Suspension, 200 mg/ 5 mL under Fasting Conditions:

A. Objective:

The objective of this study was to compare the bioavailability of Barre National's formulation of acyclovir oral suspension, 200 mg/5 mL, to that of a marketed reference formulation, acyclovir oral suspension, 200 mg/5 mL (Zovirax®), manufactured by Burroughs Wellcome.

B. Study Sites and Investigators:

Clinical and Analytical Site: [redacted]

Principal Investi[redacted]
Project Director: [redacted]
Protocol #10720 "Bioavailability of Acyclovir Oral Suspension, 200 mg/5 mL" was approved by the National Institutional Review Board [redacted]
Consent Form: A copy of volunteer informed consent form used in the study is given on page 85, vol. 1.1
Study #135-03-10720
Study Dates: Phase I February 3-5, 1995
Phase II February 10-12, 1995
Analysis Dates: May 10 to June 1, 1995

C. Study Design:

The study was designed as a randomized, two-treatment, crossover bioavailability study. The study was executed in two periods with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at least 16 hours postdose each period. The subjects were assigned to two sequences at random as follows:

Sequence	Subject number	Phase I	Phase II
1	2,4,5,8,9,12,13,16,17,19,21,24,25	A	B
2	1,3,6,7,10,11,14,15,18,20,22,23,26	B	A

Subject # 7 and 9 did not complete the study

A: Acyclovir Oral Suspension, 200 mg/5 mL; A.L.Pharma, Inc. (Barre National); Dose = 400 mg/10 mL; Lot #PP 4816; Batch size: [redacted] Manufacture Date: 11/7/94; Assay: 99.2%

B: Acyclovir (Zovirax®) Oral Suspension, 200 mg/5 mL; Burroughs Wellcome Co.; Dose = 400 mg/10 mL; Lot #4T2522; Expiration Date: September, 1996; Assay: 100.5%

The subjects fasted for no fewer than 10 hours prior to drug administration and until 5 hours postdose. Water ad lib. was allowed except within one hour of drug administration. The drug products were administered with 240 mL of water. The subjects were dosed at 2 minute intervals and were not permitted to lie down until 4 hours postdose. Identical meals were served during both phases. Blood pressure and pulse measurements were obtained predose, at 4 hours postdose and at discharge from the facility. Temperature and respirations were also measured predose and at discharge. Diagnostic blood and urine specimens were obtained along with the 16 hour blood sample collection postdose period II (at the end of the study).

D. Subject selection:

Twenty-six (twenty-three male and three female) healthy subjects were enrolled in the study. Blood samples from all subjects who completed the study were to be analyzed. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age, male or female
- no more than ±15% from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study

Subjects were excluded from this study based on the following criteria:

- history of asthma, chronic bronchitis, herpes, hypertension, cardiovascular, neurological, hepatic, renal, hematopoietic,

gastrointestinal or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to acyclovir or to related drugs
- positive serum pregnancy test at screening and a positive urine pregnancy test at check-in for each phase

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days (excluding contraceptives) or OTC medications (excluding OTC ibuprofen, aspirin, acetaminophen, vitamins, medicated lozenzes, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol consumption for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- a curfew of 11 p.m. was observed for the nights prior to dosing
- no smoking from 1 hour prior to dosing until 4 hours following drug administration
- women volunteers should not be pregnant or nursing. They should be practicing contraception with a reliable and recognized method of contraception

E. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers® at 0 (predose), 0.33,0.67,1,1.33,1.67,2,2.5,3,3.5, 4,5,6,7,8,10,12,14, and 16 hours postdose. Samples were centrifuged within 15 minutes of acquisition and were therefore processed in batches (usually 8 samples) at each time point. The plasma was transferred to prelabeled polypropylene tubes and promptly frozen at -20°C. The samples were transferred to analytical laboratory on February 13, 1995.

F. Analytical Methods:

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G. Pharmacokinetics/Statistical Analysis:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last four to six concentrations versus time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Twenty-six subjects entered the study. One subject voluntarily withdrew from the study prior to period II for personal reasons. One subject failed to return to the facility to complete period II. Both of these subjects were males. Samples from twenty-four subjects who completed the study were analyzed. Clinical vital signs were measured before dosing and at 4 and 24 hours after dosing. The firm has provided the measurements in a tabular form. The reviewer plotted mean systolic and diastolic blood pressure. There was no significant difference in these parameters between the test and reference formulations.

Adverse events:

Following four subjects experienced adverse events during the study. All events were transient in nature and resolved spontaneously without medical intervention:

Subject #	Phase	Product	Sign/Symptom
3	II	Test	Headache
5	II	Ref	Increased blood pressure
12	I	Test	Headache
	II	Ref	Headache
24	II	Ref	Nausea, silver spots in front of eyes when getting up quickly

Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation:

Subject #	Test result
9	low polysegmented neutrophils; high mean platelet volume and lymphocytes
10	high phosphorus
11	low platelets
12	high glucose, phosphorus

Deviations in the study:

No deviations from the scheduled phlebotomy time or in sample processing were reported.

Reassays:

Of the 912 samples assayed for this study, 31 samples were reassayed. Following samples were reassayed for the reasons shown against them:

# of samples	Reason for reassay
30	Chromatographic interference
1	Reassayed by mistake

2. Analytical:

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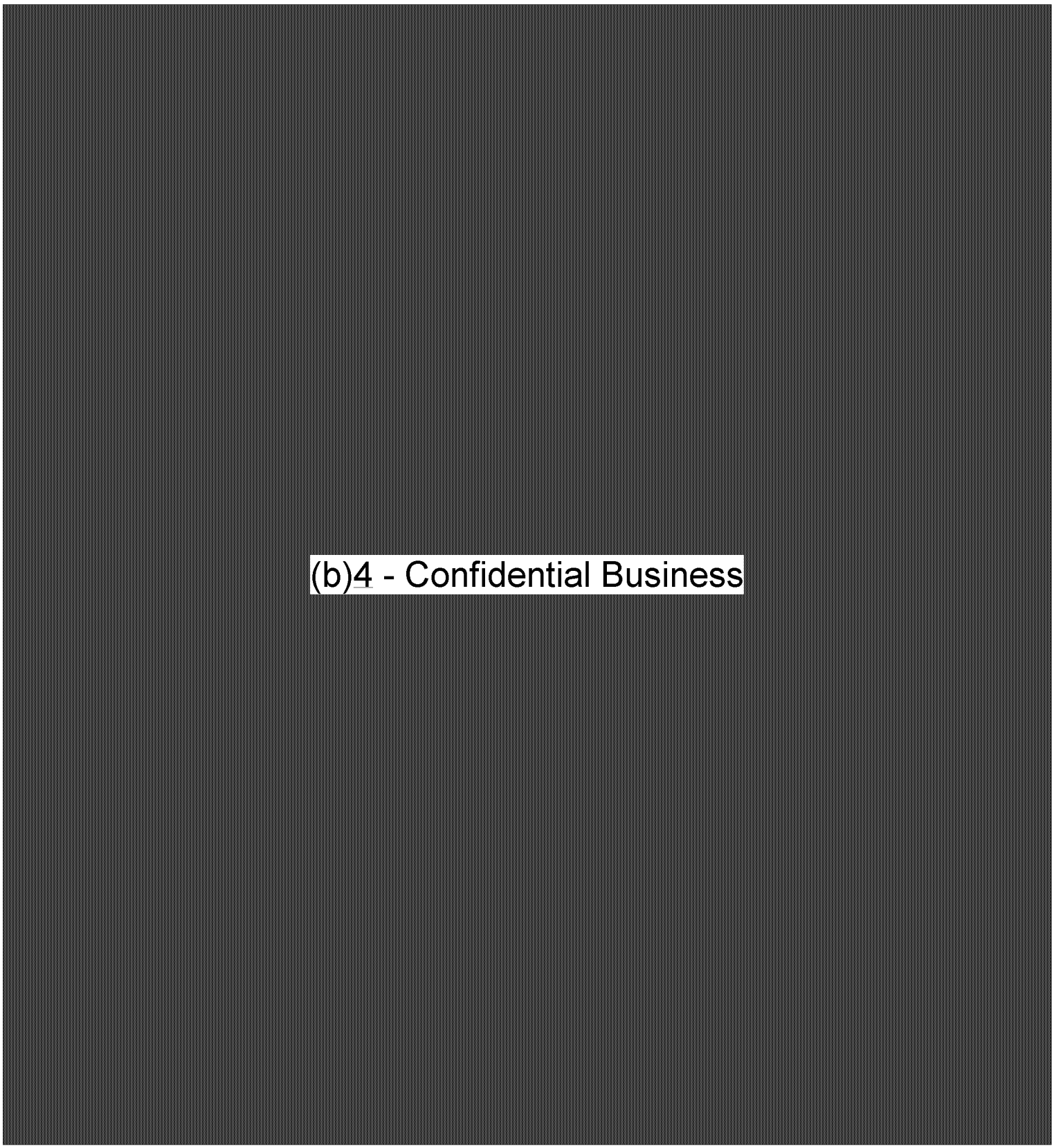
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3. Pharmacokinetics/Statistics:

The mean plasma concentrations of acyclovir at each time point after test and reference products are shown in Table 1. There is no significant ($\alpha = 0.05$) difference in mean concentrations between the formulations at any time after dosing. The time course of acyclovir concentration after the two products are plotted in Figure 1. The pharmacokinetic parameters are summarized in Table 2. There were no statistically significant differences between the formulations for any parameter. Based on the least squares means of the logarithmically transformed parameters, the AUC_{0-t} and AUC_{0-inf} for the test product were 3% and 1% higher than the respective estimates for the reference product. The C_{max} for the test product was 3% lower than that for the reference product and occurred 1% (1 minute) earlier. The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Acyclovir (Test)

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
2	(b)4 - Confidential Business		(b)4 - Confidential Business	
3				
21				

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The individual mean ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 3. The test/reference ratio for AUC_{0-t} ranged

from [redacted] (mean 1.079), AUC_{0-inf} ranged from [redacted] (mean 1.055), and for C_{max} ranged from [redacted] with a mean of 1.006.

Table 4 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from 0.77-0.95 (23 out of 24 values between 0.80 and 0.95) for test and 0.74-0.96 (22 out of 24 values between 0.80-0.96) for reference product.

The following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	91.0-116.0	91.02-115.51
$LNAUC_{0-inf}$	91.0-113.0	91.11-112.71
LNC_{max}	88.0-107.0	87.53-107.30

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. Statistical analysis of data did not show any significant treatment, period or sequence effect for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

Bioavailability of Acyclovir Oral Suspension, 200 mg/5 mL: Food Study

A. Objectives: (1) To compare the acyclovir plasma levels produced after the test formulation is administered following a standard meal with those produced after a marketed reference product is administered following a standard meal (2) To compare the acyclovir plasma levels produced after the test formulation is administered following a standard meal with those produced after administration of the test formulation following an overnight fast.

B. Study Sites and Investigators:

Clinical and Analytical Site: same as for fasting study
Principal Investi[redacted] (b)4 - Confidential Business
Project Director:
Protocol #10795A: Bioavailability of Acyclovir Oral Suspension, 200 mg/5 mL- Effect of Food Study; approved by the National Institutional Review Board [redacted] (b)4 - Confidential Business

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 06 1339, vol. 1.4
Study Dates: Period I June 13-15, 1995
Period II June 20-22, 1995
Period III June 27-29, 1995
Analysis Dates: July 1-27, 1995

C. Study Design:

The protocol was designed as a randomized, three-treatment crossover bioavailability study. The study was executed in three periods with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration, until 24 hours postdose each period. The subjects (who completed the study) were assigned as follows:

Subject number	Period I	Period II	Period III
1,10	B	A	C
2,8,13	B	C	A
3,12,14	A	C	B
5,7,16	C	B	A
6,9,15	A	B	C
11,17	C	A	B

A = Acyclovir Oral Suspension, 200 mg/5 mL following a standard meal; Barre National (A.L.Pharma); Dose = 400 mg/10 mL
B = Acyclovir Oral Suspension, 200 mg/5 mL following a standard meal; Burroughs Wellcome; Dose = 400 mg/10 mL
C = Acyclovir Oral Suspension, 200 mg/5 mL following an overnight fast; Barre National (A.L.Pharma); Dose = 400 mg/10 mL

Lot numbers of drug products administered in this study were the same as those used for the fasting study

D. Subject Selection:

Eighteen healthy subjects (2 males, 16 females) were enrolled in the study with essentially same inclusion and exclusion criteria as in the fasting study. They were subjected to same screening procedure and restrictions.

E. Study Procedure:

Treatments A and B: Subjects were given a standard breakfast after a fast lasting at least 10 hours. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, six fluid oz. of orange juice and eight fluid oz. of

whole milk. The breakfast was served 35 minutes prior to dosing. All subjects completed their entire meal within 30 minutes of being served with the exception of subject #13, who did not drink the milk served at period II. The drug was administered with 240 mL of water.

Treatment C: Subjects were given the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample Collection, Analytical methods, and Pharmacokinetics/Statistical Analysis:

Ten milliliters of venous blood were obtained in heparinized Vacutainers® at 0 (predose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours postdose. The samples were transferred to analytical facility on June 30, 1995. Analytical methods, acceptance criteria, and statistical analysis were the same as for fasting study.

G. Results:

1. Clinical:

Eighteen subjects entered the study. Sixteen subjects completed the study. Subject #4 (female) failed to return to complete periods II and III. Subject #18 (male) was withdrawn from the study on June 20, 1995 (entry of period II) due to multiple, pruritic, vesicular lesions observed on the dorsal surface of both lower arms. The subject stated that the vesicles were present after dosing I. The firm does not consider it to be drug related, no medication was given and the subject was instructed to follow-up with his private physician. Clinical vital signs were measured at predose, 4, and 24 hours postdose.

Adverse events:

Thirteen subjects reported experiencing a total of 28 adverse events following drug administration. The most commonly reported event headache required administration of acetaminophen to some of the subjects. Additionally, several subjects reported medication use between the confinement periods of the study.

Subj. #	Period	Product	Sign/Symptom
1	II	Test fed)	Headache Self administered 1x325 mg Excedrin
4	I	Test fast)	Headache

6	II	Ref	Headache, bilateral leg pain: self administered 4x325 mg Tylenol and 2x325 mg Aleve
	III	Test (fast)	Headache 2x325 mg Tylenol
7	III	Test (fed)	Headache, Diarrhea
8	II	Test (fast)	Diarrhea
	III	Test (fed)	Headache, insect bite 2x325 mg Tylenol
10	I	Ref	Diarrhea, Stomach cramps
11	II	Test (fast)	Cold symptoms 1x800 mg Amoxicillin on 2 days
	III	Ref	Rash on chest Benadryl
12	II	Test (fast)	Decreased diastolic blood pressure, headache, diarrhea
	III	Ref	Headache 2x325 mg Tylenol
13	I	Ref	Headache 2x325 mg Tylenol
	II	Test (fast)	Headache 2x325 mg Tylenol
	III	Test (fed)	Headache 2x325 mg Tylenol
14	II	Test (fast)	Headache
15	II	Ref	Nausea, Lightheaded
16	II	Ref	Loss of appetite Menstrual cramps; self administered Midol P.M.

Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation:

Subject #	Test result
4	low uric acid
6	low hematocrit
8	low hematocrit and hemoglobin
11	low hematocrit
13	low RBC count, hematocrit and high MCH
14	blood and RBC/HPF in urine
16	abnormal urinalysis

Deviations in the study:

No deviations from the scheduled phlebotomy time or in sample processing were reported.

Reassays:

Of the 912 samples assayed for this study, 25 samples were reassayed. Following samples were reassayed for the reasons shown against them:

# of samples	Reason for reassay
15	chromatographic interference
8	pharmacokinetic anomaly
2	to reexamine the presence of peak at the retention time of the drug

2. Analytical:

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3. Pharmacokinetics/Statistics:

The concentration of acyclovir measured at each time point after each product is summarized in Table 5. At 30 and 40 minutes after dosing, and from 2 to 10 hours postdose there were significant differences in acyclovir concentrations amongst the three treatments. These significant differences were due to lower

concentrations starting at 2 hours in treatment C (test-fasted). The time courses of acyclovir concentration after the three treatments are plotted in Figure 2.

Test formulation after a meal vs. reference formulation after a meal: When the test and reference formulations were administered after a meal, the least squares means for log transformed AUC_{0-t} and AUC_{0-inf} for test formulation were 2% and 1% lower than the respective means for reference formulation. The mean C_{max} for test product was 5% lower than that of the reference product and occurred 4% (5 minutes) earlier (Table 6).

Test formulation after a meal vs. test formulation after a 10 hour fast: The least squares means for log transformed AUC_{0-t} and AUC_{0-inf} after the meal were 34% and 26% higher respectively compared to 10 hour fasting. The mean C_{max} was 10% higher and 31% (30 minutes) later in test fed compared to test fasting conditions (Table 6).

Following are the ratios of the means of the pharmacokinetic parameters:

	Ratio of means (test/reference)
Test (Fed) vs. Reference (Fed)	
AUC_{0-t}	0.98
AUC_{0-inf}	0.99
C_{max}	0.95
Test (Fed) vs. Test (Fasted)	
AUC_{0-t}	1.34
AUC_{0-inf}	1.26
C_{max}	1.10

Ratios of means between test fed and reference fed are within acceptable limits.

In Vitro Dissolution Testing:

There is no USP or FDA method available for dissolution testing of acyclovir oral suspension. The agency has set following conditions for dissolution testing of acyclovir 200 mg **capsules**: Apparatus: 1, speed: 100 rpm; Medium: 900 mL water; Specifications: NLT (b)(4) Q) in 30 minutes

The firm has developed and validated a dissolution method for analysis of acyclovir suspension. The dissolution testing was done using apparatus 2 (paddle) at 50 rpm and 900 mL of 0.0847 N HCl as medium. Samples withdrawn at 60 minutes were analyzed for

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temperature. The dissolution analysis of acyclovir suspension, 200 mg/5 mL was shown to be precise, linear, specific, rugged and stability-indicating.

The firm has submitted comparative dissolution data for test and reference products using this method (Table 8). The drug products used in the dissolution tests were from the same lot used in the *in vivo* bioequivalence studies. The samples were pulled at 5, 15, 30, 45, and 60 minutes. The firm is proposing a specification of not less than (b)4(Q) in 60 minutes. The test and reference products pass the dissolution tests using this criteria.

Comments:

Fasting Study

1. Twenty-six subjects entered the study. One subject voluntarily withdrew from the study for personal reasons. One subject failed to return to the facility to complete period II. Samples from twenty-four subjects who completed the study were analyzed. Four subjects experienced adverse events like headache during the study for which no medication was required. Four subjects showed post-study laboratory results outside of the reference range and required follow-up.

2. There were no statistically significant differences between the formulations for any pharmacokinetic parameter. Based on the least squares means of the logarithmically transformed parameters, the AUC_{0-t} and AUC_{0-inf} for the test product were 3% and 1% higher than the respective estimates for the reference product. The C_{max} for the test product was 3% lower than that for the reference product and occurred 1% (1 minute) earlier. The 90% confidence intervals for log transformed data for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. There were no statistically significant treatment, period or sequence effect for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

3. The study results demonstrate that test product is bioequivalent to reference product.

Food Study

1. Eighteen subjects (2 males, 16 females) entered the study. One subject (female) failed to return to complete periods II and III. One subject (male) was withdrawn from the study at the entry of period II due to multiple pruritic, vesicular lesions observed on the dorsal surface of both lower arms. The firm does not consider it to be drug related, no medication was given and the subject was instructed to follow-up with his private physician. Thirteen subjects reported experiencing a total of 28 adverse events following drug administration. The most commonly reported event headache required administration of acetaminophen to some of the subjects. Additionally, several subjects reported medication (Excedrin, Aleve, Amoxicillin, Benadryl, Midol) use between the confinement periods of the study. Seven subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation.

2. When the test and reference formulations were administered after a meal, the least squares means for log transformed AUC_{0-t} and AUC_{0-inf} for test formulation were 2% and 1% lower than the respective means for reference formulation. The mean C_{max} for test product was 5% lower than that of the reference product and occurred 4% (5 minutes) earlier. The test/reference ratios for mean AUC_{0-t}, AUC_{0-inf}, and C_{max} are all within the 0.8-1.2 limit.

3. The least square means for log transformed AUC_{0-t} and AUC_{0-inf} were 34% and 26% higher respectively when the test drug was given with food compared to without food. The mean C_{max} was 10% higher and 31% (30 minutes) later in test fed compared to test fasting conditions.

Dissolution Testing

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Recommendations:

1. The in vivo bioequivalence study conducted under fasting conditions by Barre National, Inc. on its acyclovir oral suspension, 200 mg/5 mL, lot #PP 4816, comparing it to the

reference product Zovirax® oral suspension, 200 mg/5 mL, lot #4T2522 manufactured by Burroughs Wellcome has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Barre National's acyclovir oral suspension, 200 mg/5 mL is bioequivalent to the reference product Zovirax® oral suspension, 200 mg/5 mL manufactured by Burroughs Wellcome.

2. The *in vivo* bioequivalence study conducted under fed conditions by Barre National Inc. on its acyclovir oral suspension, 200 mg/5 mL, lot #PP 4816, comparing it to the reference product Zovirax® oral suspension, 200 mg/5 mL, lot #4T2522 manufactured by Burroughs Wellcome has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Barre National's acyclovir oral suspension, 200 mg/5 mL is similar to that of the reference product Zovirax® oral suspension, 200 mg/5 mL manufactured by Burroughs Wellcome.

3. The dissolution testing conducted on acyclovir oral suspension 200 mg/5 mL is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should however be done in 900 mL of **0.1N HCl** at 37°C using apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

> Not less than (b)4 of the labeled amount of Acyclovir in the dosage form is dissolved in **45 minutes**.

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

The firm should be informed of the above recommendations.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

PD INITIALED R.PATNAIK
PT INITIALED R.PATNAIK

/S/ Date 1/8/96

Concur: [redacted] /S/ Date 4/14/96

Keith Chan, Ph.D.
Director
Division of Bioequivalence

cc:ANDA #74738 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Dhariwal), Drug File, Division File

KRD/Draft: 040996; Final: 041296

Table 1

Acyclovir Plasma Concentrations (ng/mL) (N=24) in fasting study : Arithmetic Means and Standard Deviation (SD)

Time (h)	Test		Reference		Test/Ref	Signific. at p=0.05
	Mean	SD	Mean	SD		
0	0.0		0.0			
0.33	121.9	87.45	140.8	74.74	0.87	N.S.
0.67	335.0	148.6	364.5	139.9	0.92	N.S.
1	484.5	201.7	501.3	212.8	0.97	N.S.
1.33	544.5	195.9	558.9	241.5	0.97	N.S.
1.67	536.5	207.2	559.9	222.1	0.96	N.S.
2	510.2	182.0	548.9	209.9	0.93	N.S.
2.5	488.4	179.8	508.0	224.7	0.96	N.S.
3	430.8	151.1	448.8	199.1	0.96	N.S.
3.5	382.4	133.2	386.4	185.1	0.99	N.S.
4	360.4	145.7	340.2	156.8	1.06	N.S.
5	282.8	120.0	273.7	130.0	1.03	N.S.
6	214.3	86.76	196.8	88.57	1.09	N.S.
7	161.7	57.13	152.2	65.58	1.06	N.S.
8	133.4	46.93	123.6	51.14	1.08	N.S.
10	85.89	30.75	83.45	48.76	1.03	N.S.
12	54.02	30.38	49.69	35.49	1.09	N.S.
14	14.41	25.71	23.10	30.85	0.62	N.S.
16	12.10	24.27	8.950	20.46	1.35	N.S.
Parameter						
AUC_{0-t} (ng/mLxh)	2938	949.2	2940	1212	1.00	
AUC_{0-inf} (ng/mLxh)	3295	942.7	3312	1188	0.99	
C_{max} (ng/mL)	611	208	645	268	0.95	
T_{max} (h)	1.541	0.632	1.555	0.423	0.99	
Half-life (h)	4.053	1.42	4.249	1.543	0.95	
Rate constant (h^{-1})	0.1912	0.0626	0.1843	0.0652	1.04	

Table 2

Acyclovir Plasma Concentrations in the Fasting Study (N=24)
Pharmacokinetic Parameters: Least Square Means ± Standard Error

Parameter	Test	Reference	Test/Ref	Confidence Interval
AUC_{0-t} (ng/mLxh)	2938±159.6	2940±159.6	1.00	0.87-1.13
AUC_{0-inf} (ng/mLxh)	3295±159.4	3312±159.4	0.99	0.88-1.11
C_{max} (ng/mL)	611±27.05	645±27.05	0.95	0.85-1.05
Half-life (h)	4.053±0.214	4.249±0.214	0.95	
T_{max} (h)	1.541±0.0789	1.555±0.0789	0.99	
Rate constant (h^{-1})	0.1912±0.0075	0.1843±0.0075	1.04	
$LNAUC_{0-t}$ (Antiln)	7.9369±0.049 (2799)	7.9118±0.049 (2729)	1.03	0.91-1.16
$LNAUC_{0-inf}$ (Antiln)	8.0609±0.0438 (3168)	8.0476±0.0438 (3126)	1.01	0.91-1.13
LNC_{max} (Antiln)	6.3648±0.0419 (581)	6.3961±0.0419 (599.5)	0.97	0.88-1.07

Table 3

Test/Reference Ratios for Pharmacokinetic Parameters in the Fasting Study for Individual Subjects

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	2	[redacted]		
2	1			
3	2			
4	1			
5	1			
6	2			
8	1			
10	2			
11	2			
12	1			
13	1			
14	2			
15	2			
16	1			
17	1			
18	2			
19	1			
20	2			
21	1			
22	2			
23	2			
24	1			
25	1			
26	2			
Mean		1.079	1.055	1.006
Std Deviation		0.347	0.301	0.275
CV		32.14	28.50	27.34

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Table 4

AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects in Fasting Study

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1	(b)4 - Confidential Business	
2		
3		
4		
5		
6		
8		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		

Table 5

Acyclovir Plasma Concentrations (ng/mL) (N=16) in the Food Study: Arithmetic Means ± Standard Deviation (SD)

Time	Test-Fed	Ref-Fed	Test-Fasted			
h	A	B	C	A/B	A/C	B/C
0	0	0	0			
0.33	90.7±70.4	89.9±114	159.8±105	1.01	0.57	0.56
0.67	264.6±117	268.5±183	358.4±165	0.99	0.74	0.75
1	424.0±150	446.4±253	445.3±214	0.95	0.95	1.00
1.33	524.0±155	536.8±239	513.7±187	0.98	1.02	1.05
1.67	573.9±176	588.1±202	516.9±174	0.98	1.11	1.14
2	572.9±187	606.4±167	500.0±163	0.94	1.15	1.21
2.5	601.3±166	604.5±183	465.1±183	0.99	1.29	1.30
3	573.1±154	595.5±252	410.8±151	0.96	1.40	1.45
3.5	519.1±151	524.1±184	351.7±121	0.99	1.48	1.49
4	469.6±134	473.8±178	313.6±125	0.99	1.50	1.51
5	364.1±108	362.4±121	228.6±91	1.00	1.59	1.59
6	259.3±75	272.6±106	166.0±70	0.95	1.56	1.64
8	161.6±64	171.1±75	111.1±71	0.94	1.45	1.54
10	94.73±35	92.9±50	59.57±47	1.02	1.59	1.56
12	51.36±43	40.4±40	36.1±48	1.27	1.42	1.12
14	13.90±25	19.47±31	3.91±16	0.71	3.55	4.98
16	3.319±13	7.775±21	3.93±16	0.43	0.84	1.98
24	0	0	0	-	-	-
Parameters						
AUC_{0-t} (ng/mLxh)	3396±905	3483±1151	2551±847	0.98	1.33	1.37
AUC_{0-inf} (ng/mLxh)	3711±966	3759±1119	2976±980	0.99	1.25	1.26
C_{max} (ng/mL)	653±167	704±268	506±229	0.93	1.38	1.16
T_{max} (h)	2.11±0.66	2.19±0.64	1.60±0.64	0.97	1.32	1.36
$t_{1/2}$ (h)	3.05±0.67	2.94±0.82	3.71±2.27	1.04	0.82	0.79

- N=16

Table 6

Acyclovir Plasma Concentrations in the Food Study (N=16)
Pharmacokinetic Parameters: Least Square Means ± Standard Error

Parameter	Test-Fed	Ref-Fed	Test-Fasted			
	A	B	C	A/B	A/C	B/C
AUC$_{0-t}$ (ng/mL·h)	3306±155	3427±154	2495±154	0.96	1.32	1.37
AUC$_{0-\infty}$ (ng/mL·h)	3627±149	3705±148	2904±154	0.98	1.25	1.28
C_{max} (ng/mL)	639±36.2	695±36	596±36	0.92	1.07	1.16
T_{max} (h)	2.09±0.12	2.17±0.12	1.59±0.12	0.96	1.31	1.37
LnAUC$_{0-t}$ (Antiln)	8.07±0.048 (3191)	8.08±0.048 (3242)	7.77±0.048 (2384)	0.98	1.34	1.36
LnAUC$_{0-\infty}$ (Antiln)	8.16±0.041 (3513)	8.18±0.041 (3557)	7.93±0.042 (2783)	0.99	1.26	1.28
LnCmax (Antiln)	6.43±0.051 (619.1)	6.48±0.050 (653.4)	6.33±0.050 (561.6)	0.95	1.10	1.16

Table 7

Comparative Quantitative Composition of Acyclovir Suspension*

Ingredient	Test	Reference
Acyclovir USP	0.4% w/v	0.4% w/v
Methylparaben NF Propylparaben NF Microcrystalline Cellulose and Sodium CMC NF Glycerin USP (96%) Sorbitol Sol. USP (70%) Banana Flavor Purified Water	(b)4 - Confidential Business	

* 200 mg acyclovir/5 mL suspension
** Ingredient present, quantity unknown

Table 8. In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir Oral Suspension
Dose Strength: 200 mg/5 mL
ANDA No.: 74-738
Firm: Barre National Inc.
Submission Date: August 31, 1995
File Name: 74738SD.895

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 0.0847 N HCl Volume: 900 mL
Specifications: NLT (b)4 in 60 minutes
Reference Drug: Zovirax Oral Suspension (Burroughs Wellcome)
Assay Methodology: (b)4 - Confidential Business

II. Results of In Vitro Dissolution Testing:

Sampling Times (Min)	Test Product Lot #PP2816 Strength 200 mg/5 mL			Reference Product Lot #4T2522 Strength 200 mg/5 mL		
	Mean %	Range	%CV	Mean %	Range	%CV
5	42.3	(b)4 - Confidential Business	7.8	35.7	(b)4 - Confidential Business	14.2
15	64.5		5.1	62.0		10.0
30	81.2		4.2	84.0		7.3
45	89.8		3.8	93.6		3.7
60	94.8		3.1	97.7		2.3

Sampling Times (Min)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

Figure 1: Mean Acyclovir Plasma Levels

#135-03-10720

N = 24

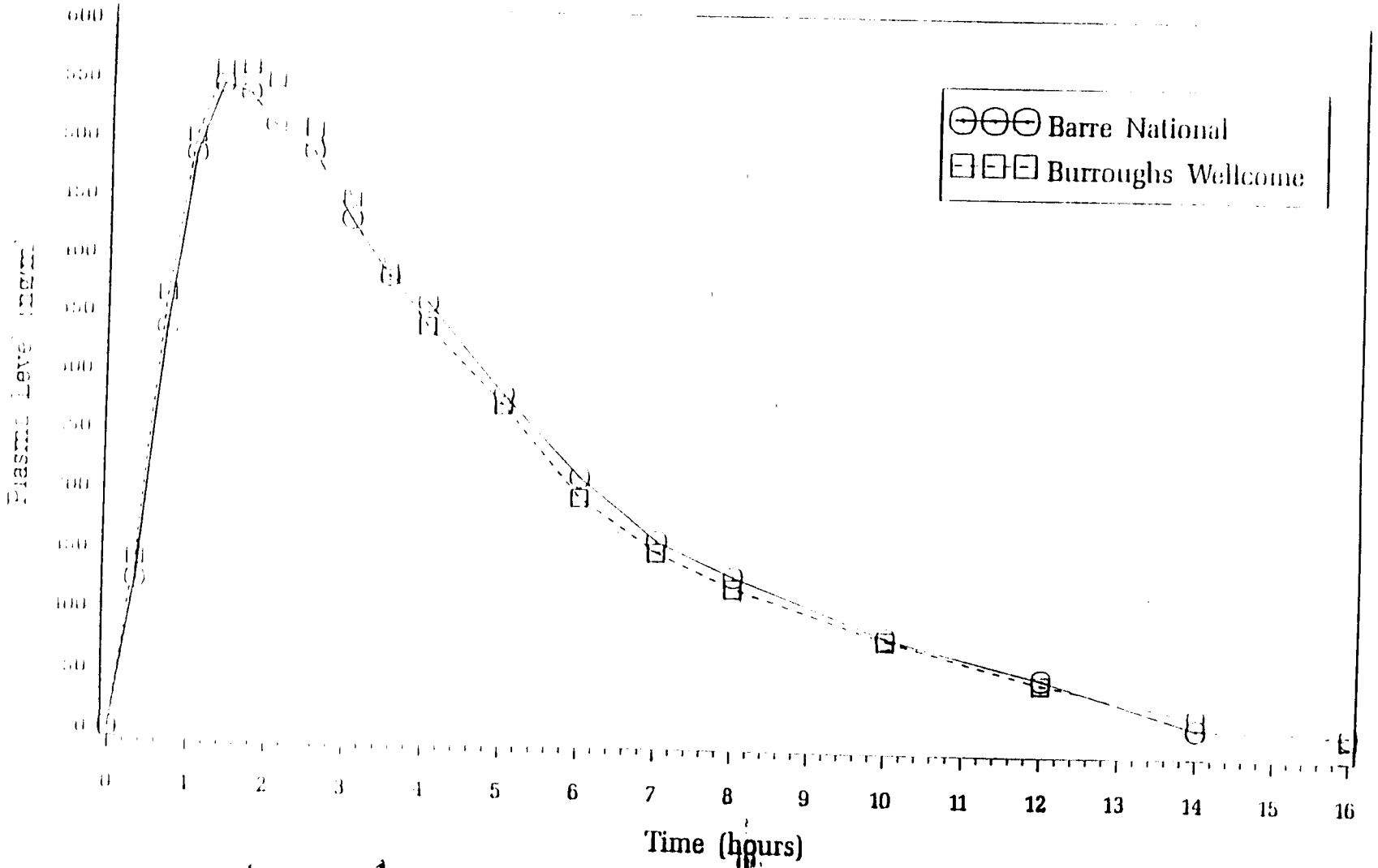

Figure 1

Figure 1: Mean Acyclovir Plasma Levels

#135 – 05 – 10795

N = 16

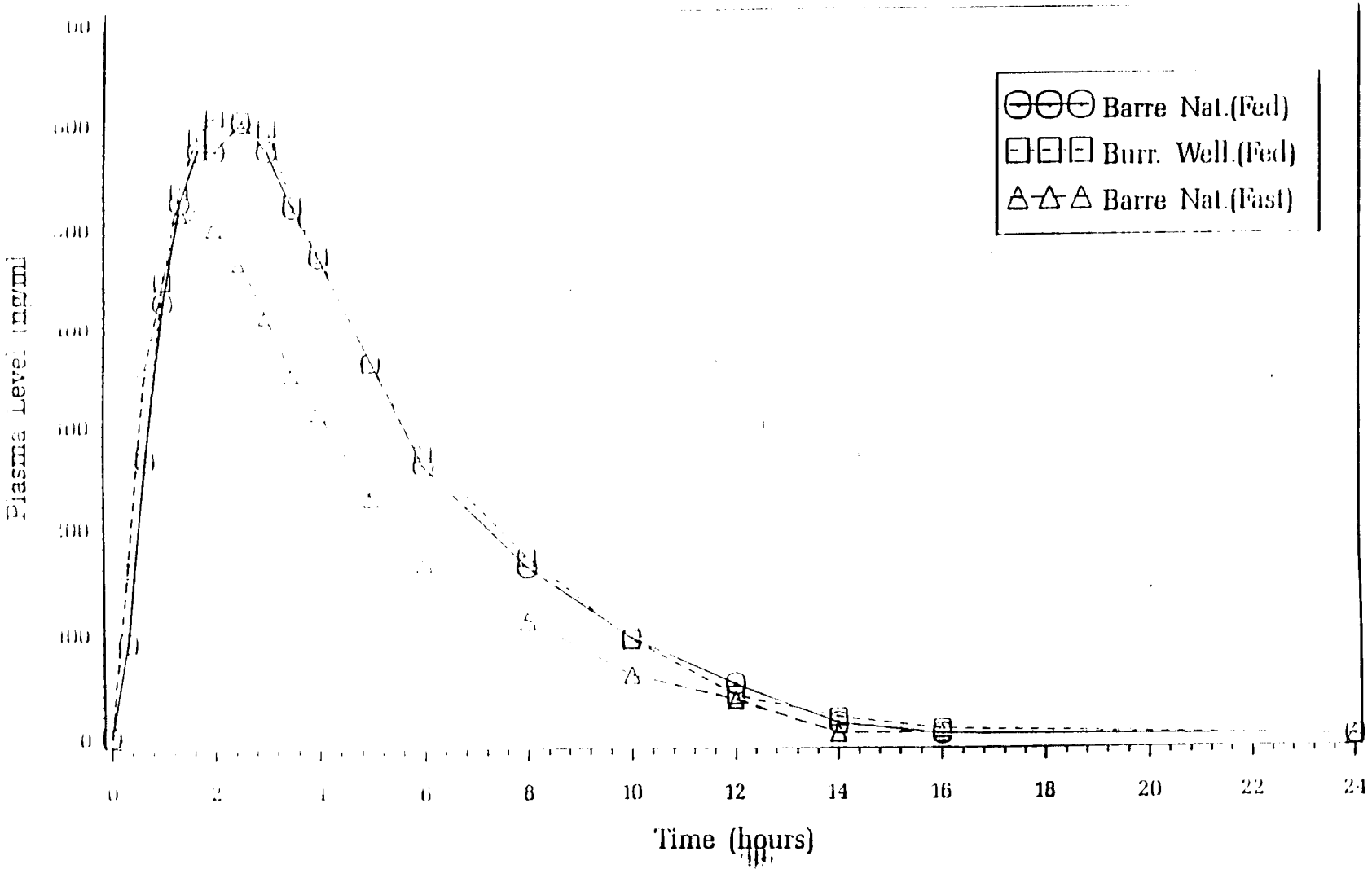

Figure 2