CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-870

Name: Acyclovir Tablets, 400 mg and 800 mg

Sponsor: Purepac Pharmaceutical Co.

Approval Date: June 5, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-870

CONTENTS

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-870

APPROVAL LETTER

ANDA 74-870

JUN -5 1997

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated March 22, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Tablets, 400 mg and 800 mg.

Reference is also made to your amendments dated June 6, 1996, August 22, 1996, November 11, 1996, and May 8, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Tablets, 400 mg and 800 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Tablets, 400 mg and 800 mg, respectively, of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

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

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

Sincerely yours,

D. L. Sporn 6/5/97

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

cc: ANDA #74-870
Division File
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HFD-600/Reading File
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HFD-210/BPoole

Endorsements:

HFD-647/NGregory/4.22.97

HFD-613/CHoppes/AVezza/5.10.97

HFD-647/SBasaran/5.22.97

HFD-617/TAmes/5.10.97

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APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-870

LABELING

SAMPLE

40-8806

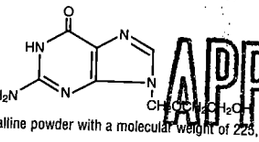
ACYCLOVIR TABLETS

Revised — May 1997

DESCRIPTION:
Acyclovir is an antiviral drug. Acyclovir tablets are formulations for oral administration. Each 400 mg tablet contains 400 mg of acyclovir and the inactive ingredients: crospovidone, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, and sodium starch glycolate.

Each 800 mg tablet contains 800 mg of acyclovir and the inactive ingredients: crospovidone, D&C yellow #10 HT aluminum lake, FD&C Blue #1 HT aluminum lake, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, and sodium starch glycolate.

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:



$C_8H_{11}N_5O_3$

Acyclovir is a white to off-white crystalline powder with a molecular weight of 225, 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 EBV[2] 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.

Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or 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/m^2 and 600 mg/m^2, 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 tablets are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir tablets are 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.

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 tablets are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS:

Acyclovir tablets are 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.

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 tablets are 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.[28]

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 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see 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 postimplantation 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 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 every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg (one 400 mg tablet) 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 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 (two 400 mg tablets or one 800 mg tablet) 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/1.73 m^2)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	> 10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	> 10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

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

HOW SUPPLIED:

Acyclovir Tablets are available as follows:

400 mg — Each unscored, white, round, flat faced beveled edge tablet imprinted with R on one side and 606 on the other side contains 400 mg of acyclovir, USP. Tablets are supplied in bottles of 100 (NDC 0228-2606-11), 500 (NDC 0228-2606-50), and 1000 (NDC 0228-2606-96).

800 mg — Each unscored, pastel green, oval tablet imprinted R 607 contains 800 mg of acyclovir, USP. Tablets are supplied in bottles of 100 (NDC 0228-2607-11), 500 (NDC 0228-2607-50), and 1000 (NDC 0228-2607-96).

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

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

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CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

40-8806

Revised — May 1997

NDC 0228-2606-11

PUREPAC

ACYCLOVIR
TABLETS

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:
Acyclovir, USP ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.

Lot No.:

JUN 5 1997
SAMPLE

3 0228-2606-11 7

USUAL DOSAGE: See accompanying package insert.
Store between 15° and 25°C (59° and 77°F).
Protect from light and moisture.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 11/96

NDC 0228-2606-50

PUREPAC

ACYCLOVIR
TABLETS

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

EACH TABLET CONTAINS:
Acyclovir, USP ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.

Lot No.:

JUN 5 1997
SAMPLE

3 0228-2606-50 6

USUAL DOSAGE: See accompanying package insert.
Store between 15° and 25°C (59° and 77°F).
Protect from light and moisture.
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 11/96

NDC 0228-2606-96

PUREPAC

ACYCLOVIR
TABLETS

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH TABLET CONTAINS:
Acyclovir, USP ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.

Lot No.:

JUN 5 1997
SAMPLE

3 0228-2606-96 4

USUAL DOSAGE: See accompanying package insert.
Store between 15° and 25°C (59° and 77°F).
Protect from light and moisture.
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 11/96

NDC 0228-2607-11

PUREPAC

ACYCLOVIR
TABLETS

800 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

USUAL DOSAGE: See accompanying package insert.
Store between 15° and 25°C (59° and 77°F).
Protect from light and moisture.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 11/96

EACH TABLET CONTAINS:
Acyclovir, USP ..... 800 mg
Dispense in a tight, light-resistant container as defined in the USP.

Lot No.:

SAMPLE

0228-2607-11

NDC 0228-2607-50

PUREPAC

ACYCLOVIR
TABLETS

800 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

USUAL DOSAGE: See accompanying package insert.
Store between 15° and 25°C (59° and 77°F).
Protect from light and moisture.
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 11/96

EACH TABLET CONTAINS:
Acyclovir, USP ..... 800 mg
Dispense in a tight, light-resistant container as defined in the USP.

Lot No.:

SAMPLE

0228-2607-50

NDC 0228-2607-96

PUREPAC

ACYCLOVIR
TABLETS

800 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

USUAL DOSAGE: See accompanying package insert.
Store between 15° and 25°C (59° and 77°F).
Protect from light and moisture.
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 11/96

EACH TABLET CONTAINS:
Acyclovir, USP ..... 800 mg
Dispense in a tight, light-resistant container as defined in the USP.

Lot No.:

SAMPLE

0228-2607-96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-870

LABELING REVIEWS

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

Date of Review: July 23, 1996

Date of Submission: March 22, 1996

Reviewer: Charlie Hoppes

ANDA Number: 74-870 Review Cycle: 1 (DRAFT)

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

Proprietary Name: none

Established Name: Acyclovir Tablets 400 mg and 800 mg

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

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

B. LABELING DEFICIENCIES

1. GENERAL

Revise your storage recommendations to read, "Store between 15° and 25°C (59° and 77°F)", on all labels and labeling.

2. CONTAINER (100s, 500s, and 1000s):

See General comment.

3. INSERT

a. General Comments

i. Use the abbreviation "mcg" rather than "µg" throughout your insert labeling.

ii. Italicize the terms "*in vitro*" and "*in vivo*" where they appear in your insert labeling.

b. DESCRIPTION

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

ii. Make the following revisions in the last paragraph:

a) ...a white to off-white crystalline...

b) Delete the word "———".

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

Delete the third paragraph.

d. INDICATIONS AND USAGE (Genital Herpes Infections, *Recurrent Episodes*)

Make the following revision in the first line, "...studies[16,26-32]...".

e. CONTRAINDICATIONS

...of the formulation. [singular]

f. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, Impairment of Fertility - Revise the last sentence of the first paragraph to read:

...schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

ii. Pediatric Use

...in pediatric patients less...

g. DOSAGE AND ADMINISTRATION

Delete reference to the capsule dosage form, e.g., "... ———————...", throughout this section.

h. HOW SUPPLIED

i. Revise your storage recommendations to read, "Store between 15° and 25°C (59° and 77°F)".

ii. We note that on the Master Formula Card (on page 3508) you describe your 400 mg tablet as "...imprinted w/'R' on one side and '606' on the other side". Please revise your description of the 400 mg tablet in this section to include this information.

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

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?		x	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		x	

Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	

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

NOTE TO CHEMISTRY REVIEWER:

See GENERAL comment. Do you concur?

FOR THE RECORD:

1. This review was based on the labeling of ZOVIRAX® (Burroughs Wellcome: Approved 9/7/95; Revised 5/95). This is a supplement for NDA 20-089/S-005 to provide a caplet dosage form. This is the same text as S-004, which we had previously used as our guidance, however, it is in FPL, rather than draft print-out.

2. Dispensing -

   USP: Not USP item.
   NDA: Tight, light-resistant
   ANDA:same

   Storage -

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

   ANDA: Requested revision to: Store between 15° and —°C(59° and —°F). Protect from light and moisture.

3. Patents/Exclusivity

   Patent expires 4/22/97. Purepac has indicated that they will not market prior to this date. No exclusivities are effective.

4. Components/Composition

Inactives are correct in DESCRIPTION section. C&C statements found on pages 3157 and 3158, VOL 1.6.

5. Container/Closure (Volume 1.7)

100s - HDPE with CRC
500s - HDPE with non-CRC
1000s - HDPE with non-CRC

6. Fasting and non-fasting BE studies were done. The insert mentions no food effect -

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

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

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

8. Comment made regarding tablet imprinting for the 400 mg strength. Otherwise correct as described in the HS section per page 3508 vol. 1.7 (400 mg tab) and 3553 (800 mg tab).

Reviewer — Date: 7/26/96

Acting Team Leader,
Labeling Review Branch — Date: 7/26/96

cc: ANDA 74-870
Division File
HFD-613/CHoppes/AVezza (no cc)
njg/7/25/96/x:\new\...\74870na1.1
review

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

ANDA Number: 74-870 Date of Submission: November 11, 1996

Applicant's Name: Purepac Pharmarmaceutical Co.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

INSERT

1. DESCRIPTION

   We note that magnesium stearate is listed in this section as an inactive ingredient. The Master Formula Cards submitted in this amendment (p 45 [400 mg] and p 107 [800 mg]) do not include this inactive ingredient. Please revise your labeling if magnesium stearate is no longer present in your product and/or comment.

2. CLINICAL PHARMACOLOGY (Pharmacokinetics)

   Make the following revision in the fourth paragraph, "In another study, the influence...", (delete " ———).

3. ADVERSE REACTIONS (Observed During Clinical Practice, *Nervous*)

   ...paresthesia, seizure, somnolence...

Please revise your package insert labeling, as instructed above, and submit final print.

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

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

Adolph Ozza for /

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

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?		x	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	

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

NOTES/QUESTIONS TO THE CHEMIST:

See comment under DESCRIPTION. Do you concur?

---

1. This review was based on the labeling of ZOVIRAX® (Burroughs Wellcome: Approved 1/8/97; Revised 5/96). This is a supplement for NDA 20-089/S-010 to include a new ADVERSE REACTION.

2. Dispensing -

USP: Not USP item.
NDA: Tight, light-resistant
ANDA:same

Storage -

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

ANDA: Firm has made the requested revision to: Store between 15° and —°C(59° and —°F). Protect from light and moisture.

3. Patents/Exclusivity

Patent expires 4/22/97. Purepac has indicated that they will not market prior to this date. No exclusivities are effective.

4. Components/Composition

See comment under DESCRIPTION and the note to the chemist.

5. Container/Closure (Volume 1.7)

100s - HDPE with CRC
500s - HDPE with non-CRC
1000s - HDPE with non-CRC

6. Fasting and non-fasting BE studies were done. The insert mentions a "no food effect" -

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

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

Bio was found acceptable in a review dated 1/15/97.

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

8. Tablet imprinting and scoring configuration are consistent between DESCRIPTION section and the Master Formula Cards submitted in this amendment (p 45 [400 mg] and p 107 [800 mg]).

9. Container labels satisfactory in FPL as of November 11, 1996 amendment.

Date of Review: March 5, 1997

Date of Submission: November 11, 1996

Primary Reviewer: Charlie Hoppes **Date:** 3/6/97

Team Leader: John Grace **Date:** 3/11/97

---

cc:

ANDA 74-870
DUP/DIVISION FILE
HFD-613/CHoppes/JGrace (no cc)
njg/3/6/97/X:\NEW\FIRMSNZ\PUREPAC\LTRS&REV\74870NA2.L
Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

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

ANDA Number: 74-870

Date of Submission: May 8, 1997

Applicant's Name: Purepac Pharmarmaceutical Company

Established Name: Acyclovir Tablets, 400 mg and 800 mg

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels 400 mg & 800 mg (100s, 500s & 1000s): Satisfactory in final print as of the 11/11/96 submission.

Professional Package Insert Labeling: Satisfactory in final print as of the 5/8/97 submission.

Revisions needed post-approval:

INSERT

CLINICAL PHARMACOLOGY (Pharmacokinetics)

Upon further review, we request you add the following as the third paragraph:

A single oral dose bioavailability study in 23 normal volunteers showed that acyclovir capsules 200 mg are bioequivalent to 200 mg acyclovir in aqueous solution; and in a separate study in 20 volunteers, it was shown that acyclovir suspension is bioequivalent to acyclovir capsules. In a different single-dose bioavailability/bioequivalence study in 24 volunteers, one acyclovir 800 mg tablet was demonstrated to be bioequivalent to four 200 mg acyclovir capsules.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 18-829

NDA Drug Name: Zovirax®

NDA Firm: Glaxo Wellcome Inc.

Date of Approval of NDA Insert and supplement #:S-010-Approved 1/8/97; Revised 5/96.

Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: ZOVIRAX® (Glaxo Wellcome)

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x

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

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

FOR THE RECORD

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

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

3. Package/market size-

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

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

   ANDA:

   400 mg tablet - 100s, 500s & 1000s
   800 mg tablet - 100s, 500s & 1000s

4. Storage recommendations:

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

5. Dispensing recommendations:

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

6. Components/Composition

The list of inactive ingredients in the DESCRIPTION section is consistent with firm's components and composition statements.
[Vol. 2.1, p. 4, 42 & 106]

7. Container/Closure (Volume 1.7)

100s - HDPE with CRC
500s - HDPE with non-CRC
1000s - HDPE with non-CRC

8. The tablet imprints described in the HOW SUPPLIED section is consistent with the firm's physical description of their tablets in the application.
[Vol. 2.1, section 6]

9. Bioequivalence/Pharmacokinetic data

-Bio. acceptable: date 1/15/97 [Vol. 2.1]
-A waiver was granted for the 400 mg tablet.
-Both fasting & fed studies were done.
-Fasting study: results from bio. review of 6/19/96
    -No statistically significant differences were found in any of the pharmacokinetics indices.
    -The ANDA & RLD t1/2 were comparable to each other & to the insert labeling [ANDA t1/2-4.65hr, RLD t1/2-4.65 hr, insert t1/2-2.5 to 3.3 hr]
-Fed study: results from bio. review of 6/19/96
    -Cmax decreased and Tmax increased.
    [The Bio. Reviewer indicated that the observed food effect for the test product will be reported to the Division of Labeling, since this runs counter to the Innovator's labeling which stated that in a small, 6-subject study the influence of food on the absorption of acyclovir was not apparent]. See FTR from previous review below.
    [Vol. B1.1]

10. The following information is from a previous reviews/reviewer's FTR.

a. The insert mentions no food effect -

In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent. Previous reviews of other BE studies have shown that food increases the AUC and Cmax by as much as 40 to 60% for both generic and reference product. Both these parameters were increased after food for the studies submitted to this ANDA as well. The DAVDP has been made aware of the food effect findings and a recommendation to change the Zovirax® labeling has been made.

b. It was decided in a meeting between OGD and DAVDP that the issue of generic firms participation in the Pregnancy Exposure Registry should be based on BW's

decision. This decision was forwarded to the Division of Antiviral Drug Products on 5/1/96 - that generic products not be allowed to refer to the pregnancy registry.

Date of Review: May 13, 1997

Date of Submission: May 8, 1997

Primary Reviewer
Jacqueline White, Pharm.D.

5-15-97
Date

Secondary Reviewer

5/15/97
Date

Acting Team Leader,
Labeling Review Branch

5/16/97
Date

cc: ANDA 74-870
Division File
x:\new\...\74870ap.1
review

Endorsements:
HFD-613 JWhite
HFD-613 CHoppes
HFD-613 JGrace

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-870

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA 74-870

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 07207

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies, that to the best of it knowledge, U.S. Patent No. 4,199,574 will expire on April 22, 1997 and the indication of varicella infections (chickenpox) expired on February 26, 1995.

Innovator: Burroughs Wellcome - Zovirax®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir

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

9. AMENDMENTS AND OTHER DATES:
Firm: 3/22/96 - Original. Subject of this review.
6/6/96 - NC, Bio. information.
8/22/96 - Response to Bio. letter.

FDA: 4/10/96 - Acknowledgment.
6/18/96 - Bio. review, unacceptable.
7/5/96 - Bio. letter.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

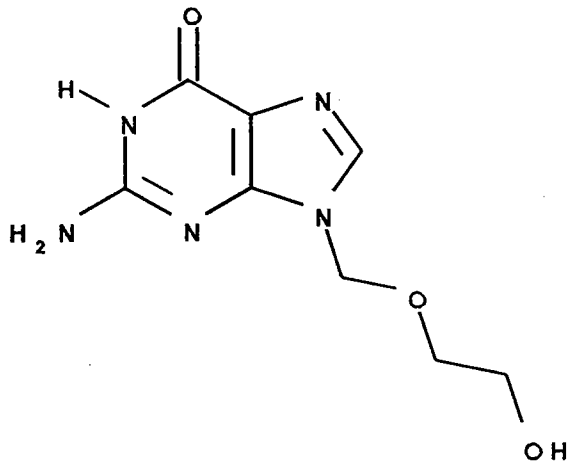
13. DOSAGE FORM
Tablet

14. POTENCIES
400 mg & 800 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

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



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

16. RECORDS AND REPORTS

N/A

17. COMMENTS

a. DMF ——, DMF —— and DMF —— listed on 356h with no reference or LoA in jacket.

b. Composition:

(1) [redacted]

(2) [redacted]

c. Active Ingredient:

(1) [redacted]

(2) [redacted]

d. Manufacturing and Processing:

[redacted]

e. Container/Closure System:
Need information on bulk package.
f. Stability:
Stability report needs formulation.
g. Container and Insert labeling not satisfactory.
h. Establishment Inspection request sent 3/29/96, pending.
I. Bioequivalence assigned to Jenny Lee on 9/6/96, pending review.

DMF and method validation acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (see item 17)

19. REVIEWER: Norman Gregory

DATE COMPLETED: 10/9/96

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1 (pp 4-9)

34. BIOEQUIVALENCY STATUS - Incomplete
Firm submitted *in-vivo* bioequivalenc study for 800 mg tablet, waiver of *in-vivo* bioequivalenc study for 400 mg tablet and *in-vitro* dissolution for 400 mg and 800 mg tablets. Bio sent letter on 7/5/96, firm responded on 8/22/96. Assigned to Jenny Lee on 9/6/96.

*** Pending review.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory (p. 4496, Orig.)
Categorical Exclusion requested. Confirm that they are in compliance with all Federal, state and local environmental laws.

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes___X___
No _____

If no, explain reason(s) below:

cc: ANDA #74-870
DUP Jacket
FIELD COPY
Division File

Endorsements:

HFD-647/NGregory/10.9.96 10/17/96

HFD-647/JSimmons/10.10.96 10.17.96

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NOT APPROVABLE (MAJOR)

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc:

ANDA 74-870
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/NGregory 10/17/96
HFD-647/JSimmons 10.17.96
HFD-617/TAmes
HFD-640/FHolcombe (final only)

CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 2

2. ANDA 74-870

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 07207

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies, that to the best of it knowledge, U.S. Patent No. 4,199,574 will expire on April 22, 1997 and the indication of varicella infections (chickenpox) expired on February 26, 1995.

Innovator: Burroughs Wellcome - Zovirax®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir

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

9. AMENDMENTS AND OTHER DATES:

Firm:
- 3/22/96 - Original.
- 6/6/96 - NC, Bio. information.
- 8/22/96 - Response to Bio. letter.
- 11/11/96 - Response to 1st def. letter (chem. & labeling). Subject of this review.
- 5/8/97 - Response to labeling comments.

FDA:
- 4/10/96 - Acknowledgment.
- 6/18/96 - Bio. review, unacceptable.
- 7/5/96 - Bio. letter.
- 10/30/96 - 1st def. letter (chem. & labeling).
- 1/7/97 - Bio. review, acceptable.
- 1/15/97 - Bio. letter.
- 5/6/97 - Labeling comments faxed.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

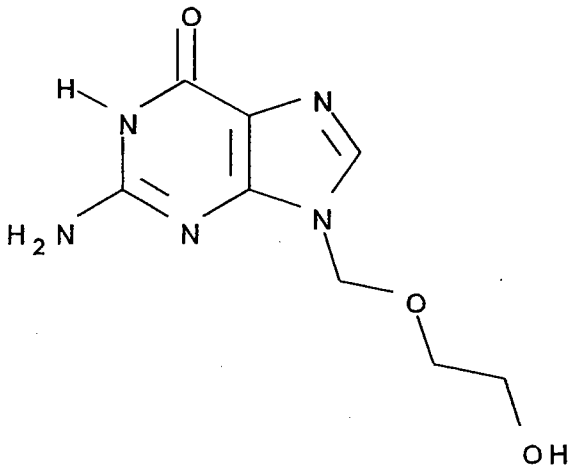
[redacted]

13. DOSAGE FORM
Tablet

14. POTENCIES
400 mg & 800 mg

15. CHEMICAL NAME AND STRUCTURE

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



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

16. RECORDS AND REPORTS
N/A

17. COMMENTS
DMF, labeling, EER, and method validation acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
Norman Gregory

DATE COMPLETED:
4/22/97 (chem.)
5/13/97 (labeling)

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

33. ESTABLISHMENT INSPECTION - Satisfactory
Sent for applicant and manufacture of active ingredient on 3/29/96. Resent 4/22/97. Acceptable for all on 4/29/97.

34. BIOEQUIVALENCY STATUS - Satisfactory
Bioequivalence studies (fasting and fed) for 800 mg tablet (Lot #PI-895) and *in vitro* dissolution testing on 400 mg tablet (Lot #PI-905) and 800 mg tablet (Lot #PI-895) acceptable on 1/7/97 by J. Lee.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory (p. 4496, Orig.)
Categorical Exclusion requested. Confirm that they are in compliance with all Federal, state and local environmental laws.

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes___X___
No _____

If no, explain reason(s) below:

cc: ANDA #74-870
FIELD COPY
Division File

Endorsements: 5/22/97

HFD-647/NGregory/5.22.97

HFD-647/SBasaran/5.22.97 S. Basaran 5/22/97

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APPROVAL

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2 (DMF Checklist)

ANDA APPROVAL SUMMARY

ANDA: 74-870 DRUG PRODUCT: Acyclovir DOSAGE FORM: Tablet

FIRM: Purepac Pharmaceutical Co. STRENGTH: 400 mg & 800 mg

CGMP STATEMENT/EIR UPDATE STATUS: Sent for applicant and manufacture of active ingredient on 3/29/96. Resent 4/22/97. Acceptable for all on 4/29/97.

BIO STUDY: Bioequivalence studies (fasting and fed) for 800 mg tablet (Lot #PI-895) and *in vitro* dissolution testing on 400 mg tablet (Lot #PI-905) and 800 mg tablet (Lot #PI-895) acceptable on 1/7/97 by J. Lee.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Active Ingredient: N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.

Finish Dosage Form: Methodology suitable for regulatory purposes from Philadelphia District on 7/17/96.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Protocol: Satisfactory.

Exp.Date: 24 months - 40°C, 75% R.H., 3 months and R.T. (25°C - 30°C), 3 months, smallest and largest container/closure system, 1 lot each strength. **Lot #PI-905** (400 mg) and **Lot #PI-895** (800 mg).

Container/closure system the same.

LABELING: Container: Satisfactory in FPL (100's, 500's & 1000's).
Insert: Satisfactory in FPL.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

_____ units _____ of 400 mg tablets (Lot #PI-905) and
_____ units _____ of 800 mg tablets (Lot #PI-895),
source of NDS _____, ok.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

_____ units _____ of 400 mg tablets (Lot #PI-905) and
_____ units _____ of 800 mg tablets (Lot #PI-895),
same process.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

_____ units _____ and _____ units _____ of 400 mg tablets and _____ units _____ and _____ units _____ of 800 mg tablets.

CHEMIST: Norman Gregory 5/22/97 DATE: 5/22/97

SUPERVISOR: Team Leader S. Bozo 5/22/97 DATE: 5/22/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-870

BIOEQUIVALENCE REVIEWS

JUN 18 1996

Acyclovir tablet
400 mg & 800 mg
NDA #74-870
Reviewer: J. Lee
74870SDW.396

Purepac Pharmaceutical Co.
Elizabeth, New Jersey
Submission date:
March 22, 1996
June 6, 1996

Review of Fasting and Fed in-vivo Bioavailability Studies, Dissolution Testing Data, and a Request for Waiver

Introduction:

Acyclovir is an antiviral drug used in the treatment of acute episodes and the management of recurrent episodes of genital herpes . It is also used for the treatment of herpes zoster (shingles) and chickenpox (varicella). Acyclovir is poorly absorbed after oral administration, with peak plasma levels occurring at about 1.5 hours after dosing. The elimination half-life is approximately 2.5-3.3 hours.

Objective:

To determine the relative bioavailability of 800 mg acyclovir tablets after administration of single doses to healthy male subjects under both fasting and fed conditions.

Fasting Study

Study Design:

The clinical study (——— P95-246, ——: 10-05-95) was conducted at ——————— in ———————, under the supervision of ———————, Pharm. D., Principal Investigator, and ———————, M.D., Medical Investigator.

Thirty male volunteers and two alternates between the ages of 18-45 years and within 15% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, clinical chemistry, HIV 1 & 2, urinalysis, and urine drug screen].

Those with any of the following conditions were excluded:

- presence of a clinically significant disorder involving cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease.
- history of allergic responses to acyclovir or related drugs.

- user of tobacco products.
- volunteers who reported taking any Rx medication in the 14 days prior to period I dosing.

OTC medications were not allowed within 7 days of the first drug administration. There was to be no alcohol or caffeine consumption at least 48 hours prior to drug administration and during the blood sampling periods.

The study was designed as a randomized, two-way crossover study with a 7 day washout period between dosings. Treatments consisted of a single 800 mg dose of the following:

A. Acyclovir
800 mg tablet, batch #PI-895
Purepac Pharmaceutical
expiry date: 09/97

B. Zovirax®
800 mg tablet, batch #5P2315
Burroughs Wellcome Co.
expiry date: 07/97

Thirty-two subjects were dosed according to the following schedule:

	Period I 10/14/95	Period II 10/21/95
sequence I	A	B
sequence II	B	A

sequence I - subj. # 1, 3, 5, 8, 9, 10, 12, 16, 21, 23, 24, 25, 26, 27, 30, 31

sequence II - subj. #2, 4, 6, 7, 11, 13, 14, 15, 17, 18, 19, 20, 22, 28, 29, 32

All 32 volunteers successfully completed the study.

After an overnight fast, subjects were given a 800 mg dose of acyclovir with 240 ml of water. Fasting continued for at least 4 hours post-dose. Blood samples (10 ml) were drawn in heparinized Vacutainers at 0 (pre-dose), 20, 40, 60, 80, and 100 minutes; and at 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours. All sampling times were within 2 minutes of scheduled time, except for several minor instances. Sampling deviations are noted on page 22 of the Clinical Final Report Section. All AUC calculations were based on the actual phlebotomy times.

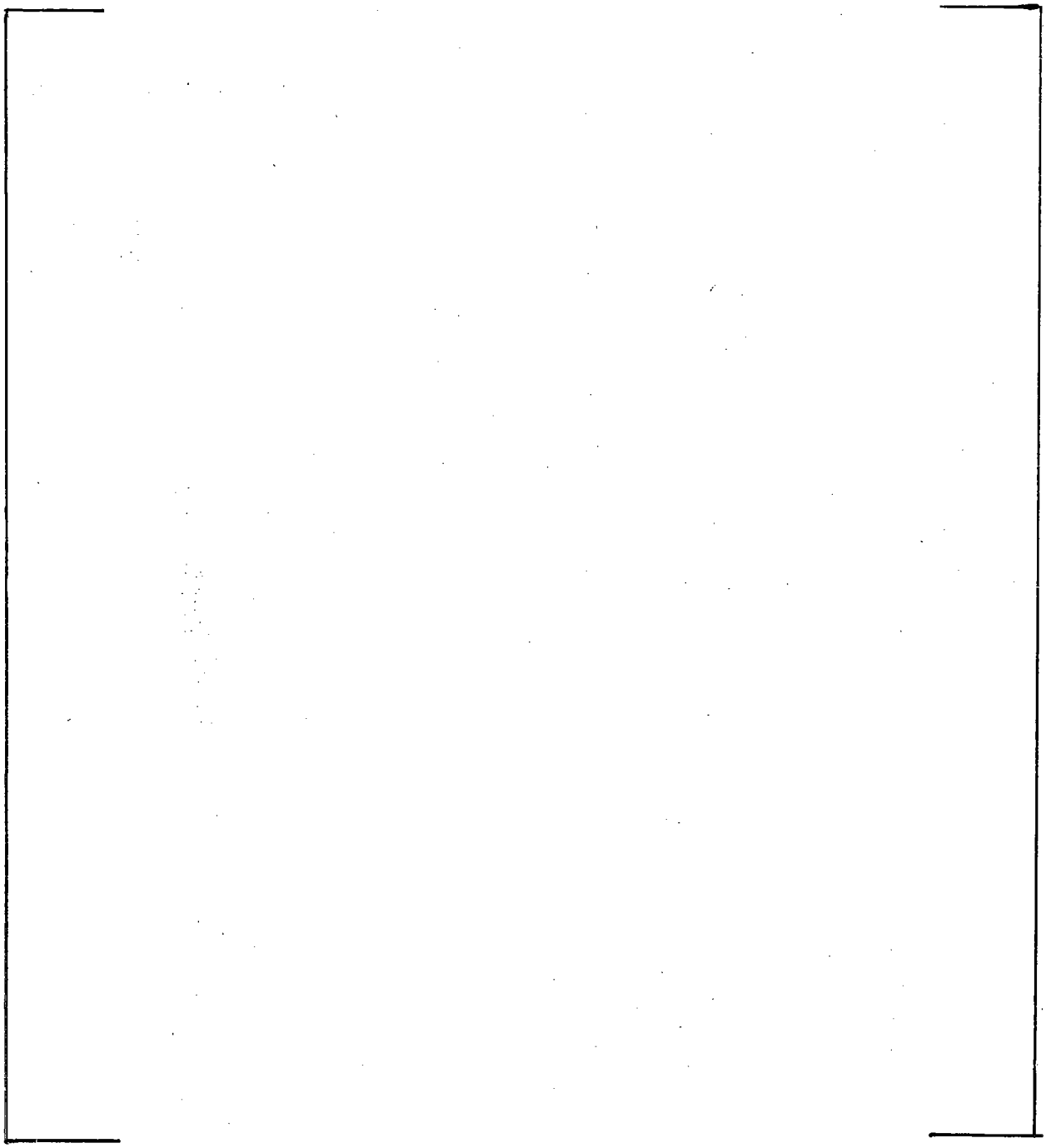
The samples were cold centrifuged and the resulting plasma transferred into duplicate polypropylene tubes and frozen at $\leq 20^{\circ}C$ pending shipment to the analytical facility.

There were ten reported instances of 'adverse events' during the study. Headache (reported by 3 subjects) was the only event that was judged possibly related to the study drug. Two instances

were attributed to the test product; one to the reference drug. The adverse events summary is attached.

There were four minor deviations from the protocol requirement of no OTC medications within 7 days of period I dosing. These medications (page 20, Clinical Report) were not expected to interfere with the integrity of the study.

Analytical: [Not for release under FOI]



Reported recovery data for acyclovir:

——————— mcg/ml (n=12)
——————— mcg/ml (n=12)

Recovery data for the internal standard:

—— % (n=24)

Zero hour samples reportedly showed no quantifiable interference at the retention time of the drug peak/IS.

Data Analysis:

The statistical analyses were performed by ——————— of ——— Plasma data was analyzed by an analysis of variance procedure (SAS-GLM ver. 6.10) and the F-test to determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. The eliminate rate constant, Ke, could not be calculated for several subjects; consequently, the $t_{½}$ and AUC_{inf} was not calculated for those subjects. All subjects enrolled in the study completed the study.

Results:

No statistically significant differences were found in any of the pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed for any of the bioavailability parameters. There was 7.5% difference between the test and reference formulations for plasma levels of acyclovir in AUC_{0-t} and AUC_{inf}. The Purepac product produced a 5% higher C_{max} than the Burroughs-Wellcome product. The protocol stated that only the samples from the original 30 subjects would be analyzed, except in case of dropouts. Since the laboratory inadvertently analyzed the samples from all the subjects, the valid statistical analyses should contain all 32 subjects. The 90% shortest confidence intervals for acyclovir, using least squares means, are presented below:

		90% CI
original scale	AUC_{0-t}	[96.5; 118.7]
	AUC_{inf}	[94.6; 120.5]
	C_{max}	[94.6; 115.9]
ln-transformed scale	AUC_{0-t}	[97.1; 119.4]
	AUC_{inf}	[94.9; 121.0]
	C_{max}	[95.0; 118.2]

Mean plasma level data and pharmacokinetic summaries are attached.

Fed Study

Study Design:

The clinical and analytical facilities for this study were the same as that employed in the fasting study. The inclusion and exclusion criteria for subject selection were also the same. ——— ———, Pharm. D., ———————, was included as a sub-investigator in this study.

The study (P95-247) was a randomized, three treatment, threee period, six sequence crossover. Treatments consisted of the same two batches of test and reference products (used in the fasting study). A 7 day washout period separated the dosings.

Eighteen subjects were dosed according to the following regimen:

	period I 01/06/96	period II 01/13/96	period III 01/20/96
sequence I	A	B	C
sequence II	B	C	A
sequence III	C	A	B
sequence IV	C	B	A
sequence V	B	A	C
sequence VI	A	C	B

sequence I - subj #6, 8, 9
sequence II - subj #2, 3, 17
sequence III - subj #15, 16, 18
sequence IV - subj #1, 5, 11
sequence V - subj #4, 12, 13
sequence VI - subj #7, 10, 14

Treatment A: 1 x 800 mg acyclovir tablet (Purepac) following an overnight fast
Treatment B: 1 x 800 mg acyclovir tablet (Purepac) following a standard breakfast*
Treatment C: 1 x 800 mg Zovirax® tablet (Burrought-Wellcome) following a standard breakfast*.

*standard breakfast:
1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
180 ml of orange juice
240 ml of whole milk

All 18 subjects enrolled in the study completed the study.

After an overnight fast, subjects on treatment B or C were served a standard breakfast 30 minutes before dosing. Fasting continued for at least 4 hours post dose. The sampling schedule followed

that used in the fasting study.

Deviations from the blood sampling schedule are noted on page 1762 of the Clinical Final Report. All blood draws were on time in periods II and III. In period I, there was a 2 minute late draw for one subject and for all subjects at the 14 hour blood draw, there was a 38-39 minute delay for some unexplained reason. All AUC calculations were based on the actual phlebotomy times.

There were a total of 26 adverse events reported, six of which (dizziness, headache, heartburn) were possibly related to the study drug. None were serious. The adverse events summary is attached.

Analytical:

The analytical method and validation was the same as that used in the fasting study.

The stability and recovery data are the same as reported in the fasting study review.

There was no reported quantifiable interference at the retention time of the drug peak or internal standard for the zero hour samples.

Data Analysis and Results:

Means, standard deviations and CV%s were calculated for AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, kel, $t_{½}$ and concentrations at each sampling time point (see attached tables). Areas under the curve showed ≤6.7% difference for T/R (fed) and a 3.3% difference in C_{max} ratios. There was a food effect observed for T(fed)/T(fasted) in both AUCs and C_{max}. The results are summarized in appended tables.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study,

using several media since there is no current USP dissolution method. Only the current FDA-recommended method will be summarized.

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Purepac product was 100.6% of label claim; range = ——— % (1.6% CV).

Batch Size:

The executed batch record for the bio-batch of Purepac's 800 mg acyclovir shows a yield of approximately ——— dosage units.

Waiver Request:

The sponsor has requested a waiver of in-vivo requirements for their 400 mg acyclovir tablet. A quantitative formulation comparison between the 800 mg and 400 mg tablet was submitted, and comparative dissolution testing results were provided between the company's 400 mg test product vs Zovirax® 400 mg tablet.

Comment:

1. The laboratory has stated in both the fasting and fed studies, there was no interference at the retention time of the drug/IS in the subjects' zero hour samples run with and without internal standard added. No evidence could be found substantiating the claim that the subjects' zero hour samples were run without internal standard added, either in the raw data section or the chromatogram section. The laboratory should supply those missing chromatograms.

2. In the fasting study report the laboratory has submitted the worksheets for only the first 9 subjects. The worksheets for all the subjects should be submitted, including those for repeat analyses. The laboratory should submit the peak heights (raw data) of the drug and internal standard, not just the ratios (which are calculated values).

3. There is no raw data for the recovery of drug and internal standard.

    a. The laboratory should supply all raw data and include the %CV.
    b. The laboratory should also state the concentration of the internal standard in the recovery data.

4. The observed food effect for the test product will be reported to the Division of Labeling, since this runs counter to the Innovator's labeling which stated that in a small, 6-subject study the influence of food on the absorption of acyclovir was not apparent.

Recommendation:

1. The fasting and fed bioequivalence studies conducted by ——— and ——— for Purepac Pharmaceutical Co. on its acyclovir 800 mg tablet, batch #PI-895,

comparing it to Zovirax® 800 mg tablet has been found incomplete per comments #1-3.

Comments #1-3 should be transmitted to the company.

R. Lee 6/17/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 6/17/1996

Concur: Date: 6/18/96

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

Jlee/jl/06-14-96

cc: NDA #74-870 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Lee, Patnaik), HFD-130, HFD-344 (Vish), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

USP XXIII Apparatus II Basket _____ Paddle x rpm 50

Medium: water @ 37°C Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Zovirax® 800 & 400 mg tablet

Assay Methodology: UV absorbance; — nm

800 mg

Results

Time (min)	Test Product Lot # PI-895 Mean % Dissolved	Range	(CV)	Reference Product Lot # 5P2315 Mean % Dissolved	Range	(CV)
10	95.1	_	(2.2)	84.4	_	(9.2)
20	101.4	_	(1.1)	96.6	_	(2.7)
30	102.0	_	(1.0)	98.4	_	(2.2)
40	102.1	_	(1.0)	99.3	_	(2.0)
50	101.8	_	(1.1)	99.9	_	(1.9)
60	102.1	_	(1.1)	100.3	_	(1.7)

400 mg

	Lot # PI-905			Lot # 3X1804		
10	98.3	_	(2.1)	87.4	_	(4.0)
20	103.0	_	(1.0)	95.2	_	(2.3)
30	103.8	_	(0.7)	97.6	_	(1.9)
40	104.0	_	(0.6)	98.9	_	(1.7)
50	104.1	_	(0.6)	99.6	_	(1.6)
60	104.2	_	(0.6)	100	_	(1.6)

FASTING

ACYCLOVIR STUDY NO. 9504920E

SUMMARY TABLES

Table 1: Comparisons of acyclovir results for Purepac's 800 mg test tablets vs. 800 mg Zovirax[R] tablets (Reference) in 32 fasted subjects.

Parameter	Least Squares Means		Observed Difference (%) [1]	Power	90% Confidence Interval [2]	
	Test	Reference			Lower (%)	Upper (%)
AUC 0-t (μg-hr/ml)	5.081	4.723	7.58	0.84	-3.5	18.7
AUCinf (μg-hr/ml)	5.546	5.157	7.55	0.72	-5.4	20.5
Cmax (μg/ml)	1.031	0.980	5.21	0.87	-5.4	15.9
Tmax (hour)	1.88	1.70	10.63	0.80	-	-
Ke (1/hour)	0.1627	0.1639	-0.74	0.95	-	-
Elimhalf (hour)	4.65	4.65	-0.10	0.69	-	-

[1] Observed difference calculated as: [(Test - Reference) / Reference] x 100. None of the differences was detected as statistically significant by ANOVA ($\alpha = 0.05$).

[2] Confidence interval on the observed difference.

Table 2: Ln-transformation of the acyclovir data (n = 32).

Parameter	Geometric Mean Ratio: Test/Reference	90% Confidence Interval on Ratio	
		Lower	Upper
AUC 0-t	1.077	0.971	1.194
AUCinf	1.072	0.949	1.210
Cmax	1.060	0.950	1.182

FASTING

ACYCLOVIR STUDY NO. 9504920E

SUMMARY TABLES

Table 3: Summary of acyclovir statistical comparisons at each sampling time comparing Purepac's 800 mg test tablets and 800 mg Zovirax[R] tablets (Reference) in 32 fasted subjects.

Sample Time	Collection (Hour)	Least Squares Means (μg/ml)		Significance *
		Test	Reference	
1	Pre-dose	0.00	0.00	-
2	0.33	0.156	0.140	None
3	0.67	0.498	0.506	None
4	1.00	0.704	0.718	None
5	1.33	0.838	0.849	None
6	1.67	0.909	0.859	None
7	2.00	0.929	0.843	None
8	2.50	0.862	0.780	None
9	3.00	0.769	0.718	None
10	4.00	0.590	0.529	None
11	5.00	0.451	0.410	None
12	6.00	0.338	0.310	None
13	8.00	0.217	0.195	None
14	10.00	0.138	0.128	None
15	12.00	0.094	0.089	None
16	14.00	0.066	0.060	None
17	16.00	0.046	0.031	A > B
18	24.00	0.005	0.009	None

* Statistical comparisons to test for the equivalence of treatment effects were performed at an α level of 0.05. The actual p-value is indicated at the time where statistically significant differences ($p < 0.05$) were detected; "None" indicates that no significance was detected ($p > 0.05$) at that time.

FASTING

ACYCLOVIR STUDY 9504920E

TRTMNT A=TEST TRTMNT B=REFERENCE

Arithmetic Means

TRTMNT=A

Variable	Label	N	Mean	Std Dev	CV	Minimum	Maximum
AUC	AUC 0-t	32	5.081363	1.836068	36.133373		
AUCINF	AUC 0-inf	26	5.625622	1.921371	34.153924		
CMAX	PEAK CONC.	32	1.031063	0.328709	31.880637		
TMAX	TIME OF PEAK	32	1.880729	0.604806	32.158068		
KE	ELIMINATION RATE	26	0.168323	0.043536	25.864534		
ELIMHALF	HALFLIFE	26	4.425538	1.327366	29.993317		
CONC1	0.00_HR	32	0.000000	0.000000	.		
CONC2	0.33_HR	32	0.156313	0.147370	94.279050		
CONC3	0.67_HR	32	0.498438	0.224840	45.108995		
CONC4	1.00_HR	32	0.704000	0.256897	36.491014		
CONC5	1.33_HR	32	0.837594	0.296741	35.427846		
CONC6	1.67_HR	32	0.909000	0.317951	34.978097		
CONC7	2.00_HR	32	0.928594	0.334657	36.039124		
CONC8	2.50_HR	32	0.861594	0.322151	37.390176		
CONC9	3.00_HR	32	0.769313	0.324033	42.119827		
CONC10	4.00_HR	32	0.590219	0.285043	48.294511		
CONC11	5.00_HR	32	0.451344	0.212448	47.070051		
CONC12	6.00_HR	32	0.338156	0.145774	43.108356		
CONC13	8.00_HR	32	0.217063	0.086525	39.861965		
CONC14	10.0_HR	32	0.137563	0.056879	41.347758		
CONC15	12.0_HR	32	0.093500	0.045170	48.310086		
CONC16	14.0_HR	32	0.065688	0.035548	54.116431		
CONC17	16.0_HR	32	0.045594	0.034644	75.983394		
CONC18	24.0_HR	32	0.005250	0.016598	316.146796		
LNAUC	LN(AUC)	32	1.551587	0.412638	26.594606		
LNAUCINF	LN(AUCINF)	26	1.660909	0.393915	23.716859		
LNCMAX	LN(CMAX)	32	-0.026252	0.358271	-1364.737235		

FASTING

TRTMNT=B

Variable	Label	N	Mean	Std Dev	CV	Minimum	Maximum
AUC	AUC 0-t	32	4.723364	1.791430	37.927000		
AUCINF	AUC 0-inf	27	5.097861	1.810770	35.520204		
CMAX	PEAK CONC.	32	0.980000	0.359852	36.719586		
TMAX	TIME OF PEAK	32	1.700000	0.639780	37.634143		
KE	ELIMINATION RATE	27	0.164131	0.047406	28.883247		
ELIMHALF	HALFLIFE	27	4.680185	1.849726	39.522487		
CONC1	0.00_HR	32	0.000000	0.000000	.		
CONC2	0.33_HR	32	0.139719	0.122285	87.522274		
CONC3	0.67_HR	32	0.505594	0.202585	40.068677		
CONC4	1.00_HR	32	0.718094	0.217514	30.290496		
CONC5	1.33_HR	32	0.849219	0.300820	35.423188		
CONC6	1.67_HR	32	0.858688	0.327055	38.087829		
CONC7	2.00_HR	32	0.842500	0.321215	38.126425		
CONC8	2.50_HR	32	0.780219	0.334201	42.834281		
CONC9	3.00_HR	32	0.717625	0.344249	47.970551		
CONC10	4.00_HR	32	0.528625	0.246992	46.723468		
CONC11	5.00_HR	32	0.409781	0.183503	44.780755		
CONC12	6.00_HR	32	0.309750	0.130561	42.150467		
CONC13	8.00_HR	32	0.195031	0.075504	38.713850		
CONC14	10.0_HR	32	0.127656	0.046599	36.503432		
CONC15	12.0_HR	32	0.088938	0.037301	41.940481		
CONC16	14.0_HR	32	0.059781	0.033121	55.404025		
CONC17	16.0_HR	32	0.030844	0.034005	110.248745		
CONC18	24.0_HR	32	0.009125	0.021762	238.490725		
LNAUC	LN(AUC)	32	1.477579	0.403811	27.329239		
LNAUCINF	LN(AUCINF)	27	1.563273	0.379197	24.256624		
LNCMAX	LN(CMAX)	32	-0.084081	0.362716	-431.387709		

Purepac Pharmaceutical Co. FASTING PRINT DATE: 12-14-95
[——— P95-246]

Adverse Events Summary by Subject

Study Period I = October 14-15, 1995
Study Period II = October 21-22, 1995

Subject No.	Init.	Event	Report Method	Occurrence	Onset (Date) (Military Time)	Resolution (Date) (Military Time)	1=Label 2=Unexpect	Serious	Intensity	Counter Measure	Outcome	Relationship to Study Drug	Study Drug
14		Left Ankle Sprain	1	1	10-09-95 2200	10-30-95 2000	2	No	1	6	1	4	-
16		Headache	2	1	10-14-95 2200	10-15-95 2000	1	No	2	5	1	2	A
17		Headache	1	1	10-14-95 1800	10-15-95 0900	1	No	1	1	1	2	B
19		Rhinitis (Plugged Nose)	1	1	10-15-95 1600	10-25-95 1700	2	No	1	1	1	4	B
21		Headache	2	1	10-14-95 1731	10-14-95 2130	1	No	1	1	1	2	A
25		Purpura (Hematoma Left Antecubital Space)	3	1	10-14-95 0925	10-30-95 0630	2	No	1	6	1	4	A
25		Purpura (Hematoma Left Antecubital Space)	3	1	10-14-95 0940	10-30-95 0630	2	No	1	6	1	4	A
25		Purpura (Hematoma Left Antecubital Space)	3	1	10-14-95 1010	10-30-95 0630	2	No	1	6	1	4	A
26		Rash (Left Hand Palm)	2	1	10-21-95 2315	10-30-95 0800	1	No	1	1	1	3	B
29		Left Ankle Injury	1	1	09-16-95 0930	10-17-95 1600	2	No	1	5	1	4	-

Adverse Events Summary

Subject No.	Init.	Event	Report Method	Occurrence	Onset (Date) (Military Time)	Resolution (Date) (Military Time)	1=Label 2=Unexpect	Serious	Intensity	Counter Measure	Outcome	Relationship to Study Drug	Study Drug
16		Headache	2	1	10-14-95 2200	10-15-95 2000	1	No	2	5	1	2	A
17		Headache	1	1	10-14-95 1800	10-15-95 0900	1	No	1	1	1	2	B
21		Headache	2	1	10-14-95 1731	10-14-95 2130	1	No	1	1	1	2	A
29		Left Ankle Injury	1	1	09-16-95 0930	10-17-95 1600	2	No	1	5	1	4	-
14		Left Ankle Sprain	1	1	10-09-95 2200	10-30-95 2000	2	No	1	6	1	4	-
25		Purpura (Hematoma Left Antecubital Space)	3	1	10-14-95 0925	10-30-95 0630	2	No	1	6	1	4	A
25		Purpura (Hematoma Left Antecubital Space)	3	1	10-14-95 0940	10-30-95 0630	2	No	1	6	1	4	A
25		Purpura (Hematoma Left Antecubital Space)	3	1	10-14-95 1010	10-30-95 0630	2	No	1	6	1	4	A
26		Rash (Left Hand Palm)	2	1	10-21-95 2315	10-30-95 0800	1	No	1	1	1	3	B
19		Rhinitis (Plugged Nose)	1	1	10-15-95 1600	10-25-95 1700	2	No	1	1	1	4	B

CLARIFICATION: The general description in parenthesis is at the request of the ——— IRB to avoid the occasional misleading terminology of WHO.

REPORT METHOD: 1 = Elicited; 2 = Spontaneous; 3 = Observed

OCCURRENCE: 1 = Single; 2 = Episodic; 3 = Continuous

ONSET: Date in calendar time and hours and minutes recorded in military time

LEGEND: 1 = Labeled; 2 = Unexpected

SERIOUS: Any adverse event that is fatal, life threatening, permanently disabling, requires or prolongs inpatient hospitalization, or results in a congenital anomaly, cancer or overdose.

INTENSITY:

1 = MILD - Events are usually transient, requiring no special treatment and do not interfere with the subject's daily activities

2 = MODERATE - Events traditionally introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

3 = SEVERE - Events interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment

COUNTER MEASURES:

1 = None
2 = Drug Discontinued Permanently
3 = Drug Discontinued and Restarted
4 = Dose Reduced
5 = Therapy Required
6 = Other

OUTCOME:

1 = Resolved
2 = Tolerated/Unalleviated
3 = Death
4 = Insufficient Follow-up

RELATIONSHIP TO STUDY DRUG:

1 = PROBABLE - Relationship suggests that a reasonable temporal sequence of the event with drug administration exists, and based upon the investigator's clinical experience, the association of the event with the study medication seems likely

2 = POSSIBLE - Relationship suggests that the association of the event with the study medication is unknown, however, the adverse clinical event is not reasonably supported by other conditions

3 = REMOTE - Relationship suggests that only a remote connection exists between the study drug and the reported event

4 = UNRELATED - The experience has been judged by the investigator to have no relationship to the treatment

DRUG: Randomization Code:

A = Test - Acyclovir Tablets 800 mg
[Purepac Pharmaceutical Co.;
Lot No. PI-895, Exp. Date: 09/97]

B = Reference - Zovirax^{R} Tablets 800 mg
[Burroughs Wellcome Co.;
Lot No. 5P2315, Exp. Date: 07/97]

FED

ACYCLOVIR STUDY NO. 9504917E

SUMMARY TABLES

Table 1.1: Comparisons of acyclovir results for Purepac's 800 mg tablets (Test) vs. Zovirax[R] tablets (Reference) after post-prandial administration in 18 subjects.

Parameter	Least Squares Means		Observed Difference (%) [1]	Power	90% Confidence Interval [2]	
	Test-Fed	Reference			Lower (%)	Upper (%)
AUC 0-t (μg-hr/ml)	6.270	6.423	-2.38	0.84	-13.5	8.7
AUCinf (μg-hr/ml)	6.157	6.601	-6.73	0.82	-18.2	4.7
Cmax (μg/ml)	1.267	1.310	-3.30	0.93	-12.8	6.2
Tmax (hour)	2.64	2.50	5.56	0.28	-	-
Ke (1/hour)	0.1817	0.1651	10.09	0.37	-	-
Elimhalf (hour)	3.93	4.71	-16.57	0.28	-	-

[1] Observed difference calculated as: [(Test-Fed - Reference) / Reference] x 100. None of the differences was detected as statistically significant by ANOVA (overall $\alpha = 0.05$).

[2] Confidence interval on the observed difference.

Table 1.2: Ln-transformation of the acyclovir data (n=18).

Parameter	Geometric Mean Ratio: Test-Fed/Reference	90% Confidence Interval on Ratio	
		Lower	Upper
AUC 0-t	0.959	0.828	1.112
AUCinf	0.909	0.772	1.071
Cmax	0.962	0.849	1.089

ACYCLOVIR STUDY NO. 9504917E FED

SUMMARY TABLES

Table 2.1: Comparisons of acyclovir results for Purepac's 800 mg tablets after post-prandial administration (Test-Fed) vs. the same tablets after a fast (Test-Fast) in 18 subjects.

Parameter	Least Squares Means		Observed Difference (%) [1]	Power	90% Confidence Interval [2]	
	Test-Fed	Test-Fast			Lower (%)	Upper (%)
AUC 0-t (μg-hr/ml)	6.270	3.672	70.75*	0.40	51.4	90.1
AUCinf (μg-hr/ml)	6.157	4.139	48.75*	0.49	31.8	65.7
Cmax (μg/ml)	1.267	0.816	55.17*	0.58	39.9	70.4
Tmax (hour)	2.64	1.51	74.63*	0.13	-	-
Ke (1/hour)	0.1817	0.1774	2.43	0.47	-	-
Elimhalf (hour)	3.93	4.23	-7.21	0.27	-	-

[1] Observed difference calculated as: [(Test-Fed - Test-Fast) / Test-Fast] x 100.

[2] Confidence interval on the observed difference.

* Detected as statistically significant by ANOVA (overall $\alpha = 0.05$).

Table 2.2: Ln-transformation of the acyclovir data (n=18).

Parameter	Geometric Mean Ratio: Test-Fed / Test-Fast	90% Confidence Interval on Ratio	
		Lower	Upper
AUC 0-t	1.755	1.515	2.035
AUCinf	1.511	1.299	1.759
Cmax	1.609	1.420	1.822

FED

ACYCLOVIR STUDY NO. 9504917E

SUMMARY TABLES

Table 3: Summary of acyclovir statistical comparisons at each sampling time comparing Purepac's tablets after a fast (Test-Fast) and after breakfast (Test-Fed), and Zovirax[R] tablets after breakfast (Reference).

Sample Time	Collection (Hour)	Least Squares Means (μg/ml)			Significance *
		Test-Fast (A)	Test-Fed (B)	Reference (C)	
1	Pre-dose	0.000	0.000	0.000	-
2	0.33	0.097	0.023	0.000	A>B,C
3	0.67	0.432	0.189	0.160	A>B,C
4	1.00	0.612	0.419	0.438	None
5	1.33	0.655	0.653	0.759	None
6	1.67	0.694	0.806	0.964	None
7	2.00	0.693	0.860	1.095	C>A
8	2.5	0.647	0.886	1.036	B,C>A
9	3.00	0.550	0.957	0.986	B,C>A
10	4.00	0.416	0.897	0.875	B,C>A
11	5.00	0.316	0.716	0.687	B,C>A
12	6.00	0.243	0.551	0.524	B,C>A
13	8.00	0.155	0.316	0.308	B,C>A
14	10.00	0.101	0.199	0.193	B,C>A
15	12.00	0.069	0.116	0.128	B,C>A
16	14.00	0.033	0.087	0.086	B,C>A
17	16.00	0.018	0.053	0.063	B,C>A
18	24.00	0.003	0.010	0.010	None

* Statistical comparisons to test for the equivalence of treatment effects were performed at an α level of 0.05. When significance was detected, pair-wise comparisons were conducted at an α level of 0.017. When significant, the pair-wise difference is indicated, e.g., A>B,C means that Treatment A was significantly greater than Treatments B and C at the collection time indicated. "None" indicates that no significance was detected (overall $p>0.05$) at that time.

FED

TRTMNT A=TEST-FASTED TRTMNT B=TEST-FED TRTMNT C=REFERENCE

Arithmetic Means

TRTMNT=A

Variable	Label	N	Mean	Std Dev	CV	Minimum	Maximum
AUC	AUC 0-t	18	3.672095	1.391739	37.900411		
AUCINF	AUC 0-inf	16	4.129614	1.507252	36.498606		
CMAX	PEAK CONC.	18	0.816389	0.297759	36.472681		
TMAX	TIME OF PEAK	18	1.511111	0.610582	40.406166		
KE	ELIMINATION RATE	16	0.178219	0.046245	25.948284		
ELIMHALF	HALFLIFE	16	4.244688	1.543060	36.352740		
CONC1	0.00_HR	18	0.000000	0.000000	.		
CONC2	0.33_HR	18	0.097444	0.110285	113.177080		
CONC3	0.67_HR	18	0.432444	0.171753	39.716852		
CONC4	1.00_HR	18	0.612444	0.158770	25.924042		
CONC5	1.33_HR	18	0.655278	0.208764	31.858913		
CONC6	1.67_HR	18	0.694167	0.284603	40.999288		
CONC7	2.00_HR	18	0.693389	0.311820	44.970451		
CONC8	2.50_HR	18	0.646667	0.300964	46.540876		
CONC9	3.00_HR	18	0.550056	0.263369	47.880437		
CONC10	4.00_HR	18	0.415833	0.219393	52.759859		
CONC11	5.00_HR	18	0.316222	0.162169	51.283227		
CONC12	6.00_HR	18	0.242889	0.109120	44.926093		
CONC13	8.00_HR	18	0.155167	0.063390	40.852707		
CONC14	10.0_HR	18	0.100500	0.036175	35.994846		
CONC15	12.0_HR	18	0.068944	0.030506	44.247880		
CONC16	14.0_HR	18	0.033333	0.036059	108.176327		
CONC17	16.0_HR	18	0.018444	0.031217	169.248417		
CONC18	24.0_HR	18	0.003222	0.013671	424.264069		
LNAUC	LN(AUC)	18	1.235311	0.374468	30.313691		
LNAUCINF	LN(AUCINF)	16	1.356641	0.365848	26.967208		
LNCMAX	LN(CMAX)	18	-0.263487	0.359719	-136.522746		

FED

ACYCLOVIR STUDY NO. 9504917E

TRTMNT A=TEST-FASTED TRTMNT B=TEST-FED TRTMNT C=REFERENCE

Arithmetic Means

TRTMNT=B

Variable	Label	N	Mean	Std Dev	CV	Minimum	Maximum
AUC	AUC 0-t	18	6.270153	1.697785	27.077246		
AUCINF	AUC 0-inf	13	6.358554	1.580901	24.862590		
CMAX	PEAK CONC.	18	1.266778	0.284627	22.468615		
TMAX	TIME OF PEAK	18	2.638889	1.426007	54.038170		
KE	ELIMINATION RATE	13	0.176450	0.037687	21.358281		
ELIMHALF	HALFLIFE	13	4.109231	0.930349	22.640461		
CONC1	0.00_HR	18	0.000000	0.000000	.		
CONC2	0.33_HR	18	0.023389	0.072831	311.391881		
CONC3	0.67_HR	18	0.189389	0.260198	137.388285		
CONC4	1.00_HR	18	0.419222	0.386366	92.162675		
CONC5	1.33_HR	18	0.652611	0.476507	73.015522		
CONC6	1.67_HR	18	0.806000	0.487268	60.455119		
CONC7	2.00_HR	18	0.859611	0.441082	51.311774		
CONC8	2.50_HR	18	0.885556	0.347999	39.297293		
CONC9	3.00_HR	18	0.957056	0.342332	35.769316		
CONC10	4.00_HR	18	0.897056	0.366004	40.800605		
CONC11	5.00_HR	18	0.716333	0.349924	48.849352		
CONC12	6.00_HR	18	0.550944	0.299465	54.354936		
CONC13	8.00_HR	18	0.315667	0.180923	57.314508		
CONC14	10.0_HR	18	0.198944	0.103671	52.110307		
CONC15	12.0_HR	17	0.119059	0.049437	41.523527		
CONC16	14.0_HR	18	0.087389	0.042222	48.315405		
CONC17	16.0_HR	18	0.053222	0.041332	77.658527		
CONC18	24.0_HR	18	0.010167	0.023400	230.163687		
LNAUC	LN(AUC)	18	1.798008	0.290792	16.172994		
LNAUCINF	LN(AUCINF)	13	1.818584	0.267435	14.705650		
LNCMAX	LN(CMAX)	18	0.211887	0.231098	109.066410		

FED

TRTMNT A=TEST-FASTED TRTMNT B=TEST-FED TRTMNT C=REFERENCE

Arithmetic Means

TRTMNT=C

Variable	Label	N	Mean	Std Dev	CV	Minimum	Maximum
AUC	AUC 0-t	18	6.422920	1.334499	20.777135		
AUCINF	AUC 0-inf	13	6.699266	1.267666	18.922464		
CMAX	PEAK CONC.	18	1.310056	0.259722	19.825241		
TMAX	TIME OF PEAK	18	2.500000	1.054093	42.163702		
KE	ELIMINATION RATE	13	0.166401	0.051943	31.215775		
ELIMHALF	HALFLIFE	13	4.698923	2.036669	43.343319		
CONC1	0.00_HR	18	0.000000	0.000000	.		
CONC2	0.33_HR	18	0.000000	0.000000	.		
CONC3	0.67_HR	18	0.160056	0.185886	116.138390		
CONC4	1.00_HR	18	0.438278	0.339657	77.498006		
CONC5	1.33_HR	18	0.758667	0.448025	59.054238		
CONC6	1.67_HR	18	0.964389	0.460734	47.774759		
CONC7	2.00_HR	18	1.094889	0.443512	40.507444		
CONC8	2.50_HR	18	1.036000	0.342784	33.087235		
CONC9	3.00_HR	18	0.986111	0.284858	28.887034		
CONC10	4.00_HR	18	0.875222	0.263966	30.159836		
CONC11	5.00_HR	18	0.686500	0.273617	39.856842		
CONC12	6.00_HR	18	0.523611	0.229156	43.764498		
CONC13	8.00_HR	18	0.307556	0.140241	45.598475		
CONC14	10.0_HR	18	0.193278	0.080025	41.404063		
CONC15	12.0_HR	18	0.127667	0.047894	37.515268		
CONC16	14.0_HR	18	0.085889	0.035885	41.781023		
CONC17	16.0_HR	18	0.062778	0.032939	52.469900		
CONC18	24.0_HR	18	0.009722	0.022741	233.907545		
LNAUC	LN(AUC)	18	1.839614	0.206984	11.251479		
LNAUCINF	LN(AUCINF)	13	1.885525	0.188895	10.018151		
LNCMAX	LN(CMAX)	18	0.251103	0.202182	80.517358		

Adverse Events Summary by Summary

Subject No.	Init.	Event	Report Method	Occurrence	Onset (Date)	Onset (Military Time)	Resolution (Date)	Resolution (Military Time)	1=Labeled 2=Unexpected	Serious	Intensity	Counter Measure	Outcome	Relationship to Study Drug	Study Drug
05		Cough (Coughing)	1	1	01-15-96	0800	01-20-96	1000	2	No	1	1	1	4	B
02		Dizziness (Lightheaded)	1	1	01-06-96	1000	01-06-96	1300	1	No	1	1	1	2	B
05		Dizziness (Lightheaded)	1	1	01-13-96	0200	01-13-96	1800	1	No	1	1	1	4	C
06		Dyspepsia (Heartburn)	1	1	01-13-96	1900	01-14-96	0705	2	No	1	1	1	2	B
15		Epistaxis (Bloody Nose)	1	1	01-06-96	1300	01-06-96	1305	2	No	1	1	1	3	C
02		Headache	1	1	01-06-96	1000	01-06-96	1300	1	No	1	1	1	2	B
05		Headache	1	1	01-13-96	0200	01-13-96	1800	1	No	1	1	1	4	C
06		Headache	1	1	01-06-96	1730	01-07-96	0600	1	No	1	1	1	2	A
08		Headache	2	1	01-20-96	1130	01-20-96	1530	1	No	1	1	1	2	C
09		Headache	1	1	01-12-96	1900	01-13-96	0300	1	No	1	1	1	4	A
14		Headache	1	1	01-15-96	0830	01-15-96	0930	1	No	1	1	1	4	C
14		Headache	1	1	01-16-96	0830	01-16-96	0900	1	No	1	1	1	4	C
18		Laceration (Left Eye)	1	1	01-07-96	1530	01-12-96	1530	2	No	2	5	1	4	C
15		Laryngitis	1	1	01-20-96	0700	01-22-96	1800	2	No	1	1	1	4	A
01		Myalgia (Sore Arm Muscles)	1	1	01-10-96	1000	01-15-96	1500	1	No	1	1	1	4	C
01		Myalgia (Sore Back Muscles)	1	1	01-10-96	1000	01-15-96	1500	1	No	1	1	1	4	C
01		Myalgia (Sore Chest Muscles)	1	1	01-10-96	1000	01-15-96	1500	1	No	1	1	1	4	C
01		Myalgia (Sore Leg Muscles)	1	1	01-10-96	1000	01-15-96	1500	1	No	1	1	1	4	C
08		Pharyngitis (Scratchy Throat)	1	1	01-05-96	0500	01-10-96	0800	2	No	1	1	1	4	-
01		Pharyngitis (Sore Throat)	1	1	01-21-96	0700	01-22-96	1500	2	No	1	1	1	3	A
10		Pharyngitis (Sore Throat)	1	1	01-20-96	1100	01-22-96	2000	2	No	1	1	1	2	B
14		Pharyngitis (Sore Throat)	1	1	01-21-96	0700	01-22-96	1030	2	No	1	1	1	3	B
15		Pharyngitis (Sore Throat)	1	1	01-20-96	0700	01-23-96	0830	2	No	1	1	1	4	A
08		Respiratory Disorder (Nasal Congestion)	1	1	01-05-96	0500	01-10-96	0800	2	No	1	1	1	4	-
05		Rigors (Chills)	1	1	01-13-96	0200	01-13-96	0900	2	No	1	1	1	4	C
06		Vomiting	1	2	01-14-96	0700	01-14-96	1200	1	No	1	1	1	3	B

CLARIFICATION: The general description in parenthesis is at the request of the ——— IRB to avoid the occasional misleading terminology of WHO.

REPORT METHOD: 1 = Elicited; 2 = Spontaneous; 3 = Observed

OCCURRENCE: 1 = Single; 2 = Episodic; 3 = Continuous

ONSET: Date in calendar time and hours and minutes recorded in military time

LEGEND: 1 = Labeled; 2 = Unexpected

SERIOUS: Any adverse event that is fatal, life threatening, permanently disabling, requires or prolongs inpatient hospitalization, or results in a congenital anomaly, cancer or overdose.

ENSITY: 1 = MILD - Events are usually transient, requiring no special treatment and do not interfere with the subject's daily activities

2 = MODERATE - Events traditionally introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

3 = SEVERE - Events interrupt a subject's usual daily activity and traditionally require systematic drug therapy or other treatment

COUNTER MEASURES:
1 = None
2 = Drug Discontinued Permanently
3 = Drug Discontinued and Restarted
4 = Dose Reduced
5 = Therapy Required
6 = Other

OUTCOME:
1 = Resolved
2 = Tolerated / Unalleviated
3 = Death
4 = Insufficient Follow-up

RELATIONSHIP TO STUDY DRUG:

1 = PROBABLE - Relationship suggests that a reasonable temporal sequence of the event with drug administration exists, and based upon the investigator's clinical experience, the association of the event with the study medication seems likely

2 = POSSIBLE - Relationship suggests that the association of the event with the study medication is unknown, however, the adverse clinical event is not reasonably supported by other conditions

3 = REMOTE - Relationship suggests that only a remote connection exists between the study drug and the reported event

4 = UNRELATED - The experience has been judged by the investigator to have no relationship to the treatment

DRUG: Randomization Code

A = **FASTING** - Test Product - Acyclovir Tablets 800 mg
[Purepac Pharmaceutical Co.; Lot No. PI-895,
Exp. Date: 09/97]

B = **FED** - Test Product - Acyclovir Tablets 800 mg
[Purepac Pharmaceutical Co.; Lot No. PI-895,
Exp. Date: 09/97]

C = **FED** - Reference Product - Zovirax® Tablets 800 mg
[Burroughs Wellcome Co.; Lot No. 5P2315,
Exp. Date: 07/97]

CONFIDENTIAL

A FULL STATEMENT OF THE COMPOSITION OF THE DRUG PRODUCTS

ACYCLOVIR TABLETS, 400 MG AND 800 MG

Components	Acyclovir Tablets, 400 mg	Acyclovir Tablets, 800 mg
1) Acyclovir USP		
2) Microcrystalline Cellulose NF,		
3) Crospovidone NF,		
4) Sodium Lauryl Sulfate, NF		
5) Sodium Starch Glycolate, NF		
6) D&C Yellow #10 HT Aluminum Lake,	-	
7) FD&C Blue #1 HT Aluminum Lake	-	
8)	**	**
9) Magnesium Stearate, NF		
Total Tablet Weight	**525 mg**	**1050 mg**

* [redacted]

** [redacted]

JAN 7 1997

Acyclovir tablet
400 mg & 800 mg
NDA #74-870
Reviewer: J. Lee
74870O.896

Purepac Pharmaceutical Co.
Elizabeth, New Jersey
Submission date:
August 22, 1996

Review of a Study Amendment

This submission responds to deficiencies conveyed to the company on its bio-studies for acyclovir 800 mg tablet.

1. Zero hour Samples

The zero hour sample chromatograms (run without internal standard added) in the fasting and fed studies were submitted as requested. The chromatograms confirmed the absence of interference at the retention time of the internal standard.

2. Subject Worksheets

The sponsor was requested to submit the worksheets for all subjects in the fasting study, and not just those for the first nine subjects. The raw data for all subjects in both the fasting and fed studies were submitted as requested.

3. Recovery Data

The laboratory has supplied all raw data for the recovery of drug and internal standard. This data shows:

	Conc.	Recovery	%CV	
Acyclovir	[redacted]	[redacted]	4.16	(n=12)
	[redacted]	[redacted]	1.10	(n=12)
[redacted] (IS)	[redacted]	[redacted]	4.41	(n=24)

Comment:

1. All deficiencies have been satisfactorily addressed.

Recommendation:

1. The bioequivalence studies (fasting and fed) conducted by [redacted] and [redacted] for Purepac Pharmaceutical Co. on its acyclovir 800 mg tablet, batch #PI-895,

comparing it to Zovirax® 800 mg tablet, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Purepac's test product is bioequivalent (under fasting and fed conditions) to the reference product, Zovirax® manufactured by Burroughs-Wellcome Co.

2. The in-vitro dissolution testing data on the 400 mg tablet (batch #PI-905) and 800 mg tablet using the FDA method is also acceptable. The formulation for the 400 mg tablet is proportionally similar to the 800 mg tablet, which underwent a bioequivalence study. The waiver of in-vivo study requirements for the 400 mg tablet is granted. Purepac's acyclovir 400 mg tablet is deemed bioequivalent to Zovirax® 400 mg tablet manufactured by Burroughs-Wellcome.

3. The in-vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

Not less than —% of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

4. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 1/7/1997

Concur: Rabi Patnaik Date: 1/7/97

Rabi Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

JLee/jl/12-12-96

cc: NDA #74-870 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-870 SPONSOR: Purepac Pharmaceutical

DRUG: Acyclovir

DOSAGE FORM: tablet

STRENGTHS/(s): 400 & 800 mg

TYPE OF STUDY: Single__ Multiple__ Fasting ✓ Fed ✓

STUDY SITE: _____ [clinical]

_____ [Analytical]

STUDY SUMMARY: Fasting study is acceptable. PK indices within 80-125%
Fed study is acceptable. Point estimates for PK values ± 20%
Food effect noted in fed study. Convey info to labeling Division

DISSOLUTION: OK. using current FDA method. No USP method at this time

PRIMARY REVIEWER: Jenny Lee BRANCH: II

INITIAL: J.L. DATE 5/15/97

TEAM LEADER: S. Nerurkar, Ph.D BRANCH: II

INITIAL: _____ DATE 5/15/97

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Nicholas Fleischer, Ph.D

INITIAL: _____ DATE 5/15/97

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-870

ADMINISTRATIVE DOCUMENTS

ANDA/AADA OFFICE LEVEL APPROVAL ROUTING SUMMARY

ANDA # 74-870
AADA #
Drug Acyclovir Tablets 400mg & 800mg
sage Form
rength
Applicant Purepac
Proposed Action (AP) TA

REVIEWER:

Draft

RECEIPT

ACTION

1. T. Ames, Project Manager
Review Support Branch

Date 5/19/97
Initials

Date 5/22/97
Initials MA

Original Rec'd date 3/25/96
Date Acceptable for Filing 3/25/96
Open Amendment Date(s) 6/6/96, 8/22/96, 11/11/96
Chemistry Reviewer NGregory
Supervisor J Smith 5/8/97
Bio Reviewer J Lee
Supervisor VJ Nerurkar
Date of Office Level Bio Review
Pending Legal Case Yes ____ No ✓
Comments:

EER Status OK 4/29/97
OAI Status Yes ____ No ✓
Patent Certification ~~PII~~ patent exp. 4/22/97
Citizen Petition Yes ____ No ____ ~~If~~ YES attach Email from Project Manager to Petition Coordinator of pending approval

2. Director of Chem. I or II
Office of Generic Drugs
Comments: Chemistry is satisfactory.

Date 5/22/97
Initials

Date 5/28/97
Initials

3. Office Level Chem Review
(1st Generic Only)
Div. Dir. of Chem I or II
Comments: Multiple generic tablet formulations are approved. Request 5/30/97

Date
Initials

Date
Initials

4. P. Rickman
Supv., Reg. Support Branch

Date 5/29/97
Initials

Date 5/29/97
Initials

Contains certification required by the GDEA if sub after 6/1/92
Yes ✓ No ____ //// Determination of involvement? Yes ____ No ✓
Paragraph 4 Certification ____ Yes ____ No (checklist)
Comments:
exclusivity has expired
patent '574 expired 4/22/97
multiple generics approved

Office Bio 5/15/97

5. J. Phillips
Director Division of LPS
Office of Generic Drugs
Comments:

1=2
TTT: 14 months

Date 5/29/97 Request
Initials

Date 5/30/97 Request for
Initials

Acceptable EES dated 4/29/97 (faxed 5/30/97). No O.A.I. alerts indicated. Fasting + fed bioequivalency study found acceptable (800mg tablets) on 1/7/97. Waiver granted on 400mg tablet because of dose proportionality. Office level bio endorsed 5/15/97 (N Fleischer). Methods validation acceptable 11/7/96. CMC acceptable Chemistry review #2. FPL Acceptable 5/16/97. No controlled correspondence or Citizens Petitions pending. No patent or exclusivity issues.
Recommend: Approval.

OK SPhillips 6/3/97

6. G.Johnston
Deputy Director
Office of Generic Drugs
Patent Cert - P_4 - Yes___ No___ ✓
Petition status None
Pend. Legal Actions - Yes___ No___ ✓
Comments:

Date 6/3/97 Initials GJ
Date 6/4/97 Initials GJ

7. D. Sporn
Director
Office of Generic Drugs

R. Williams, MD
1st Generic ~~X~~
PD or clinical for BE
Special Scientific or Reg Issues
Comments:

Date 6/5/97 Initials DSS
Date 6/5/97 Initials DSS

8. T. Ames, Project Manager T. Ames

Date 6/5/97 Initials JA
Date Initials

Company Notified
4:00p Time notified of approval via telephone
4:01p Time notified of approval via facsimile

Refaxed 6/6/97 9:10 AM JA

LETTER SIGNED: D. Sporn 6/5/97
(Name and Date)

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-870

CORRESPONDENCE

A Trusted Name For Over Half A Century

PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
1-800-526-6978 In New Jersey: 1-908-527-9100
Fax: 1-908-527-0649

3/29/96

4/2/96 Phone

UPS OVERNIGHT COURIER

March 22, 1996

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

RE: Abbreviated New Drug Application for Acyclovir Tablets, 400 mg and 800 mg

Dear Mr. Sporn:

In accordance with the regulations promulgated under Section 505 of the Federal Drug and Cosmetic Act as amended, Purepac Pharmaceutical Co. is submitting this Abbreviated New Drug Application (Archival and Review Copy) for Acyclovir Tablets, 400 mg and 800 mg.

This Abbreviated New Drug Application has been prepared in accordance with Policy and Procedure Guide #30-91, dated April 10, 1991, and contains a total of (16) volumes comprising the Archival Copy and the Review Copy (chemistry, manufacturing and controls review part and bioavailability/ bioequivalence review part).

In conjunction with this submission, Purepac has provided a Field Copy of this application to our local district office in accordance with 21CFR 314.94. Please note that the required Field Copy Certification is contained in Section XXI of our abbreviated application.

In addition, a certification in accordance with Section 306(K) of the Federal Food Drug and Cosmetic Act as amended by the "Generic Drug Enforcement Act" is contained in Section IX of this application. Three (3) separately bound copies of analytical methods and related descriptive information are also included.

In support of this application, Purepac has manufactured Acyclovir Tablets, 400 mg and 800 mg, Test Batches #PI-905 and #PI-895, respectively. These batches were manufactured and packaged in compliance with Policy and Procedure Guide #41-95 entitled "Guidance on the Packaging of Test Batches" and specifically, meet the criteria established under Section 3.E.2 of this guide for partial packaging. Full documentation supporting Test Batches #PI-905 and #PI-895 is included in Section XII of this application.

Purepac Pharmaceutical Co. trusts that you will find this application complete and well organized, and looks forward to the review process.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Director, Regulatory Affairs

JJ:ljl
Enclosures

ANDA 74-870

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

APR 10 1996

Dear Madam:

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

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

DATE OF APPLICATION: March 22, 1996

DATE OF RECEIPT: March 25, 1996

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

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

Jerry Phillips 4/10/96

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

ANDA 74-870
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB 4/4/96 date
HFD-615/HGreenberg, CSO date
HFD-647/JSimmons, Sup. Chem. 4.4.96 date
File x:\new\firmsnz\ltrs&rev\Purepac\74870ac.f
F/T hrw 4-3-96
ANDA Acknowledgement Letter!

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
1-800-526-6978 In New Jersey: 1-908-527-9100
Fax: 1-908-527-0649

Larry
BIOAVAILABILITY
NEW CORRESP
NC/Bio

NAI
"Bio Assigned"
(6 JUN 96)
6/13/96

UPS OVERNIGHT COURIER

CORRESPONDENCE TO ANDA FILE
BIOEQUIVALENCE INFORMATION

June 6, 1996

RECEIVED
JUN 07 1996
GENERIC DRUGS

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

RE: ANDA #74-870, Acyclovir Tablets, 400 mg and 800 mg

Dear Mr. Sporn:

In accordance with a request from Mr. Larry Galvin, CSO in the Division of Bioequivalence, Purepac Pharmaceutical Co. is providing our bioavailability/bioequivalence data on diskette (ASCII, space-delimited files). The diskettes cover both the two-way crossover (Study No. 9504920E) and three-way crossover (Study No. 9504917E) studies.

Purepac Pharmaceutical Co. trusts that this information will assist in the review of the bioavailability/bioequivalence portion of our Abbreviated New Drug Application.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge

Elizabeth Trowbridge, R.A.C.
Senior Associate, Regulatory Affairs

ET:ljl
Enclosure

Mailed 6-7-96 w/ diskette, etc.

ANDA 74-870

JUL 5 1996

Purepac Pharmaceutical Company
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Ms. Janulis:

Reference is made to the bioequivalence data submitted March 22, 1996 and June 6, 1996 for Acyclovir Tablets, 400 mg and 800 mg.

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

1. The laboratory has stated in both the fasting and fed studies, there was no interference at the retention time of the drug/IS in the subjects' zero hour samples run with and without internal standard added. No evidence could be found substantiating the claim that the subjects' zero hour samples were run <u>without</u> internal standard added, either in the raw data section or the chromatogram section. The laboratory should supply those missing chromatograms.

2. In the fasting study report the laboratory has submitted the work sheets for only the first 9 subjects. The work sheets for <u>all</u> the subjects should be submitted, including those for repeat analyses. The laboratory should submit the peak heights (raw data) of the drug and internal standard, not just the ratios (which are calculated values).

3. There are no raw data for the recovery of drug and internal standard.

   a. The laboratory should supply all raw data and include the %CV.

   b. The laboratory should also state the concentration of the internal standard in the recovery data.

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 Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

cc: Date _____
ANDA 74-870 , Orig File, Dup File
Div File
Field Copy
HFD-615 PRickman
HFD-650 Anderson, J. Lee, CST

BIO-LETTER INCOMPLETE

Endorsements:

J. Lee E.S. 7/1/96
S. Nerurkar 7/1/1996
M. Anderson M Anderson 7/3/96

DRAFTED	JAG.	6/21/96	X:\WPFILE\BIO\N74870
FINAL PRINT	STM	7/01/96	X:\WPFILE\BIO\FINAL\N74870

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

NAI
Bio Amendment
noted & assigned
9/3/96

UPS OVERNIGHT COURIER

BIOEQUIVALENCE AMENDMENT

NEW CORRESP BIOAVAILABILITY

August 22, 1996

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

RECEIVED
AUG 23 1996
GENERIC DRUGS

RE: ANDA #74-870, Acyclovir Tablets, 400 mg and 800 mg

Dear Mr. Sporn:

Reference is made to our March 22, 1996 submission of an Abbreviated New Drug Application for Acyclovir Tablets, 400 mg and 800 mg, ANDA #74-870. Purepac Pharmaceutical Co. is in receipt of your letter dated July 5, 1996 regarding the bioavailability/bioequivalence portion of the referenced Abbreviated New Drug Application.

This amendment represents a complete response to your comments and was prepared in cooperation with ———, the Clinical Research Organization that conducted the bioavailability study supporting this application. We trust that it will fully address all open issues related to the bioavailability/bioequivalence review of our application. Provided below are the Agency's comments (in bold type) followed by our response.

Agency's Comment

1. **The laboratory has stated in both the fasting and fed studies, there was no interference at the retention time of the drug/IS in the subjects' zero hour samples run with and without internal standard added. No evidence could be found substantiating the claim that the subjects' zero hour samples were run without internal standard added, either in the raw data section or the chromatogram section. The laboratory should supply those missing chromatograms.**

Purepac's Response

The chromatograms for both the fasting (Study No. 9504920E) and Fed (Study No. 9504917E) studies contained in Sections 2 and 3 respectively, reflect pre-dose samples run without internal standards added. Each of the chromatograms contains a sample identification number which is referenced in the original application. For the fasting study, the sample identification numbers for all periods are listed on pages 1065 through 1072 of the original application. The fed study references the sample identification numbers for all periods on pages 2417 through 2422 of the original application.

Agency's Comment

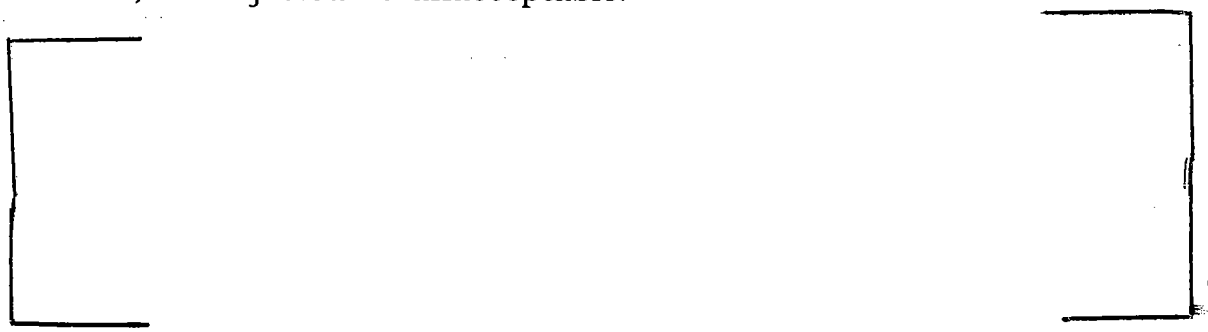
2. **In the fasting study report the laboratory has submitted the work sheets for only the first 9 subjects. The work sheets for all the subjects should be submitted, including those for repeat analyses. The laboratory should submit the peak heights (raw data) of the drug and internal standard, not just the ratios (which are calculated values).**

Purepac's Response

Worksheets #10-36 are included in our original application on pages 1014 to 1063. For the reviewer's convenience, these pages are provided in Section 4 on pages 136 to 185 of this response.

The individual peak heights (raw data) of the drug and the internal standard for Studies No. 9504920E (fasting study) and 9504917E (fed study) are provided in Sections 5 and 6, respectively. ——— does not currently have data capture capabilities. Therefore, these data have been manually entered and double-checked. Please note that the "entry date", appearing at the end of each completed worksheet, is the original entry date for the ratio data. The peak response data was entered within the past week (August 1-8, 1996).

Peak responses are monitored as a part of normal study conduct. Samples, standards, and controls with an internal standard peak responses which deviates more than ±25% from the mean within-run peak response of the internal standard (calculated for all standards and controls) are rejected as unacceptable.



Agency's Comment

3. There are no raw data for the recovery of drug and internal standard.

a. The laboratory should supply all raw data and include the %CV.

b. The laboratory should also state the concentration of the internal standard in the recovery data.

Purepac's Response

See Tables 1.0 through 4.0 in Section 7 of this response. Recovery tests for the internal standard (IS) were conducted at the concentration specified by the analytical procedure [redacted].

In addition, please note that Section 8 contains a photocopy of the Acyclovir validation as a supplement to the information provided in the original submission. This document remains the same, but now includes an updated Quality Assurance Statement (page 297 of this submission).

Purepac Pharmaceutical Co. trusts that the information provided in this **BIOEQUIVALENCE AMENDMENT** is complete and in order, and looks forward to the approval of this Abbreviated New Drug Application.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Helena Goncalves, RPh
Associate, Regulatory Affairs

HG:cch
Enclosures

ANDA 74-870

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

OCT 30 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated March 22, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Tablets, 400 mg and 800 mg.

Reference is also made to your amendments dated June 6, 1996 and August 22, 1996.

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

A. Chemistry Deficiencies

1. On your form 356h you list DMF ——, DMF —— and DMF ——. These DMF's are not referenced in the ANDA jackets nor are there Letters of Authorization (LoA) included. Please make the appropriate revisions and resubmit.

2. Regarding Composition:

a. [redacted]

b.

3. Regarding Active Ingredient:

a. [redacted]

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

10/30/1996 FDA LETTER

B. Labeling Deficiencies

1. GENERAL

Revise your storage recommendations to read, "Store between 15° and 25°C (59° and 77°F)", on all labels and labeling.

2. CONTAINER (100s, 500s, and 1000s):

See General comment.

3. INSERT

a. General Comments

i. Use the abbreviation "mcg" rather than "µg" throughout your insert labeling.

ii. Italicize the terms "*in vitro*" and "*in vivo*" where they appear in your insert labeling.

b. DESCRIPTION

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

ii. Make the following revisions in the last paragraph:

a) ...a white to off-white crystalline...

b) Delete the word "——— ".

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

Delete the third paragraph.

d. INDICATIONS AND USAGE (Genital Herpes Infections, *Recurrent Episodes*)

Make the following revision in the first line, "...studies[16,26-32]...".

e. CONTRAINDICATIONS

...of the formulation. [singular]

f. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, Impairment of Fertility - Revise the last sentence of the first paragraph to read:

...schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

ii. Pediatric Use

...in pediatric patients less...

g. DOSAGE AND ADMINISTRATION

Delete reference to the capsule dosage form, e.g., "... ——————— ...", throughout this section.

h. HOW SUPPLIED

i. Revise your storage recommendations to read, "Store between 15° and 25°C (59° and 77°F)".

ii. We note that on the Master Formula Card (on page 3508) you describe your 400 mg tablet as "...imprinted w/'R' on one side and '606' on the other side". Please revise your description of the 400 mg tablet in this section to include this information.

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

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

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

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

Sincerely yours,

10/29/96

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

cc: ANDA #74-870
DUP Jacket
Division File
FIELD COPY
HFD-600/Reading File

Endorsements:

HFD-647/NGregory/10.9.96 10/17/96

HFD-613/CHoppes/10.15.96 10/18/96

HFD-647/JSimmons/10.10.96 10.17.96

HFD-617/TAmes/10.11.96 10/18/96

X: WPFILE BRANCH7 GREGORY 74870N01.LNG
F/T by pah/10/16/96
x: new firmsnz purepac ltrs&rev 74870no1.naf
NOT APPROVABLE (MAJOR)

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

MAJOR AMENDMENT

NDA ORIG AMENDMENT

FPL

N/A C

UPS OVERNIGHT COURIER

November 11, 1996

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

RECEIVED
NOV 12
GENERIC DRUGS

RE: ANDA #74-870, Acyclovir Tablets, 400 mg and 800 mg

Dear Mr. Sporn:

Reference is made to our March 22, 1996 submission of an Abbreviated New Drug Application for Acyclovir Tablets, 400 mg and 800 mg, ANDA #74-870. Further reference is made to your major chemistry deficiency letter dated October 30, 1996. Your comments are provided in bold type, followed by our response.

A. Chemistry Deficiencies

Agency's Comments

1. **On your form 356h you list DMF ——, DMF —— and DMF ——. These DMF's are not referenced in the ANDA jackets nor are there Letters of Authorization (LoA) included. Please make the appropriate revisions and resubmit.**

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

11/11/1996 PUREPAC LETTER

Purepac's Response: ok

Section 6 of this amendment contains stability reports for the 400 mg and 800 mg drug products. Please note that the Master Formula Card, which defines the product formulation, has been included at the end of each report. The corresponding Master Formulae number is located on the top, left hand corner of each stability data sheet. The stability reports are otherwise identical to the reports previously sent in our original ANDA.

B. Labeling Deficiencies

1. GENERAL

Revise your storage recommendations to read, "Store between 15° and 25°C (59° and 77°F)", on all labels and labeling.

Purepac's Response

In accordance with your request, the storage recommendations have been revised to read, "Store between 15° and 25° (59° and 77°F)", on all our labeling.

2. CONTAINER: (100s, 500s, and 1000s)

See General comment.

3. INSERT *[specific comments are not provided in this letter]*

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

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

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

Purepac's Response:

Twelve final printed container labels for each drug product package size are included in Section 7 of this amendment. We have also incorporated your requested revisions into our insert. Section 7 contains twelve final printed inserts for your review.

Additionally, Section 8 of this amendment contains a comparison of our October 1995 insert, submitted in or original ANDA, and our November 1996 insert, containing the requested revisions. All differences have been annotated and explained.

In conjunction with this submission, Purepac has provided a Field Copy of this amendment to our local district office in accordance with 21 CFR 314.94. Please note that the required Field Copy Certification is contained in Section 9 of this amendment.

This concludes our MAJOR AMENDMENT in response to your letter of October 30, 1996. Purepac Pharmaceutical Co. trusts that you will find this Major Amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Helena Goncalves, RPh
Associate, Regulatory Affairs

HG:cch
Enclosures

ANDA 74-870

Purepac Pharmaceutical Company
Attention: Helena Goncalves, R.Ph.
200 Elmora Avenue
Elizabeth NJ 07207

JAN 15 1997

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 Tablets, 400 mg and 800 mg.

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

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

   The dissolution testing should be conducted in 900 ml of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   > Not less than −% of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

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

Sincerely yours,

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

cc: ANDA 74-870, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
J. Lee

Letter Out, Bio Acceptable

Endorsements:

L. Sanchez

DRAFTED: STM 01/09/97 X:\WPFILE\BIO\FINAL\N74870.APP

APPEARS THIS WAY
ON ORIGINAL

MAY 6 19

FACSIMILE AMENDMENT

ANDA/~~AADA~~: 74-870

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

TO: APPLICANT Purepac PHONE 908-527-9100
ATTN: Joan Janulis FAX 908-527-0649

FROM: Tim Ames, PROJECT MANAGER (301-~~594-5599~~)
827-5849

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 3/22/96, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Acyclovir Tablets, 400 mg & 800 mg

Reference is also made to your amendment(s) dated 11/11/96.

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

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

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\faxtrak\faxcov.fax

MAY 6 1997

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

ANDA Number: 74-870 Date of Submission: November 11, 1996

Applicant's Name: Purepac Pharmarmaceutical Co.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

INSERT

1. DESCRIPTION

   We note that magnesium stearate is listed in this section as an inactive ingredient. The Master Formula Cards submitted in this amendment (p 45 [400 mg] and p 107 [800 mg]) do not include this inactive ingredient. Please revise your labeling if magnesium stearate is no longer present in your product and/or comment.

2. CLINICAL PHARMACOLOGY (Pharmacokinetics)

   Make the following revision in the fourth paragraph, "In another study, the influence...", (delete "[redacted]").

3. ADVERSE REACTIONS (Observed During Clinical Practice, *Nervous*)

   ...paresthesia, seizure, somnolence...

Please revise your package insert labeling, as instructed above, and submit final print.

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

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

Adolph Uzzo for /

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

APPEARS THIS WAY
ON ORIGINAL

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

FACSIMILE AMENDMENT

NEW CORRESP
NC
MAI 5/22/97
MRC

UPS OVERNIGHT COURIER

May 8, 1997

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room
MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-870, Acyclovir Tablets, 400 mg & 800 mg

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Acyclovir Tablets, ANDA 74-870. Further reference is made to the agency's May 6, 1997 telefax correspondence requesting revisions to our package insert labeling.

Purepac Pharmaceutical Co. has revised our package insert labeling in accordance with the agency's comments, and is enclosing twelve (12) final printed copies, as required. Also enclosed is a side-by-side comparison of our revised insert versus the version contained in our last submission. All differences have been annotated and explained.

With regard to comment #1 ("DESCRIPTION" section of our package insert), please note the following:

Magnesium Stearate is an inactive ingredient utilized ——— in Acyclovir Tablets, 400 mg and 800 mg. Magnesium stearate is listed on the Master Formula cards for the total batch formulae of the 400 mg and 800 mg products on pages 42 and 106, (respectively) of our Major Amendment dated November 11, 1996. The master formula cards noted in the Agency's comment (page 45 for the 400 mg tablet and page 107 for the 800 mg tablet) reflect ——

[redacted]

MAY 09 1997

GENERIC DRUGS

Accordingly, the description section of the insert accurately lists all of the ingredients contained in Acyclovir Tablets, 400 mg and 800 mg.

This completes our Facsimile Amendment in response to the agency's correspondence dated May 6, 1997. Purepac trusts that this submission is complete and in order and looks forward to the approval of our Abbreviated New Drug Application.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs
and Analytical Development

/cs

Enclosures

APPEARS THIS WAY
ON ORIGINAL