

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

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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-92
HFD-210/BPoole

Endorsements:

P. Du 3/22/97
HFD-647/NGregory/4.22.97
HFD-613/CHoppes/AVEzza/5.10.97 *C. Holquist for 5/22/97* *Choppes for 5/22/97*
HFD-647/SBasaran/5.22.97 *S. Basaran 5/22/97*
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J Phillips 6/2/97

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 74-870

LABELING

SAMPLE

40-8806

ACYCLOVIR TABLETS

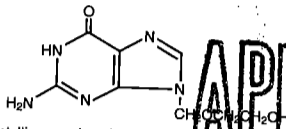
Revised — May 1997

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]-6H-purin-6-one; it has the following structural formula:



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

Microbiology: The quantitative relationship between the *in vitro* susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID₅₀), vary greatly depending upon the particular assay used,⁷ the cell type employed,⁸ and the laboratory performing the test.¹ The ID₅₀ 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 ID₅₀ 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 ID₅₀ 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, isolates were sensitive to ≤ 2.2 mcg/mL and 50% of all isolates were sensitive to ≤ 0.7 mcg/mL of acyclovir. 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.¹¹⁻¹⁵ Strains with alterations in viral TK²⁰ or viral DNA polymerase²¹ 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 ID₅₀ 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 ID₅₀ values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.¹

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

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

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

In another study, the influence of food on the absorption of acyclovir was not apparent. Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy)methyl]guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

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

INDICATIONS AND USAGE:

Acyclovir 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 reinstatement 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 orally 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 298 (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.

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

PUREPAC

NDC 0228-2606-11

ACYCLOVIR TABLETS

400 mg

CAUTION: Federal law prohibits dispensing without prescription.



100 TABLETS

Rev. 11/96

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



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.

Rev. 11/96

PUREPAC

NDC 0228-2606-50

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



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.

Rev. 11/96

PUREPAC

NDC 0228-2606-96

ACYCLOVIR TABLETS

400 mg

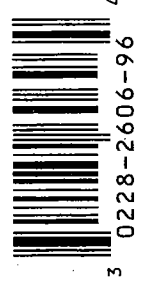
CAUTION: Federal law prohibits dispensing without prescription.



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



NDC 0228-2607-11

PUREPAC

ACYCLOVIR TABLETS

800 mg

100 TABLETS

P

CAUTION: Federal law prohibits dispensing without prescription.

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. _____

SEARCHED



3 0228-2607-11 4

NDC 0228-2607-50

PUREPAC

ACYCLOVIR TABLETS

800 mg

500 TABLETS

P

CAUTION: Federal law prohibits dispensing without prescription.

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. _____

SEARCHED

JUN 5 1996

SAMPLE



3 0228-2607-50 3

NDC 0228-2607-96

PUREPAC

ACYCLOVIR TABLETS

800 mg

1000 TABLETS

P

CAUTION: Federal law prohibits dispensing without prescription.

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. _____

SEARCHED



3 0228-2607-96 1

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 bioequivalency values: insert to study. List C_{max}, T_{max}, 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.

