CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-090

Name: Acyclovir Capsules USP, 200 mg

Sponsor: Stason Industrial Corporation

Approval Date: January 26, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-090

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-090

APPROVAL LETTER

ANDA 75-090

JAN 26 1999

Stason Industrial Corporation
Attention: Harry T. Fan
11 Morgan
Irvine, CA 92618-2005

Dear Sir:

This is in reference to your abbreviated new drug application dated March 10, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules USP, 200 mg.

Reference is also made to your amendments dated November 20, 1997; and January 19, June 26, September 3, October 6, October 19 and November 5, 1998.

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

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 1/26/99

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

cc: ANDA 75-090
Division File
FIELD COPY
HFD-610/JPhillips
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Endorsements: R. Permisohn 12/21/98
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Robert Lewis 1/26/99

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APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-090

APPROVED LABELING

STASON™

NDC 60763-2041-0
100 Capsules

Acyclovir Capsules
200 mg

R_x only
Made in USA

Each Capsule contains: 200 mg Acyclovir, USP.
For indications, dosage, precautions, etc., see accompanying literature.

Dispense in a tight container as defined in the USP.

Store between 15° and 25° C (59° to 77° F) and protect from moisture.

Manufactured by:
Stason Pharmaceuticals, Inc., Irvine, CA 92618

EXP: JAN 2 0 1999

LOT:

may 2

STASON™

NDC 60763-2041-4
400 Capsules

Acyclovir Capsules 200 mg

R_x only
Made in USA

Each Capsule contains: 200 mg Acyclovir, USP.

For indications, dosage, precautions, etc., see accompanying literature.

Dispense in a tight container as defined in the USP.

Store between 15° and 25° C (59° to 77° F) and protect from moisture.

Manufactured by:
Stason Pharmaceuticals, Inc., Irvine, CA 92618

EXP.:

LOT: JAN 26 1999

Mayo

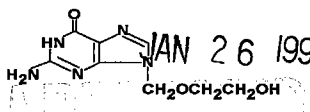
ACYCLOVIR CAPSULES, USP

Revised November, 1998
145-P-0

ACYCLOVIR CAPSULES, USP

DESCRIPTION: Acyclovir is an antiviral drug. Acyclovir capsules are formulated for oral administration. Each capsule contains 200 mg of acyclovir and the inactive ingredients lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycolate. The capsule shell consists of gelatin, FD&C Blue No. 1, and titanium dioxide. Additives present are sodium lauryl sulfate and silicon dioxide. Printed with edible black ink containing D & C Yellow No. 10 Aluminum Lake, FD &.C Blue No. 1 Aluminum Lake, FD &.C Blue No. 2 Aluminum Lake, FD &.C Red No. 40 Aluminum Lake, n-butyl alcohol, pharmaceutical glaze (modified) in SD-45, propylene glycol, SDA-3A alcohol, and synthetic black iron oxide.

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



Chemical formula:
$C_8H_{11}N_5O_3$

Acyclovir is a white to off-white crystalline powder with a molecular weight of 225.21. The maximum solubility in water at 37° C is 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25.

VIROLOGY:

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

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

Antiviral Activities: The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/mL.

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

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

CLINICAL PHARMACOLOGY:

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

Table 1: Acyclovir Pharmacokinetic Characteristics (Range)

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

*Bioavailability decreases with increasing dose

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

Table 2: Acyclovir Peak and Trough Concentrations at Steady State

Parameter	200 mg	400 mg	800 mg
C^{ss}_{max}	0.83 mcg/mL	1.21 mcg/mL	1.61 mcg/mL
C^{ss}_{trough}	0.46 mcg/mL	0.63 mcg/mL	0.83 mcg/mL

There was no effect of food on the absorption of acyclovir (n=6); therefore, Acyclovir capsules may be administered with or without food.

The only known urinary metabolite is 9-[(carboxymethoxy) methyl]guanine.

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

Pediatrics: In general, the pharmacokinetics of acyclovir in pediatric patients is similar to that of adults. Mean half-life after oral doses of 300 mg/m^2 and 600 mg/m^2 in pediatric patients ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

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

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

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

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

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

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

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

Adults greater than 50 years of age showed greater benefit.

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

INDICATIONS AND USAGE:

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

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

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

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

WARNINGS: Acyclovir capsules are intended for oral ingestion only.

PRECAUTIONS: Dosage administration is recommended when administering acyclovir to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

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

Herpes Zoster: There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes Infections: Patients should be informed that acyclovir is not a cure for genital herpes. There are no data evaluating whether acyclovir will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

Chickenpox:
Chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity. Adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course.

Drug Interactions: See CLINICAL PHARMACOLOGY: **Pharmacokinetics:**

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see 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. Maximum plasma concentrations were three to six times human levels in the mouse bioassay and one to two times human levels in the rat bioassay.

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

A positive result was demonstrated in one of two *in vitro* cell transformation assays, and morphologically transformed cells obtained in this assay formed tumors when inoculated into

immunosuppressed, syngeneic, weaning mice. No mutagenic activity was demonstrated in another, possibly less sensitive, *in vitro* cell transformation assay.

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

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

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

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

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

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

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

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

ADVERSE REACTIONS:

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

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

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

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

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

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

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

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

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

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

DOSAGE AND ADMINISTRATION:

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

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

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

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

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

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

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

Intravenous acyclovir is indicated for the treatment of var zoster infections in immunocompromised patients.

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

Patients with Acute or Chronic Renal Impairment:
In patients with renal impairment, the dose of acyclovir capsules should be modified as shown in Table 3:

Table 3: Dosage Modification for Renal Impairment

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73 m^2)	Adjusted Dosage Regimen Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5 x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5 x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

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

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.

Bioequivalence of Dosage Forms: Acyclovir Suspension was shown to be bioequivalent to Acyclovir Capsules (n=20) and one Acyclovir 800-mg tablet was shown to be bioequivalent to four Acyclovir 200-mg capsules (n=24).

HOW SUPPLIED: Acyclovir capsules (aqua blue op and light blue opaque cap) containing 200 mg Acyclo printed with "ACYCLOVIR 200" on the body, "STASC cap and are available in bottles of 100 (NDC 60763-204₂ 400 (NDC 60763-2041-4). Store between 15° and 25°C (59 77F) and protect from moisture.

Stason Pharmaceuticals, Inc.
Irvine, CA 92618

Revised November, 1998
145-P-0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-090

LABELING REVIEW(S)

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

ANDA Number: 75-090

Date of Submission: March 10, 1997

Applicant's Name: Stason Industrial Corporation

Established Name: Acyclovir Capsules, 200 mg

Labeling Deficiencies:

1. CONTAINER:

   Revise to read, "ACYCLOVIR CAPSULES 200 mg".

2. INSERT

   a. Title

      Please note "Acyclovir capsules" is not listed in the USP. Therefore, delete "USP" from the title.

   b. General Comment

      i. Due to recent and significant changes in the insert labeling of the listed drug Zovirax® (Glaxo Wellcome Inc.; revised March 1997 and approved May 29, 1997), please revise your package insert labeling to be in accord with the enclosed insert labeling.

      ii. When abbreviating micrograms we encourage the use of "mcg" rather than "μg". Please revise your insert labeling accordingly.

   c. DESCRIPTION

      i. We note you have listed edible black ink and the components of the capsule shell in your list of inactive ingredients. However, these components are not listed in your components statements. Please revise and/or comment.

      ii. List any dyes in the imprinting ink.

      iii. Revise the second paragraph to read, "... following structural formula:".

iv. Relocate the chemical formula, "$C_8H_{11}N_5O_3$" to appear on a separate line.

v. To be in accord with USP 23, make the following revisions in the last paragraph:

...a white to off-white crystalline powder with a molecular weight of 225.21, and ...

d. HOW SUPPLIED

Revise your "Manufactured by" statement to be consistent with your container label.

Please revise your container labels and package insert labeling, as instructed above, and submit final printed container labels and draft (or if you prefer final printed) insert labeling.

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 the enclosed insert labeling with all differences annotated and explained.

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

Enclosure: Insert labeling of the reference listed drug-**Zovirax®**.

Copy of Reference Listed Drug Labeling Removed

NOTE TO THE CHEMIST

It makes no difference
RC 10/1/97

The firm lists "acyclovir empty capsule" in their composition statement. Should they revise this to read "empty capsule"?

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x, for unit dose		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			x
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?* See comment under HOW SUPPLIED.			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients of the innovator slightly differ from this ANDA].	X		

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. * [See comment under DESCRIPTION].	x*		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [pending]			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. [See FTR].			

FOR THE RECORD:

1. Labeling review was based on the labeling of ZOVIRAX® (Glaxo Wellcome: March 1997 and approved May 29, 1997).

2. DISPENSE/STORAGE recommendations:

   -Dispensing recommendations:

   USP: Not USP [However, USP packaging and storage for the active ingredient "acyclovir" is "Preserve in tight containers"].
   PF: tight container
   NDA: tight container
   ANDA:tight container

   -Storage recommendations:

   PF: tight containers
   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) and protect from moisture.

3. Patents/Exclusivity

   RLD patent expired on 4/22/97.

4. Components/Composition

   The list of inactive ingredients in the DESCRIPTION section is consistent with the firm's components statement.
   [Vol. 1.1, Section p.162].
   See comment under DESCRIPTION.

5. Container/Closure

   100's & 400's - HDPE/metal non-CRC screw caps
   [Vol. 1.1, p. 260]

6. The firm's imprints described in the HOW SUPPLIED section is consistent with the firm's physical description of their finished dosage form.
   [Vol. 1.1, p.343]

7. The following information is from a previous review/reviewer FTR.

   a. The insert mentions no food effect -

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

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

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

Date of Review: August 20, 1997

Date of Submission: March 10, 1997

Primary Reviewer:
Jacqueline White, Pharm.D. Date:
Jacqueline White, Pharm.D 9-4-97

Team Leader: Date:
9/5/97

cc
ANDA 75-090
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes (no cc)
njg/9/4/97/x:\new\...75090na1.1
Review

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

ANDA Number: 75-090

Date of Submission: November 20, 1997

Applicant's Name: Stason Industrial Corporation

Established Name: Acyclovir Capsules, 200 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

   Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only" on your labels and labeling. We refer you to the Guidance for Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CONTAINER: 100s and 400s

   a. See GENERAL COMMENT.

   b. In the storage statement replace revise "at" to read "between" and "to" to read "and".

3. INSERT

   a. GENERAL COMMENT

      Use italic print for the text "*in vitro*" and "*in vivo*" where it appears throughout the package insert labeling.

   b. DESCRIPTION

      i. We note that you list "[redacted]' as an inactive ingredient for the capsule shell. However, in your components statement "FD&C Blue No. 1" is listed. Please revise and/or comment.

ii. Add a comma following "propylene glycol" in the last sentence of the first paragraph.

c. VIROLOGY (Antiviral Activities)

Revise as follows:

... for HSV-2. The IC_{50} for acyclovir ...
[Note: subscript]

d. CLINICAL PHARMACOLOGY

i. Revise the first paragraph to read as follows:

- "administration" instead of "administration"
- "simplex or" instead of "simplexor"

ii. Table 1

Revise "1 0% to 20%" to read "10% to 20%*". [Delete extra space and add asterisk].

iii. Table 2

A). Revise "C_{max}^{css}" to read "C_{max}^{ss}"

B). 200 mg

Revise "—— mcg/mL" to read "0.83 mcg/mL".

C). 800 mg

Revise "—— mcg/mL" to read "0.83 mcg/mL".

iv. Pediatrics

Revise "————————————" to read "300 mg/m^2 and 600 mg/m^2".

v. Add the following subsection immediately following the "Pediatrics" subsection.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir

has been shown to increase acyclovir half-life and systemic exposure. Urinary excretion and renal clearance were correspondingly reduced.

vi. Clinical Trials (Recurrent Genital Herpes)

Revise "1 0 years" to read "10 years". [Delete the extra space].

e. INDICATIONS AND USAGE

In each of the three subsections, revise " ——————— " to read "Acyclovir capsules are".

f. PRECAUTIONS

i. Drug Interactions

Delete the extra space appearing in the text.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

A) In the last sentence of the first paragraph, correct the spelling of "acyclovir" and revise to read as follows:

... dosing schedules (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

B) In the sixth paragraph revise "I 1" to read "11".

C) Revise the seventh paragraph to read as follows:

... 60 mg/kg/day orally for 1 year ...

iii. Pregnancy

A) First paragraph

- See comment 3(f)(~~iii~~ii)(B).
- Revise "1 00" to read "100".
- Revise "1 0" to read "10".

- Revise " [redacted] " to read "anomalies".

g. DOSAGE AND ADMINISTRATION

i. Revise "reevaluated" to read "re-evaluated".

ii. Treatment of Chickenpox

Print "**per dose**" in bold print.

iii. Add the following paragraph as the penultimate paragraph of this subsection:

> Intraveous acyclovir is indicated for the treatement of varicella-zoster infections in immunocompromised patients.

iv. Table 3

Revise " [redacted] " to read "(mL/min/1.73 m^2)".

v. Bioequivalence of Dosage Forms

Throughout this section revise [redacted] to read "acyclovir".

h. HOW SUPPLIED

See GENERAL COMMENT.

Please revise your labels and labeling, as instructed above, and submit in 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.

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

NOTES/QUESTIONS TO THE CHEMIST

We plan to send the following comment to the firm:

We note that you list "[redacted]" as an inactive ingredient for the capsule shell. However, in your components statement "FD&C Blue No. 1" is listed. Please revise and/or comment.

Do you concur? yes RCh 7/16/98

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x, for unit dose		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			x
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?* See comment under HOW SUPPLIED.			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration? [Some of the inactive ingredients of the innovator slightly differ from this ANDA].	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [pending]			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. [See FTR].			

FOR THE RECORD:

1. Labeling review was based on the labeling of ZOVIRAX® (Glaxo Wellcome: March 1997 and approved May 29, 1997).

2. DISPENSE/STORAGE recommendations:

   -Dispensing recommendations:

   USP: Not USP [However, USP packaging and storage for the active ingredient "acyclovir" is "Preserve in tight containers"].
   PF: tight container
   NDA: tight container
   ANDA: tight container

   -Storage recommendations:

   PF: tight containers
   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) and protect from moisture.

3. Patents/Exclusivity

   RLD patent expired on 4/22/97.

4. Components/Composition

   The firm has revised the list of inactive ingredients in the DESCRIPTION section and it is consistent with the components and composition statements submitted with the 11/20/97 submissions, EXCEPT for the capsule shell.
   [See comment to firm under DESCRIPTION].
   [Vol. B1.1, p. 023 & Vol. 3.1, June or July 1998 submission].

5. Container/Closure

   100's & 400's - HDPE/metal non-CRC screw caps
   [Vol. 1.1, p. 260 & Vol. B1.1, 085]

6. The firm's imprints described in the HOW SUPPLIED section is consistent with the firm's physical description of the finished dosage form.
   [Vol. 1.1, p.343]

7. The physical description of the capsuels in the HOW SUPPLIED section is consitent with the firm's finished dosage form and physical description in the application.

   [Vol. B.1.1, p. 20 (11/20/97 submisiion) and p. 344]

8. Bioavailability/Bioequivalence

   [The bio. review dated 12/15/97 (Vol. B1.1) contained deficiencies].

   Bio. in vivo bioequivalence study waiver was granted on ____.

   Bio. acceptable letter out was dated ___ [Vol.]

9. Manufacture:

   Stason Pharmaceuticals, Inc.
   11 Morgan, Irvine, California 92618
   [Vol. B1.1, p.195]

10. Package size:

    RLD - 100s & unit-dose 100s
    ANDA - 100s & 400s

11. The following information is from a previous review/reviewer FTR.

    a. The insert mentions no food effect -

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

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

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

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

Date of Review: 7/10/98

Jacqueline White, Pharm.D. 7/9/98
Primary Reviewer — Date
Jacqueline White, Pharm.D.

Team Leader — 7/15/98
Date

cc

ANDA 75-090
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes (no cc)
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Review

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

ANDA Number: 75-090

Date of Submission: September 3, 1998

Applicant's Name: Stason Industrial Corporation

Established Name: Acyclovir Capsules, 200 mg

Labeling Deficiencies:

1. CONTAINER: 100s and 400s

   Satisfactory, however, at the time of next printing, revise as follows:

   ... (59° and 77°F) ...
   ["and" instead of "to"]

2. INSERT

   a. GENERAL COMMENT

      Your insert labeling is difficult to read, especially the asterisks, superscripts, subscripts and the tables. Improve the readability of the text of your insert labeling, by increasing the print size to a minimum of 4 point, including the text found in the tables.

   b. PRECAUTIONS (Drug Interactions)

      ... PHARMACOLOGY: Pharmacology.
      [Delete the extra space appearing between the text].

   c. DOSAGE AND ADMINISTRATION (Treatment of Chickenpox)

      Relocate the paragraph, "Intravenous acyclovir is ...patients" to appear immediately following the paragraph "***Adults and Children over 40 kg:*** ... 5 days". In addition, correct the spelling of "acyclovir".

d. HOW SUPPLIED

See our comment under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in 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.

_____

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