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

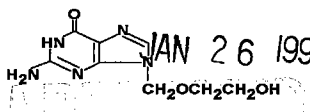
ACYCLOVIR CAPSULES, USP

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)
x:\new\...75090na2.1
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

NOTE TO THE CHEMIST

DESCRIPTION section:

The firm revised "[redacted]" to read "FD&C Blue No. 1 in the list of inactive ingredients for the capsule shell.

Do you concur? I concur /
RCB 9/24/98

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	
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	
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)			
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.
   [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: 9/10/98*

Primary Reviewer
Jacqueline White, Pharm.D.

9/23/98
Date

Team Leader

9/23/98
Date

cc

ANDA 75-090
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes (no cc)
x:\new\...75090na2.1
Review

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* Reviewer at remote site.

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

ANDA Number: 75-090

Date of Submission: October 6, October 19 & November 5, 1998

Applicant's Name: Stason Industrial Corporation

Established Name: Acyclovir Capsules, 200 mg

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

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS: 100s & 400s

Satisfactory in FPL as of September 3, 1998 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of November 5, 1998 submission

REVISIONS NEEDED POST-APPROVAL:

CONTAINER (100s and 400s) - Revise to read as follows:

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

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 20-089

NDA Drug Name: Zovirax®

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: May 29, 1997/S-011

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Other Comments:

The text of the final printed insert labeling submitted on November 5, 1998 is identical to that submitted on October 6, 1998 with increased readability as requested by the Agency. Part of the text has been removed by the punching hole in the process of filing in the documentation room. I have brought this issue to the attention of the documentation personnel. We will approve this insert labeling without asking the firm to resubmit.

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.
[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 capsules in the HOW SUPPLIED section is consistent with the firm's finished dosage form and physical description in the application.
[Vol. B.1.1, p. 20 (11/20/97 submission) and p. 344]

8. Manufacture:

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

9. Package size:

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

10. 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.

11. See Other Comments in the approval summary.

Date of Review: December 1, 1998

Primary Reviewer
Chan Park

12/1/98
Date

Team Leader
Charlie Hoppes

12/1/98
Date

Concur: John Sheu 12/1/98

cc

ANDA 75-090
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
X:\NEW\FIRMSNZ\STASON\LTRS&REV\75090AP.1
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-090

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA 75-090

3. NAME AND ADDRESS OF APPLICANT
Stason Industrial Corporation
11 Morgan
Irvine, CA 92718-2005

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies , that to the best of its knowledge, U.S. Patent No. 4,199,574 expired on April 22, 1997, and the product is not covered by any exclusivity provisions.

Innovator: Glaxo Wellcome - Zovirax®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir

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

9. AMENDMENTS AND OTHER DATES:
Firm: 3/10/97 - Original. Subject of this review.
5/7/97 - Response to refuse to file. Subject of this review.
6/9/97 - Amendment, analytical methods.

FDA: 3/28/97 - Phone memo, regarding patent certification.
5/1/97 - Refuse to file, incomplete dissolution data.
5/16/97 - Acknowledgment, need analytical methods.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

[redacted]

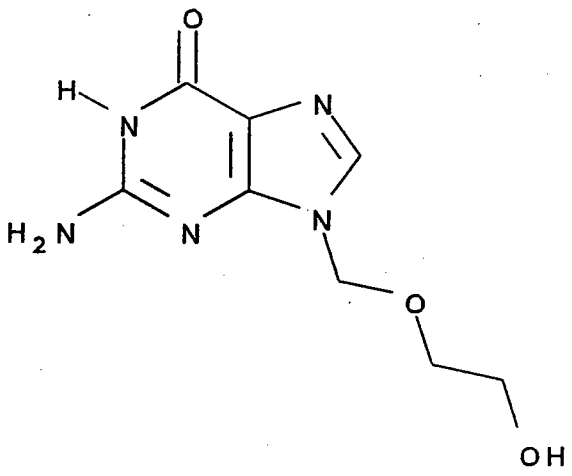
13. DOSAGE FORM
Capsule

14. POTENCIES
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

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



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

16. RECORDS AND REPORTS

N/A

17. COMMENTS

a. Composition:

(1)

(2)

b. Active Ingredient:

(1)
(2)
(3)

c. Inactive Ingredients:

d. Manufacturing and Processing:

(1)

(2) [redacted]

(3)

e. Laboratory Controls (Finished Dosage Form):
(1) [redacted]

(2) Dissolution pending Bio. acceptance.

f. Stability:
(1) [redacted]

(2)
(3)

(4)

(5) Dissolution pending Bio. acceptance.

g. Finished product method validation pending Bio. acceptance of dissolution method.

h. Container, Carton, and Insert labeling not satisfactory.

I. Bio. assigned to Zakaria Wahba on 5/20/97, pending.

DMF and EER acceptable.

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

19. REVIEWER: Norman Gregory

DATE COMPLETED: 10/6/97

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information from

CHEMISTRY REVIEW #1

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please be advised that the suitability of the proposed dissolution procedure and specification will be established upon completion of review by the Division of Bioequivalence.

Sincerely yours,

10/24/97

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-090
DUP File
DIVISION FILE
Field Copy

Endorsements:

HFD-647/NGregory/10.6.97

HFD-647/UVenkataram/10.7.97

HFD-617/TAmes/10.16.97

HFD-640/FHolcombe/

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X:\NEW\FIRMSNZ\STASON\LTRS&REV\75090N01.NAF

F/T by VLJ\10/17/97

NOT APPROVABLE - Major

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 2

2. ANDA 75-090

3. NAME AND ADDRESS OF APPLICANT
Stason Industrial Corporation
11 Morgan
Irvine, CA 92718-2005

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies , that to the best of its knowledge, U.S. Patent No. 4,199,574 expired on April 22, 1997, and the product is not covered by any exclusivity provisions.

Innovator: Glaxo Wellcome - Zovirax®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir

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

9. AMENDMENTS AND OTHER DATES:

Firm:
- 3/10/97 - Original.
- 5/7/97 - Response to refuse to file.
- 6/9/97 - Amendment, analytical methods.
- 11/20/97 - Response to 1st def. letter (Chem. & labeling). Subject of this review.
- 1/19/98 - Response to 1st def. letter (Bio.).

FDA:
- 3/28/97 - Phone memo, regarding patent certification.
- 5/1/97 - Refuse to file, incomplete dissolution data.
- 5/16/97 - Acknowledgment, need analytical methods.
- 10/27/97 - 1st def. letter (Chem. & labeling).
- 11/3/97 - Phone memo, clarification of questions in 10/27/97 amendment.
- 12/15/97 - 1st def. letter (Bio.).

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

[redacted]

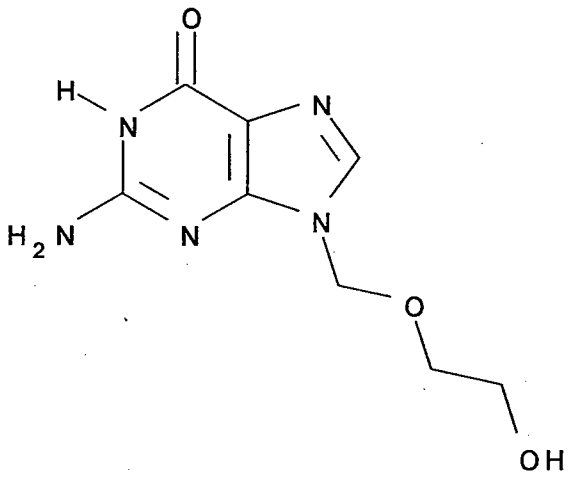
13. DOSAGE FORM
Capsule

14. POTENCIES
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

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



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

16. RECORDS AND REPORTS
N/A

17. COMMENTS
a. Composition:
(1)
(2)

[redacted]

(3) [redacted]

b. Manufacturing and Processing:

[redacted]

c. Laboratory Controls (Finished Dosage Form):
Dissolution pending Bio. acceptance.

d. Stability:
Dissolution pending Bio. acceptance.

e. Finished product method validation pending Bio. acceptance of dissolution method.

f. Container, Carton, and Insert labeling pending review.

g. Bio. assigned to Zakaria Wahba on 5/20/97, pending review of 1/9/98 amendment.

DMF and EER acceptable.

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

19. REVIEWER: Norman Gregory

DATE COMPLETED: 4/22/98

APPEARS THIS WAY
ON ORIGINAL

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CHEMISTRY REVIEW #2 PP. 4-9

*** Finish Dosage Form: Pending acceptable dissolution method from Bio.

32. LABELING - by on
*** Container: **Pending review.**
*** Insert: **Pending review.**

33. ESTABLISHMENT INSPECTION - Satisfactory
Sent for applicant and manufacture of active ingredient on 5/29/97. Acceptable 8/26/97.

34. BIOEQUIVALENCY STATUS - Not Satisfactory
Bioequivalence deficiency letter issued 12/15/97, firm responded 1/19/98, assigned to Zakaria Wahba on 1/21/98.

*** Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory (p. 431, Orig.)
Categorical Exclusion requested. Certifies that they will comply with all Federal, State and Local environmental laws.

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

If no, explain reason(s) below:

37. **DMF CHECKLIST FOR ANDA #75-090 REVIEW # 2**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/[redacted]	3	SAT	10/3/97

Comments: by Norman Gregory

[redacted]	III [redacted]	4		

Comments:

[redacted]	III,[redacted]	4		

Comments:

[redacted]	III/[redacted]	4		

Comments:

[redacted]	IV/[redacted]	4		

Comments:

Comments:

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no relevant revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Checklist page 1 of 1 .

Norman Gregory		4/22/98
Reviewer	Signature	Date

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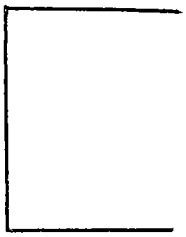
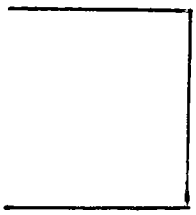
confidential commercial

information from

CHEMISTRY REVIEW #2





B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please be advised that the suitability of the proposed dissolution procedure and specification will be established upon completion of review by the Division of Bioequivalence.

Sincerely yours,

6/8/98

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

cc: ANDA 75-090
DUP File
DIVISION FILE
Field Copy

Endorsements:

HFD-647/NGregory/4.22.98 for U.V. Venkataram

HFD-647/UVenkataram/4/23/98 U.V. Venkataram 5/12/98

HFD-617/TAmes/5/11/98 5/15/98

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F/T by pah/5/12/98

NOT APPROVABLE - FACSIMILE

APPEARS THIS WAY ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.
3

2. ANDA
75-090

3. NAME AND ADDRESS OF APPLICANT
Stason Pharmaceuticals, Inc.
Attn: Monica M. Tinio
11 Morgan
Irvine, CA 92718-2005

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies , that to the best of its knowledge, U.S. Patent No. 4,199,574 expired on April 22, 1997, and the product is not covered by any exclusivity provisions. (per reviews # 1 and # 2)

Innovator: Glaxo Wellcome - Zovirax®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir

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

9. AMENDMENTS AND OTHER DATES:

Firm:
- **3/10/97** - Original.
- **5/7/97** - Response to refuse to file.
- **6/9/97** - Amendment, analytical methods.
- **11/20/97** - Response to 1st def. FAX dated **10/27/97** (Chem. & labeling).
- **1/19/98** - Response to 1st def. FAX dated **12/15/97** (Bio.).
- **6/26/98** - Response to 2nd def. FAX dated **6/9/98** (Chem.). **Subject of this review.**

FDA:
- **3/28/97** - Phone memo, regarding patent certification.
- **5/1/97** - Refuse to file, incomplete dissolution data.
- **5/16/97** - Acknowledgment, need analytical methods.

10/27/97 - 1st def. FAX (Chem. & labeling).
11/3/97 - Phone memo, clarification of questions in **10/27/97**, amendment.
12/15/97 - 1st def. letter (Bio).
6/9/98 - 2nd def. FAX (Chem.).

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
℞

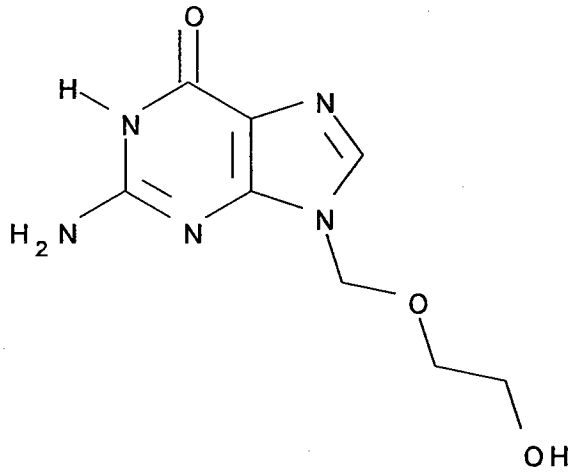
12. RELATED IND/NDA/DMF(s)
DMF _____

13. DOSAGE FORM
Capsules

14. POTENCIES
200 mg

15. CHEMICAL NAME AND STRUCTURE

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



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

16. RECORDS AND REPORTS
N/A

17. COMMENTS
6/26/98, Amendment: Response to our **6/9/98**, chemistry def. FAX addressing the following:

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confidential commercial

information from

CHEMISTRY REVIEW #3 pp. 3-12

32. LABELING - Unsatisfactory.
Draft container labels and insert labeling that were submitted in the **11/20/97**, amendment require revision per the Jacqueline White review dated **7/10/98**, FAXed on **7/15/98**, to the firm.

33. ESTABLISHMENT INSPECTION - Satisfactory
Sent for applicant and manufacture of active ingredient on 5/29/97. Acceptable 8/26/97.

34. BIOEQUIVALENCY STATUS - Unsatisfactory
The Zakaria Wahba DOB review dated **5/29/98**, recommends that "The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions...have been found acceptable by the Division of Bioequivalence.". However, the same review makes reference to the *PF Jan. - Feb. 1998*, as a source for a dissolution procedure in which the dissolution medium differs from that used by Stason. As a consequence, in a separate BIO communication endorsed on **5/29/98**, by Dale Conner, the conditions in the *PF* were recommended to be incorporated into the stability and qc programs. The cited dissolution medium is 0.1 *N* HCl rather than degassed water. The actual reference is the *PF, Vol. 24, No. 1, January - February 1998, pp. 5547 - 5548.*

*** Pending acceptance of the recommended dissolution medium by the firm.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory (p. **431**, Orig.)
Categorical Exclusion requested. Certifies that they will comply with all Federal, State and Local environmental laws.

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

If no, explain reason(s) below:

The previous review and FAX to the firm designated the response as a MINOR AMENDMENT and this submission had a higher review priority.

37. **DMF CHECKLIST FOR ANDA #75-090 REVIEW # 3**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/ [redacted]	3	SAT	10/3/97

Comments: As per Chemistry Review # 2 by Norman Gregory.

[redacted]	III/ [redacted]	4	

Comments: As per Chemistry Review # 2 by Norman Gregory.

[redacted]	III/ [redacted]	4	

Comments: As per Chemistry Review # 2 by Norman Gregory.

[redacted]	III/ [redacted]	4	

Comments: As per Chemistry Review # 2 by Norman Gregory.

[redacted]	IV/ [redacted]	4	

Comments: As per Chemistry Review # 2 by Norman Gregory.

Comments:

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no relevant revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Checklist page 1 of 1. Robert C. Permisohn (Reviewer) _____ (Signature) 7/17/98 (Date)

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CHEMISTRY REVIEW #3

B. Labeling Deficiencies

Labels and labeling revisions are required as per our facsimile dated July 15, 1998.

C. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The evaluation of all firms involved in the manufacture and testing of the drug product with the current good manufacturing practices regulations will be undertaken by our Office of Compliance. A satisfactory evaluation is required prior to approval of this application.

2. Please provide any additional data for ongoing stability studies for the exhibit batch if available.

3. The evaluation of the analytical methods to be used for release and stability purposes will be undertaken by an FDA field laboratory at such time that the dissolution testing criteria have been finalized.

Sincerely yours,

8/27/98

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

cc: ANDA 75-090
DUP File
DIVISION FILE
Field Copy

Endorsements:

HFD-647/RCPermisohn/7-16-98 U.V. Venkataram for 8/19/98
HFD-647/UVenkataram/7/27/98 U.V. Venkataram 8/19/98
HFD-647/TAmes/8/5/98 PM Burkhart for TA. 8/20/98
HFD-613/JWhite 8/24/98

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F/T by pah/8/11/98
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NOT APPROVABLE - MINOR AMENDMENT

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.
   4

2. ANDA
   75-090

3. NAME AND ADDRESS OF APPLICANT
   Stason Pharmaceuticals, Inc.
   Attn: Monica M. Tinio
   11 Morgan
   Irvine, CA 92718-2005

4. LEGAL BASIS FOR SUBMISSION
   The applicant certifies , that to the best of its knowledge, U.S. Patent No. 4,199,574 expired on April 22, 1997, and the product is not covered by any exclusivity provisions. (per reviews # 1 and # 2)

   Innovator: Glaxo Wellcome - Zovirax®

5. SUPPLEMENT(s)
   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME
   Acyclovir

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

9. AMENDMENTS AND OTHER DATES:

Firm:	**3/10/97**	- Original.
	5/7/97	- Response to refuse to file.
	6/9/97	- Amendment, analytical methods.
	11/20/97	- Response to 1st def. FAX dated **10/27/97** (Chem. & labeling).
	1/19/98	- Response to 1st def. FAX dated **12/15/97** (Bio.).
	6/26/98	- Response to 2nd def. FAX dated **6/9/98** (Chem.).
	9/3/98	- Response to 3rd def. FAX dated **8/31/98** **Subject of this review.**
FDA:	**3/28/97**	- Phone memo, regarding patent certification.
	5/1/97	- Refuse to file, incomplete dissolution data.

5/16/97 - Acknowledgment, need analytical methods.
10/27/97 - 1st def. FAX (Chem. & labeling).
11/3/97 - Phone memo, clarification of questions in **10/27/97**, amendment.
12/15/97 - 1st def. letter (Bio).
6/9/98 - 2nd def. FAX (Chem.).
8/31/98 - 3rd def. FAX's (Chem. & BIO).

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF ———————————

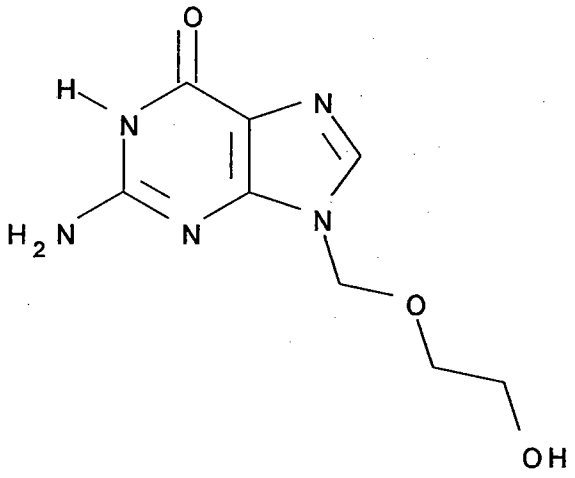
13. DOSAGE FORM
Capsules

14. POTENCIES
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

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



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

16. RECORDS AND REPORTS
N/A

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confidential commercial

information from

CHEMISTRY REVIEW #4 pp. 3-4

be revised as per the same review. There is a "NOTE TO THE CHEMIST" pointing out that the firm has revised "[redacted]" to read "FD&C Blue No. 1" in the list of inactive ingredients for the capsule shell. Concurrence is questioned. The revision in the DESCRIPTION section of labeling is correct.

C. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The evaluation of all firms involved in the manufacture and testing of the drug product with the current good manufacturing practices regulations will be undertaken by our Office of Compliance. A satisfactory evaluation is required prior to approval of this application.

   Stason Response: So acknowledged.

2. Please provide any additional data for ongoing stability studies for the exhibit batch if available.

   Stason Response: An updated stability report for the [redacted] batch size with lot # PI96001 that was packaged in sub-lots PI96001F in 100's and PI96001L in 400's have been submitted. Data for these packages that were stored at 25°C/60% RH for 18 mos. include the results of testing for appearance, assay, dissolution (w/water as the dissolution medium), LOD, and related cpds. Data are within specs.

3. The evaluation of the analytical methods to be used for release and stability purposes will be undertaken by an FDA field laboratory at such time that the dissolution testing criteria have been finalized.

   Stason Response: So acknowledged.

18. CONCLUSIONS AND RECOMMENDATIONS
The Stason responses to the outstanding issues in the FDA FAX dated **8/31/98**, are not completely satisfactory.

Not Approvable - MINOR FAX

19. REVIEWER: Robert C. Permisohn — DATE COMPLETED: 9/24/98 10/8/98

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CHEMISTRY REVIEW #4 pp 6-13

14.
~~15~~ Rec.

firm has revised finished product (per the firm/actually in-process of bulk capsules) specs. and stability specs. to include the recommended parameters.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory (p. **431**, Orig.)
Categorical Exclusion requested. Certifies that they will comply with all Federal, State and Local environmental laws.

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

If no, explain reason(s) below:

The previous review and FAX to the firm designated the response as a MINOR AMENDMENT and this submission had a higher review priority.

SPOT Yes____ No__X__

37. **DMF CHECKLIST FOR ANDA #75-090 REVIEW # 4**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/[redacted]	3	SAT	10/3/97

Comments: As per Chemistry Review # 2 by Norman Gregory.

[redacted]	III/[redacted]	4		

Comments: As per Chemistry Review # 2 by Norman Gregory.

[redacted]	III/[redacted]	4		

Comments: As per Chemistry Review # 2 by Norman Gregory.

[redacted]	III/[redacted]	4		

Comments: As per Chemistry Review # 2 by Norman Gregory.

[redacted]	IV/[redacted]	4		

Comments: As per Chemistry Review # 2 by Norman Gregory.

Comments:

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no relevant revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Checklist page 1 of 1.

Robert C. Permisohn
Reviewer

Signature

10/8/98
9/24/98
Date

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-090 APPLICANT: Stason Pharmaceuticals, Inc.

DRUG PRODUCT: Acyclovir Capsules, 200 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Chemistry Deficiencies:

1. Regarding Laboratory Controls (Finished Dosage Form):

a. [redacted]

b.

B. Labeling Deficiencies

1. CONTAINER: 100s and 400s

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

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

ANDA 75-090
Stason/Acyclovir Capsules

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.

C. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

ANDA 75-090
Stason/Acyclovir Capsules

18.
~~19~~ Feb.

The evaluation of the analytical methods to be used for release and stability purposes will be undertaken by an FDA field laboratory. Samples will be requested in the near future.

Sincerely yours,

10/14/98

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-090
Stason/Acyclovir Capsules

cc: ANDA 75-090
DUP File
DIVISION FILE
Field Copy

Endorsements:

HFD-647/RCPermisohn/9-24-98 10/8/98
HFD-647/UVenkataram/9-29-98 U.V. Venkataram 10/8/98
HFD-617/TAmes/10-5-98
HFD-640/FHolcombe 10/13/98

F/T by pah/10-6-98
X:\new\firmsnz\stason\ltrs&rev\75090na4.naf

X:\WPFILE\BRANCH7\PERMISOH\75090na4.d

NOT APPROVABLE - Facsimile

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.
   5

2. ANDA
   75-090

3. NAME AND ADDRESS OF APPLICANT
   Stason Pharmaceuticals, Inc.
   Attn: Monica M. Tinio
   11 Morgan
   Irvine, CA 92718-2005

4. LEGAL BASIS FOR SUBMISSION
   The applicant certifies , that to the best of its knowledge, U.S. Patent No. 4,199,574 expired on April 22, 1997, and the product is not covered by any exclusivity provisions. (per reviews # 1 and # 2)

   Innovator: Glaxo Wellcome - Zovirax®

5. SUPPLEMENT(s)
   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME
   Acyclovir

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

9. AMENDMENTS AND OTHER DATES:
   Firm:
   - **3/10/97** - Original.
   - **5/7/97** - Response to refuse to file.
   - **6/9/97** - Amendment, analytical methods.
   - **11/20/97** - Response to 1st def. FAX dated **10/27/97** (Chem. & labeling).
   - **1/19/98** - Response to 1st def. FAX dated **12/15/97** (Bio.).
   - **6/26/98** - Response to 2nd def. FAX dated **6/9/98** (Chem.).
   - **9/3/98** - Response to 3rd def. FAX dated **8/31/98.**
   - **10/6/98** - Response to labeling FAX dated **9/23/98** **(Subject of this review).**

10/19/98 - Response to 4th NA FAX dated **10/16/98** **(Subject of this review).**
11/5/98 - Response to telecon dated **11/4/98** **(Subject of this review).**

FDA:
3/28/97 - Phone memo, regarding patent certification.
5/1/97 - Refuse to file, incomplete dissolution data.
5/16/97 - Acknowledgment, need analytical methods.
10/27/97 - 1st def. FAX (Chem. & labeling).
11/3/97 - Phone memo, clarification of questions in **10/27/97**, amendment.
12/15/97 - 1st def. letter (Bio).
6/9/98 - 2nd def. FAX (Chem.).
8/31/98 - 3rd def. FAX's (Chem. & BIO).
9/23/98 - Labeling FAX.
10/16/98 - 4th def. FAX (Chem. and Labeling).

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
DMF ——————————————————

13. DOSAGE FORM
Capsules

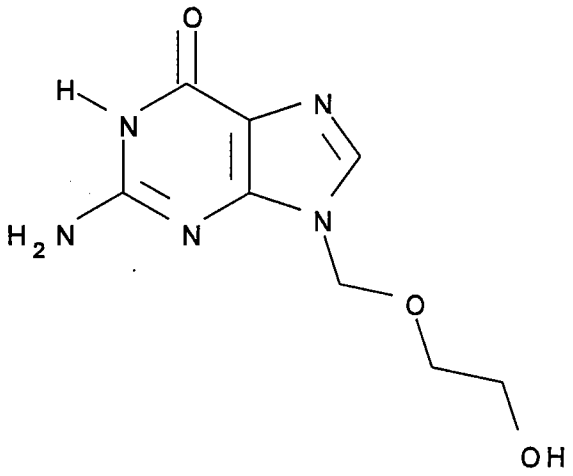
14. POTENCIES
200 mg

APPEARS THIS WAY
ON ORIGINAL

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

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



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

16. RECORDS AND REPORTS

N/A

17. COMMENTS

10/6/98, Amendment: Response to our **9/23/98** FAX for labels/labeling. The amendment contains revised draft insert labeling. A **10/28/98**, J. White review notes deficiencies including a comment that the insert is difficult to read and a larger type size is recommended (the review was not FAXed to the firm). A Chan Park telecon dated **11/4/98**, conveyed the result of the J. White review to the applicant, and asks for submission of revised FPL.

11/5/98, Amendment: Response to the **11/4/98**, telecon containing FPL inserts. The FPL has not been reviewed as of the date of this CMC review.

10/19/98, Amendment: Response to our FAX dated **10/16/98.** The comment nos. are taken from our FAX to the applicant.

A. Chemistry Deficiencies:

The outstanding chemistry issues, namely Comment nos. 1.a. and 1.b., are discussed in item 28. of this review.

B. Labeling Deficiencies

The outstanding label/labeling issues are discussed in item 32. of this review.

C. Note and Acknowledge

Methods evaluation by an FDA lab is discussed in item 31. of this review.

18. CONCLUSIONS AND RECOMMENDATIONS
The Stason responses to the outstanding CMC issues in the FDA FAX dated **10/16/98**, are satisfactory.

Recommend Approval - Pending acceptable labels/labeling.

19. REVIEWER: DATE COMPLETED:
Robert C. Permisohn 11/20/98
11/20/98

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confidential commercial

information from

CHEMISTRY REVIEW #5

100's and **PI96001L** in 400's is discussed in Chemistry Review #4. Data are within specs.

30. CONTROL NUMBERS - Satisfactory, pending field review (pp. **422-429**, Original filing).
The review of this operation falls within the purview of field investigators as per a CDER/field agreement.

31. SAMPLES AND RESULTS - Satisfactory per this review.
Active Ingredient and Finished Dosage Form are compendium items. Subsequent to the previous review, a monograph for the Finished Dosage form in *Supplement 9 of the USP 23/NF 18* became Official on **11/15/98**. On **10/13/98**, Tom Savage of the Seattle District Laboratory mentioned to this reviewer a discussion held with Stason regarding the need for performing the methods evaluation since the product will be the subject of a compendium monograph on/about the time that the firm will submit an amendment that would be ready for review. Upon consultation, U.V. Venkataram, Team Leader, confirmed Stason's position. Attached to this review is a copy of a letter dated **10/13/98**, to Stason indicating that methods validation will not be necessary.

32. LABELING - Unsatisfactory, pending review of insert labeling in **11/5/98**, amendment.
FP container labels for 100's and 400's in the **9/3/98**, are satisfactory, but should be revised at the time of the next printing per J. White review dated **9/10/98**. Draft insert labeling in the **10/6/98**, amendment were submitted in response to our labeling FAX dated **9/23/98**. A **10/28/98**, J. White review notes deficiencies including a comment that the insert is difficult to read and a larger type size is recommended (the review was not FAXed to the firm). A Chan Park telecon dated **11/4/98**, informed the applicant of the result of the J. White review, and to submit revised FPL. The **11/5/98**, amendment containing FPL inserts was submitted in response to the telecon.

33. ESTABLISHMENT INSPECTION - Satisfactory.
EER initiated on **5/29/97**, ACCEPTABLE per EER dated **8/26/97** (in Vol. 1.1).

34. BIOEQUIVALENCY STATUS - Satisfactory.
The Zakaria Wahba DOB review dated **5/29/98**, recommends that "The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions...have been found acceptable by the Division of Bioequivalence.". Dissolution is per *Supplement 9 of the USP 23/NF 18*.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory (p. **431**, Orig.)
Categorical Exclusion requested. Certifies that they will comply with all Federal, State and Local environmental laws.

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

If no, explain reason(s) below:

The previous review and FAX to the firm designated the response as a MINOR AMENDMENT and this submission had a higher review priority.

SPOT? Yes _____ No XXX

If yes, complete a SPOT form.

37. **DMF CHECKLIST FOR ANDA #75-090 REVIEW # 4**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
———	II/————	3	SAT	10/3/97

Comments: As per Chemistry Review # 2 by Norman Gregory.

———— III/———— 4

Comments: As per Chemistry Review # 2 by Norman Gregory.

———— III/———— 4

Comments: As per Chemistry Review # 2 by Norman Gregory.

———— III/———— 4

Comments: As per Chemistry Review # 2 by Norman Gregory.

———— IV/———— 4

Comments: As per Chemistry Review # 2 by Norman Gregory.

Comments:

Comments:

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no relevant revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").

Checklist
page 1 of 1. Robert C. Permisohn 11/23/98 12/21/98

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Seattle District
Pacific Region
22201 23rd Drive S.E.
P.O. Box 3012
Bothell, WA 98041-3012

Telephone: 425-486-8788
FAX: 425-483-4996

Monica Tinio
Manager, Regulatory Affairs
Stason Pharmaceuticals, Inc.
11 Morgan
Irvine, CA 92718

Ref. ANDA 75-090

October 13, 1998

Dear Ms. Tinio:

You are correct in pointing out that Acyclovir Capsules are now compendial products. We had not been aware that this monograph had appeared in the USP 9th Supplement. I have discussed this with Robert Permisohn of the Office of Generic Drugs. He has confirmed that there will be no need for our lab to perform a method validation on this application.

Therefore, please disregard the request for samples that we had sent by letter dated October 6, 1998. Feel free to contact me at 425-483-4883 if you have questions.

Thomas S. Savage, Team Manager
Drug Chemistry Team
Seattle Laboratory

cc. Robert Permisohn, HFD-647
Robert Tollefsen, Methods Validation Coordinator
Barbara Neuhaus, Methods Validation Coordinator
SEA lab method validations file

ANDA 75-090
Stason/Acyclovir Capsules

cc: ANDA 75-090
Division File
FIELD COPY

Endorsements:

HFD-647/RCPermisohn/11-23-98
HFD-647/UVenkataram/12/17/98 U.V. Venkataram 12/21/98

F/T by pah/12/21/98
X:\new\firmsnz\stason\ltrs&rev\75090no5.apf

APPROVAL

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-090
Stason/Acyclovir Capsules

ANDA APPROVAL SUMMARY

AADA OR ANDA NUMBER: 75-090

DRUG PRODUCT: Acyclovir Capsules

FIRM: Stason Pharmaceuticals, Inc.

DOSAGE FORM: Capsules **STRENGTH:** 200 mg

CGMP STATEMENT/EER UPDATE STATUS: Satisfactory in original filing/ACCEPTABLE per EER dated ~~8/26/97.~~ 1/11/99 BJ

BIO STUDY: The Zakaria Wahba DOB review dated **5/29/98**, recommends that "The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions...have been found acceptable by the Division of Bioequivalence.". Dissolution is per *Supplement 9 of the USP 23/NF 18*.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Both the ds and the drug product are subjects of compendium monographs. For this reason, methods validation was not conducted.

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

Container/closure systems: Yes, described below.

100's - 150 cc round, white, HDPE bottles ——— with ——— white ——— metal screw cap ———

400's - 500 cc round, white, HDPE bottles ——— with ——— white ——— metal screw cap ———

ANDA 75-090
Stason/Acyclovir Capsules

[redacted]

Stability Protocol: Satisfactory.
Stability Data: Satisfactory in support of the proposed expiration dating period of 24 mos. for the following lot:

Blend Lot #	Batch Size	Batch Record	Stability Conditions
PI96001[a]	[redacted] Capsules	Satisfactory	40°C/75% RH/3 mos. 25°C/60% RH/18 mos.

[a] Package Lot # PI96001F for 100's [redacted] capsules).
Lot # PI96001L for 400's [redacted] capsules).

LABELING: Pending review of insert labeling in **11/5/98**, amendment. FP container labels for 100's and 400's in the **9/3/98**, are satisfactory, but should be revised at the time of the next printing per J. White review dated **9/10/98**. Draft insert labeling in the **10/6/98**, amendment were submitted in response to our labeling FAX dated **9/23/98**. A **10/28/98**, J. White review notes deficiencies including a comment that the insert is difficult to read and a larger type size is recommended (the review was not FAXed to the firm). A Chan Park telecon dated **11/4/98**, informs the applicant of the result of the J. White review, and to submit revised FPL. The **11/5/98**, amendment containing FPL inserts was submitted in response to the telecon. Satisfactory 12/1/98.

STERILIZATION VALIDATION (IF APPLICABLE): N/A.

SIZE OF BIO BATCH (FIRM'S SOURCE OF DS O.K.?):
Bio batch is the same as the stability batch. See **STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN THE CONTAINER SECTION?**

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
The stability batch is the same as BIO batch. See **STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN THE CONTAINER SECTION?**

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
The manufacturing process for the proposed batch size of [redacted] capsules is the same as for the executed batch. A comparison

ANDA 75-090
Stason/Acyclovir Capsules

of the manufacturing processes between the two batch sizes is located on pp. 219 ff. of the original filing.

CHEMIST: Robert C. Permisohn 12/21/98 **DATE:** November 23, 1998

TEAM LEADER: Ubrani V. Venkataram U.V. Venkataram **DATE:** December 10, 1998 12/21/98

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-090

BIOEQUIVALENCE REVIEW(S)

Acyclovir
200 mg Capsules
ANDA #**75-090**
Reviewer: Z.Z. Wahba
File #75090sw.m97

Stason Industrial Corp.
Irvine, CA
Submission Date:
March 10, 1997
May 07, 1997
June 09, 1997

REVIEW OF TWO IN-VIVO BIOEQUIVALENCE STUDIES AND IN VITRO DISSOLUTION TESTING DATA

I. OBJECTIVE:
Review the following:

1. Stason's in vivo bioequivalence study under fasting and non-fasting conditions comparing its drug product Acyclovir Capsules, 200 mg to the reference drug product Glaxo Wellcome's Zovirax® Capsules, 200 mg.

2. Dissolution data for the test and reference drug products.

II. INTRODUCTION:

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside analog with in vivo and in vitro inhibitory activity against (in decreasing order) herpes simplex types 1 and 2 viruses, varicella zoster virus, Epstein-Barr virus, and cytomegalovirus. Acyclovir is converted by enzymes present in virus-infected cells into an active form, acyclovir triphosphate, which interrupts viral DNA replication. Acyclovir capsules and suspension are indicated for treatment of initial episodes and management of recurrent herpes simplex virus genitalia in certain patients. The capsule, suspension, and tablet dosage forms are indicated for treatment of acute herpes zoster and chicken pox.

Acyclovir oral absorption is slow, variable, and incomplete, with absolute bioavailability estimated at about 15-30%. Peak blood concentrations occur approximately 1.5-2.5 hours following oral dosing. There are no active metabolites. Studies in which 0.5 to 15 mg/kg were administered I.V. to patients with normal renal function yielded elimination half-lives of 2 to 3 hours. Renal

excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine.

Acyclovir is marketed as Zovirax® (Glaxo-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 800 mg and 400 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 ml (NDA #19-909, 12/22/89).

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITION
Clinical Study #1782

A. Sponsor:

Stason Industrial Corp.
11 Morgan Avenue
Irvine, CA 92718-2005

Study Site:
Clinical, Analytical Statistical and Facilities

[redacted]

Investigators:
Clinical Investigator: [redacted] M.D.
Study Director: [redacted], Ph.D.

Clinical Study Dates:
Period I: September 29, 1996
Period II: October 06, 1996

B. Study design:

Single dose, randomized, two-way crossover study under fasting conditions.

C. Subjects:

Thirty-six (36) healthy male subjects were recruited and completed the study . The subjects were within 18 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:

Only medically and physically healthy subjects with clinically normal ranges of laboratory tests (blood chemistry, hematology, urinalysis) were enrolled in the study.

Subject Exclusion Criteria:

- A history of cardiovascular, pulmonary, renal, gastrointestinal, hepatic, endocrine, neurological or hematological disease.
- A history of drug or alcohol addiction or abuse.
- A history of allergic responses to the class of drug being tested.
- Blood donation within the past 30 days prior to the study.
- Use of tobacco products.

Subject Restrictions:

- No subject took any medications, including OTC products for at least two week prior to the beginning of the study and until completion of the study.
- No alcoholic, xanthine and caffeine containing foods and beverages were allowed, beginning with 48 hours prior to dosing and until completion of the study.

D. Food and Fluid Intake:

Subjects fasted overnight for at least 10 hours (overnight) before dosing and 4.5 hours after dosing. The drug products were administered with 240 mL tap water. Water was not permitted for 1 hour before and 1 hour after the dose, but was allowed at all other times. The subjects received their medication according to randomized dosing schedule. Standard meals were provided at appropriate times thereafter (at 4.5 and 9.5 hours after drug administration).

E. Treatment Plan:

Test product: 4 X 200 mg Acyclovir Capsules (Stason), Lot #PI96001F, Batch size: ——— capsules, assay potency: 98.6%, content uniformity: 98.5%, manufacturing date:

09/04/96.

Reference product: 4 X 200 mg Zovirax® Capsules (Glaxo-Wellcome), Lot #6N2240, assay potency: (not given), content uniformity: (not given), expiration date: 06/99.

Washout period: 7 days.
A single 800 mg dose was given in each period of the study.

F. Blood Sampling:

Blood samples (10 mL each) were collected in vacutainers, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16, 18.0, 24.0 and 36 hours post-dosing. The plasma samples were separated, collected and stored frozen at -25°C ± 5°C until analysis.

G. Assay Methodology:
(pp #230-272, Vol. B1.2, section "Analytical Report")

1. Methods:
The plasma assay of acyclovir was performed by ———

———

The assay validation data are summarized as follows:

2. Sensitivity:
The lower limit of quantitation was —— ng/mL for acyclovir in human plasma. Samples with assayed values below —— ng/mL were reported as zero.

3. Linearity: ——— ng/mL.
Correlation coefficients (r) determined from the calibration curves were ——— for acyclovir.

5. Study Validation : (pp #235-237, Vol. B1.3)
Results are summarized in the following two tables.

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW

H. In Vivo BE Study and Statistical Analysis:

Thirty-six (36) healthy male subjects were recruited and completed the study.

Adverse Events: The adverse reactions are reported on page #03, Vol. B1.2, section 'Record'.
Two adverse events were reported by two subjects during the study, both adverse events were occurred during Phase I. Subject #11 experienced a mild episode of nausea for 2 hours. Subject #15 experienced a mild headache lasting for 11 hours.
No treatment was administered and none of the adverse events was considered serious or resulted in terminating any subject from study participation.

The pharmacokinetic parameters of acyclovir were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters for the plasma acyclovir concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

Table #1
Mean Plasma Concentrations (ng/mL) of Acyclovir in 36 Subjects Following a Single Oral Dose of 4X200 mg Acyclovir Under Fasting Conditions
(Test Lot #PI96001F, Reference Lot #6N2240)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	1.14	5.16	0.00	0.00	.
0.25	14.24	20.86	15.10	24.27	0.94
0.5	276.91	165.04	233.83	143.63	1.18
0.75	519.23	201.10	491.18	201.87	1.06
1	681.09	241.02	650.55	215.58	1.05
1.33	771.91	272.52	747.20	248.55	1.03
1.67	785.39	292.27	787.96	263.82	1.00
2	756.38	271.75	787.00	250.05	0.96
2.5	705.73	261.84	721.54	269.59	0.98
3	610.25	234.43	632.48	251.57	0.96
4	453.44	195.04	492.24	273.37	0.92
6	268.21	113.73	297.56	144.97	0.90
8	163.47	71.83	171.54	78.48	0.95
12	77.57	32.62	75.74	31.67	1.02
16	45.30	15.54	45.98	15.13	0.99
18	38.75	12.17	38.24	12.51	1.01
24	29.36	8.53	30.58	8.80	0.96
36	21.69	12.78	24.82	12.01	0.87

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table #2
Mean Pharmacokinetic Parameters (Arithmetic) in 36 Subjects Following a Single Oral Dose of 4X200 mg Acyclovir Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	5926.38	2291.17	6129.88	1840.59	0.97
AUCT	4733.47	1429.71	4908.94	1548.32	0.96
CMAX	932.09	272.76	921.30	258.21	1.01
KE	0.04	0.02	0.03	0.02	1.11
*LAUCI	5552.04	0.36	5882.66	0.29	0.94
*LAUCT	4523.45	0.31	4709.77	0.28	0.96
*LCMAX	893.84	0.30	885.67	0.29	1.01
THALF	28.85	30.29	29.77	21.41	0.97
TMAX	1.59	0.65	1.87	0.82	0.85

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
* The values represent the geometric means (antilog of the means of the logs).

Table #3
LSMeans And The 90% Confidence Intervals in 36 Subjects Following a Single Oral Dose of 4X200 mg Acyclovir Under Fasting Conditions (Under Fasting Conditions)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	5552.04	5767.31	0.96	86.12	107.61
LAUCT	4523.45	4709.77	0.96	86.97	106.06
LCMAX	893.84	885.67	1.01	90.47	112.59

UNIT: AUC=NG HR/ML CMAX=NG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

1. The mean plasma acyclovir levels reached a maximum level of concentration around 1.67 hours (Table #1 and Figures #1 and 2).

2. The 90% confidence intervals for the LSMeans log-transformed AUCT, AUCI and CMAX were within the acceptable range of 80-125% (Table #3). The T/R mean ratios (RLSM12) for the log-transformed AUCT, AUCI and CMAX were within the acceptable range of 0.8-1.25% (Table #3).

There were no significant period, sequence or treatment

effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCT, AUCI and CMAX.

Note: There were two subjects (#22 and 34) that showed acyclovir plasma concentration at zero time point. The following table shows the Lsmean and 90% confidence interval values for all subjects excluding subjects #22 and 34.

Table #4
LSMeans And The 90% Confidence Intervals in 34 Subjects Following a Single Oral Dose of 4X200 mg Acyclovir Under Fasting Conditions (Under Fasting Conditions)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	5425.39	5830.95	0.93	83.31	103.91
LAUCT	4398.93	4751.62	0.93	84.24	101.75
LCMAX	878.29	890.70	0.99	88.38	110.02

UNIT: AUC=NG HR/ML CMAX=NG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
* The values represent the LSMEANS (antilog of the means of the logs).

Results and Conclusion: Tables #3 and #4 obtained from the statistical analysis of all subject (36 subjects) and the 34 subjects (excluding subjects 22 and 34), respectively, show that there is no difference in the outcome if the two subjects (#22 and 34) either included or excluded from the statistical analysis. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax for the data either including or excluding the two subjects were within the acceptable range of 80-125%.

IV. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS (clinical study project #1783)

A. Sponsor:
Stason Industrial Corp.
11 Morgan Avenue
Irvine, CA 92718-2005

Study Site:
Clinical, Analytical Statistical and Facilities

Investigators:
Clinical Investigator: ———————, M.D.
Study Director: ——————— Ph.D.

Clinical Study Dates:
Period I: November 03, 1996
Period II: November 10, 1996
Period III: November 17, 1996

B. Study design:

Randomized, three-way crossover, single dose study, under fasting and non-fasting conditions.

C. Subjects:

Eighteen (18) subjects were recruited for this study. Seventeen (17) subjects completed the entire clinical portion of the study (subjects #1-16 and 18). Subjects #17 withdrew during Phase I for personal reasons. The subjects were 18 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Exclusion Criteria:
Same as in study #1782 under fasting conditions

Subject Restrictions:
Same as in study #1782 under fasting conditions

D. Treatment Plan:

Test Product:

Treatment A: 4 X 200 mg Acyclovir Capsules (Stason), Lot #PI96001F, Batch size: ——— capsules, assay potency: 98.6%, content uniformity: 98.5%, manufacturing date:

09/04/96, under non-fasting conditions.

Treatment B: 4 X 200 mg Zovirax® Capsules (Glaxo-Wellcome), Lot #6N2240, assay potency: (not given), content uniformity: (not given), expiration date: 06/99, under non-fasting conditions.

Treatment C: 4 X 200 mg Acyclovir Capsules (Stason), Lot #PI96001F, Batch size:[redacted] capsules, assay potency: 98.6%, content uniformity: 98.5%, manufacturing date: 09/04/96, under fasting conditions.

Washout period: 7 days between doses.
A single 4X200 mg dose was given in each period of the study.

E. Drug, Food and Fluid Intake:

Subjects who were fed standard recommended breakfast prior to dosing (treatments A and B) only fasted for 9.5 hours. Subjects who received treatment C, fasted overnight for 10 hours before dosing and for 4 hours after drug administration. Treatments A and B differed from treatment C in that the subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 8 fluid ounces (240 mL) of room temperature tap water according to randomized dosing schedule. Water was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times. Standard meals were provided at appropriate times thereafter (at 4.5 and 9.5 hours after dosing).

F. Blood Sampling:

Blood samples (10 mL each) were collected in vacutainers, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16, 18.0, 24.0 and 36 hours post-dosing. The plasma samples were separated, collected and stored frozen at -25°C ± 5°C until analysis.

G. **Assay Methodology**:
Same as in study #1782 (under fasting conditions).

H. **In Vivo BE Study and Statistical Analysis**:
Eighteen (18) subjects were recruited for this study. Seventeen (17) subjects completed the entire clinical portion of the study (subjects #1-16 and #18). Subjects #17 withdrew during Phase I for personal reasons. Samples from 17 subjects were assayed for acyclovir.

Adverse Events: One adverse event was reported by a subject during the study. During Phase II, subject #4 experienced a mild headache lasting for two hours. No treatment was administered. The adverse event was resolved and the subject was able to complete the study.

The pharmacokinetic parameters of acyclovir were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters of the level of plasma concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the tables below:

Table #5
Mean Plasma Concentrations of
Acyclovir (ng/mL) in 17 Subjects
Following 4X200 mg Oral Doses of Acyclovir
Under Non-Fasting Conditions
(Test Lot #PI96001F, Reference Lot #6N2240)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.67	2.76	.
0.25	0.00	0.00	0.66	2.71	8.38	14.19	0.00
0.5	10.09	21.93	39.57	68.05	236.19	158.75	0.26
0.75	69.88	96.12	191.56	160.61	535.00	237.23	0.36
1	203.61	212.55	394.96	242.09	706.71	188.78	0.52
1.33	396.29	333.02	664.86	299.54	790.97	211.27	0.60
1.67	652.14	451.07	867.47	326.98	803.75	212.00	0.75
2	858.63	498.08	1044.71	284.41	760.75	275.68	0.82
2.5	1022.49	497.50	1153.20	292.79	693.38	286.20	0.89
3	1065.18	361.45	**1174.43**	296.72	613.51	283.99	0.91
4	**1067.65**	335.76	1082.23	313.42	502.66	322.20	0.99
6	653.14	218.75	647.46	253.68	280.53	149.96	1.01
8	371.95	134.70	367.54	145.54	167.91	86.77	1.01
12	149.10	50.16	141.77	52.33	71.68	25.05	1.05
16	71.73	23.12	68.10	26.46	43.94	12.60	1.05
18	55.75	17.69	50.34	16.84	36.62	8.43	1.11
24	34.18	11.29	32.06	10.88	27.74	7.73	1.07
36	27.29	14.51	23.26	11.43	21.37	13.14	1.17

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	0.00	0.00
0.25	0.00	0.08
0.5	0.04	0.17
0.75	0.13	0.36
1	0.29	0.56
1.33	0.50	0.84
1.67	0.81	1.08
2	1.13	1.37
2.5	1.47	1.66
3	1.74	1.91
4	2.12	2.15
6	2.33	2.31
8	2.22	2.19
12	2.08	1.98
16	1.63	1.55
18	1.52	1.37
24	1.23	1.16
36	1.28	1.09

1=Test-nonFast 2=Ref.-NonFast 3=Test-Fast

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table #6

Mean Pharmacokinetic Parameters in 17 Subjects Following a Single Oral Dose of 4X200 mg Acyclovir Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	8563.74	1813.81	8923.81	2303.89	6112.21	1876.42	0.96
AUCT	7618.13	1836.45	7984.09	1936.34	4795.56	1589.34	0.95
CMAX	1278.41	392.37	1314.55	269.37	913.48	289.18	0.97
KE	0.05	0.02	0.05	0.05	0.04	0.03	0.89
*LAUCI	**8381.79**	0.22	**8655.47**	0.25	5882.17	0.28	**0.97**
*LAUCT	**7397.58**	0.26	**7765.20**	0.24	4571.55	0.31	**0.95**
*LCMAX	**1220.99**	0.32	**1290.59**	0.19	868.97	0.33	**0.95**
THALF	19.59	10.28	23.36	20.68	31.68	27.78	0.84
TMAX	3.27	1.10	2.88	0.88	1.56	0.76	1.14

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.40	1.46
AUCT	1.59	1.66
CMAX	1.40	1.44
KE	1.09	1.22
*LAUCI	1.42	1.47
*LAUCT	1.62	1.70
*LCMAX	1.41	1.49
THALF	0.62	0.74
TMAX	2.10	1.84

1=Test-nonFast 2=Ref.-NonFast 3=Test-Fast
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma acyclovir levels reached the maximum around 3.0-4.0 hours (Table #5 and Figures #3 and #4).

2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN1/2) for the log-transformed AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 (Table #6).

Note: There was one subject (#3) that showed acyclovir plasma concentration at zero time point. The following table shows the T/R ratio values for all subjects excluding subject #3.

Table #7
Mean Pharmacokinetic Parameters
in 16 Subjects Following a Single Oral Dose of
4X200 mg Acyclovir Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	8499.46	1853.18	8805.36	2325.37	6170.65	1921.91	0.97
AUCT	7568.61	1884.92	7843.34	1907.91	4901.11	1578.72	0.96
CMAX	1293.48	400.12	1321.05	276.82	942.57	271.76	0.98
KE	0.05	0.02	0.05	0.05	0.04	0.03	0.90
*LAUCI	**8311.42**	0.22	**8535.61**	0.25	5929.30	0.28	**0.97**
*LAUCT	**7338.48**	0.26	**7632.27**	0.24	4683.26	0.31	**0.96**
*LCMAX	**1233.50**	0.33	**1295.75**	0.20	905.70	0.29	**0.95**
THALF	19.68	10.61	23.98	21.19	31.35	28.65	0.82
TMAX	3.10	0.88	2.88	0.91	1.58	0.78	1.08

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.38	1.43
AUCT	1.54	1.60
CMAX	1.37	1.40
KE	1.07	1.18
*LAUCI	1.40	1.44
*LAUCT	1.57	1.63
*LCMAX	1.36	1.43
THALF	0.63	0.77
TMAX	1.97	1.82

1=Test-nonFast 2=Ref.-NonFast 3=Test-Fast
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

Results and Conclusion: Tables #6 and #7 obtained from the statistical analysis of all subjects (17 subjects) and the 16 subjects (excluding subject #3), respectively, show that there is no difference in the outcome if subject #3 either included or excluded from the statistical analysis. The T/R ratio for the log-transformed AUCt, AUCi and Cmax for the data either including or excluding the subject were within the acceptable range of 0.8-1.25.

V. FORMULATION COMPARISON

(P #164, Vol. B1.1, Section VIII "Drug Product")

The following table shows the composition of the test product, 200 mg Acyclovir Capsules.

Composition of Stason's Acyclovir Capsules

Ingredient	200 mg Capsule	
	mg/Capsule	W/W%
Acyclovir, USP		
Lactose Monohydrate, NF		
Sodium Starch Glycolate, NF		
Sodium Lauryl Sulfate, NF		
Magnesium Stearate, NF		
Total	423.00	100.00

VI. IN VITRO DISSOLUTION TESTING

Method: USP 23 apparatus 1 (Basket) at 100 rpm
Medium: 900 mL of water
Sampling Time: 30, 45 and 60 minutes.
Test Product: Stason's Acyclovir Capsules
200 mg, lot #PI96001
Reference Product: Glaxo Wellcome's Zovirax® Tablets
200 mg, lot #6N2235

Number of Units: 12 Capsules
The dissolution testing results are shown in the following table

Table. In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir Capsules
Dose Strength: 200 mg
ANDA No.: 75-090
Firm: Stason Industrial
Submission Date: March 10, 1997
File Name: 75090sw.m97

I. Conditions for Dissolution Testing:

USP 23 Basket:X Paddle: RPM: 100
No. Units Tested: 12
Medium: 900 mL water
Specifications: NLT —% in 30 minutes
Reference Drug: Zovirax®
Assay Methodology: UV

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #PI96001 Strength(mg) 200			Reference Product Lot #6N2235 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
30	100		2.6	87		8.2
45	101		2.5	96		3.8
60	101		2.8	99		3.0

1. The dissolution data for the test and reference listed products pass the dissolution specification at 30 minutes. However, the firm has not provided any data earlier than 30 minutes to review the release rate profile.

2. There is no USP dissolution methodology for acyclovir. The firm conducted the dissolution testing according to the FDA dissolution methodology.

VII. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test

product, Stason's Acyclovir Capsule 200 mg is bioequivalent to the reference product, Glaxo Wellcome's Zovirax® Capsule 200 mg. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%.

2. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Stason's Acyclovir Capsule 200 mg is bioequivalent to the reference product, Glaxo Wellcome's Zovirax® Capsule 200 mg. The T/R mean ratios for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.

3. The dissolution testing data have met the FDA dissolution requirements.

VIII. DEFICIENCIES

1. The firm should submit the analytical raw data for all subjects included in this study (under fasting and non-fasting conditions). In addition, the firm should provide summary for the analytical methodology and its method of acyclovir plasma calculation accompanied by an example(s) of the calculation method.

2. Provide the recovery data for acyclovir plasma concentration in ng/mL, in addition to peak height measurements for the different concentration levels (low, medium and high). The mean and coefficient of variation (%CV) recovery for each concentration level (in ng/mL) should be separate from each other, not shown as overall results.

3. The lot number is given in two different ways #PI96001F and #PI96001, please provide clarification.

4. The firm is advised to submit dissolution data showing the dissolution behavior of the drug below the specification time point (30 minutes). For example, dissolution data for the drug at sampling time 10, 20 and 30 minutes, for both the test and reference products.

IX. RECOMMENDATION

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, conducted by Stason Industrial Corp. on its Acyclovir 200 mg Capsules, lot #PI96001F, comparing it to the reference product Glaxo Wellcome's Zovirax® Capsules 200 mg, lot #6N2240, have been found to be incomplete due to the deficiencies #1-3.

2. The dissolution testing conducted by the firm on its Acyclovir Capsules 200 mg (lot #PI96001) has been found incomplete due to the deficiency #4.

The firm should be informed of the deficiencies and recommendations.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-090 APPLICANT: Stason Industrial Corp.

DRUG PRODUCT: Acyclovir 200 mg capsules

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. Please submit the analytical raw data for all subjects included in this study (under fasting and non-fasting conditions). In addition, you should provide a summary for the analytical methodology and its method of acyclovir plasma calculation accompanied by an example(s) of the calculation method.

2. Provide the recovery data for acyclovir plasma concentration in ng/mL, in addition to peak height measurements for the different concentration levels (low, medium and high). The mean and coefficient of variation (%CV) recovery for each concentration level (in ng/mL) should be separate from each other, not shown as overall results.

3. The lot number is given in two different ways #PI96001F and #PI96001, please provide clarification.

4. Please submit dissolution data showing the dissolution behavior of the drug below the specification time point (30 minutes). For example, dissolution data for the drug at sampling time 10, 20 and 30 minutes, for both the test and reference products.

Sincerely yours,

for Dale Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-090
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements: (Draft and Final with Dates)
HFD-658/ Z. Wahba Z. Wahba
HFD-650/ R. Mhatre RM 12/5/97
HFD-617/ N. Chamberlin nchamberlin 12/5(97)
HFD-650/ R. Patnaik [illegible] 12/10/97

Printed in draft on 12-3-97 zw
Printed in final on 12-5-97
x:\new\firmsnz\stason\ltrs&rev\75090sw.m97

BIOEQUIVALENCY - DEFICIENCIES

May 7, 97

1. **FASTING STUDY** (STF) Strengths: 200mg

Clinical: [redacted]
Analytical: "

Outcome: **IC**

2. **FOOD STUDY** (STP) Strengths: 200mg

Clinical: [redacted]
Analytical: "

Outcome: **IC**

OUTCOME DECISIONS:**IC** - Incomplete

AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

Jun 9, 97 3. STA 40mg IC

ANDA # 75-090
(under fasting conditions)

MEAN PLASMA ACYCLOVIR CONCENTRATIONS

STUDY # (1782)

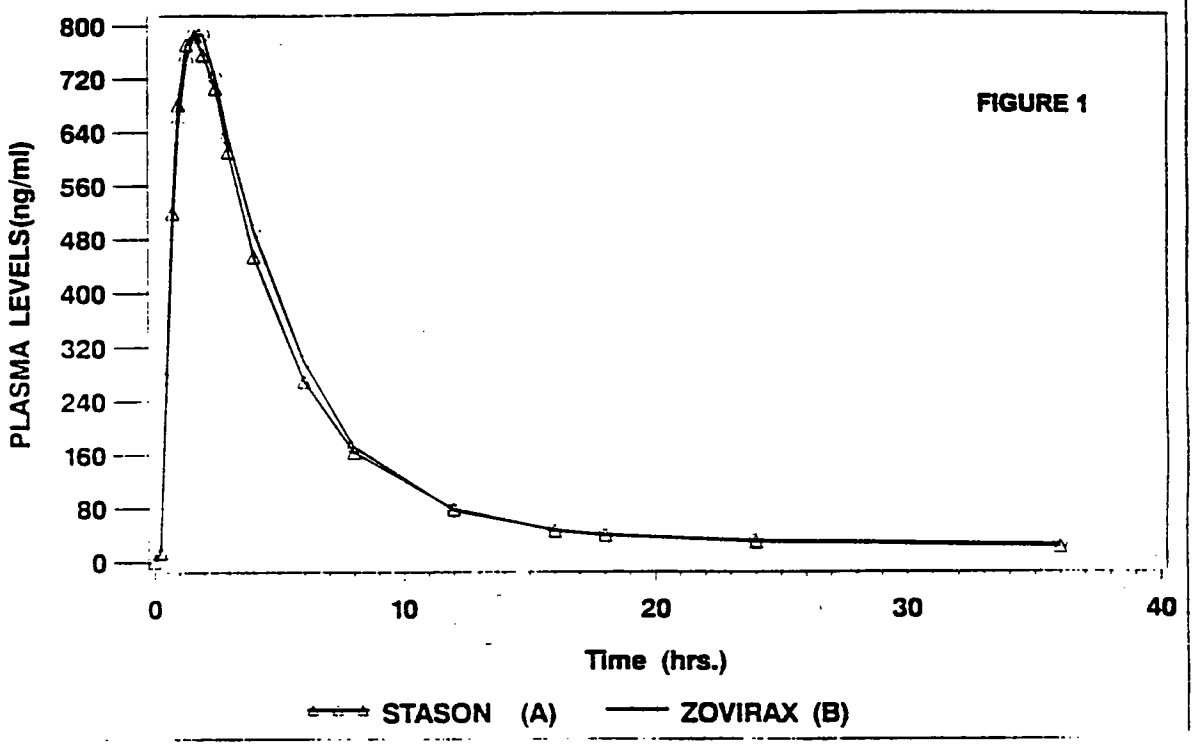


FIGURE 1

SEMI LOG MEAN PLASMA ACYCLOVIR CONCENTRATIONS

STUDY # (1782)

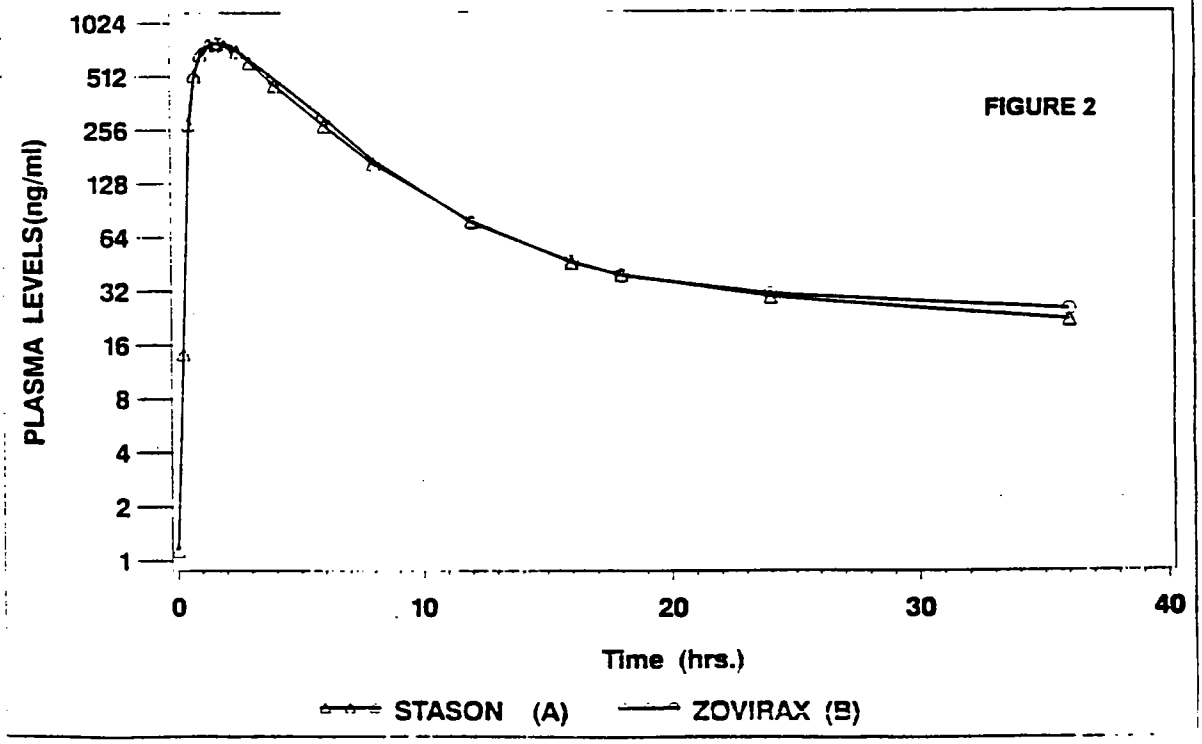


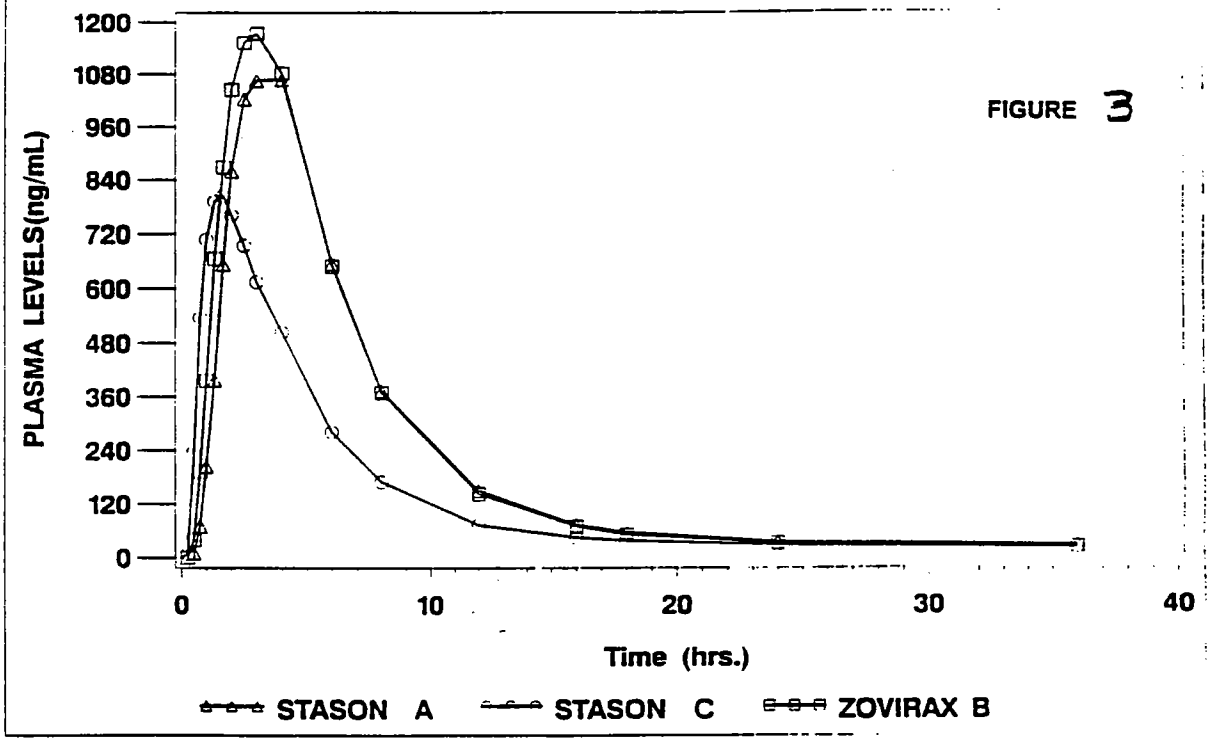
FIGURE 2

ANDA #75-090
(under non-fasting conditions)

MEAN PLASMA ACYCLOVIR CONCENTRATIONS

STUDY # (1783)

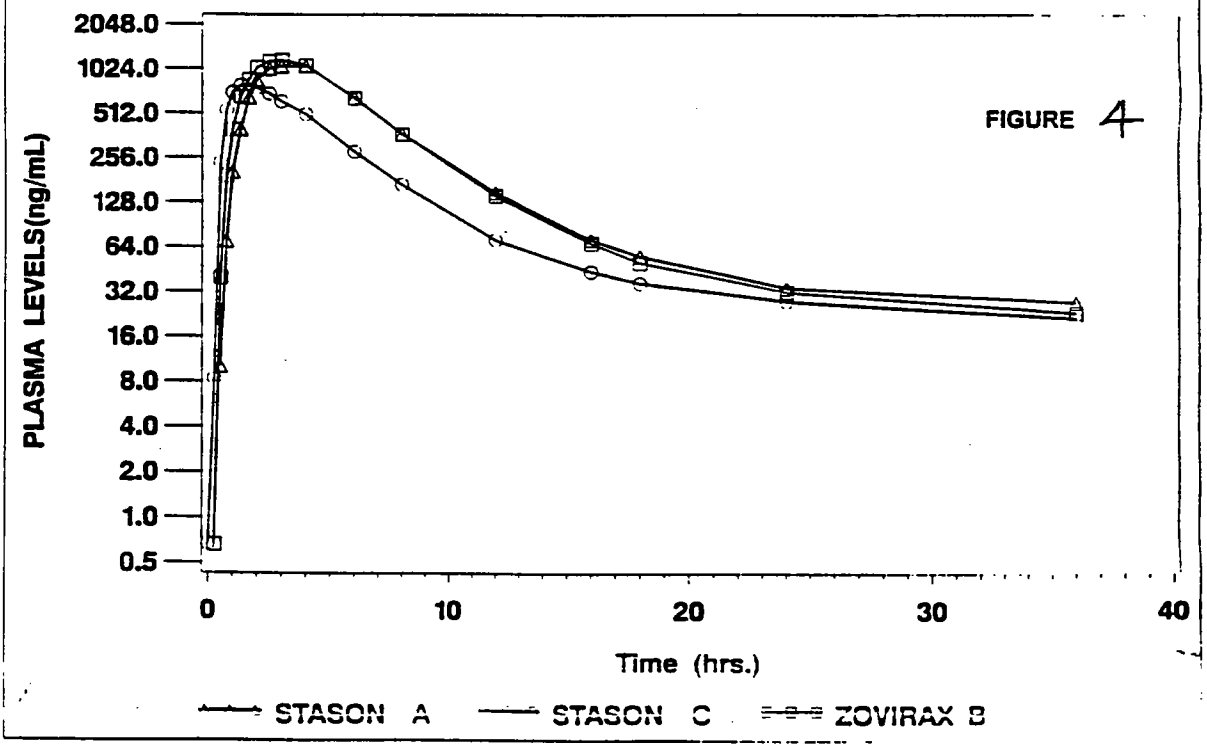
FIGURE 3



SEMI LOG MEAN PLASMA ACYCLOVIR CONCENTRATIONS

STUDY # (1783)

FIGURE 4



MAY 29 1998

Acyclovir
200 mg Capsules
ANDA #**75-090**
Reviewer: Z.Z. Wahba
File #75090a.198

Stason Industrial Corp.
Irvine, CA
Submission Date:
January 19, 1998

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm has previously submitted in vivo bioequivalence studies under fasting and non-fasting conditions comparing its drug product Acyclovir Capsules, 200 mg to the reference drug product Glaxo Wellcome's Zovirax® Capsules, 200 mg.

2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated December 10, 1997, ANDA #75-090) due to problems cited in the deficiency comments.

3. In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

DEFICIENCY COMMENT #1:

Please submit the analytical raw data for all subjects included in this study (under fasting and non-fasting conditions). In addition, you should provide a summary for the analytical methodology and its method of acyclovir plasma calculation accompanied by an example(s) of the calculation method.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT #1

A hard copy of the data was provided (see the firm's correspondence on January 19, 1998; Appendix A for study #1782 and Appendix B for study #1783). Also the firm has described the method of calculation and provided an example.

The firm's response to comment #1 is acceptable.

DEFICIENCY COMMENT #2:

Provide the recovery data for acyclovir plasma concentration in ng/mL,

in addition to peak height measurements for the different concentration levels (low, medium and high). The mean recovery for each concentration level (in ng/mL) should be separate from each other, not shown as overall results.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT #2

The percentage of recovery for QC samples were [redacted] ng/mL, respectively.

The firm's response to comment #2 is acceptable.

DEFICIENCY COMMENT #3:

The lot number is given in two different ways #PI96001F and #PI96001, please provide clarification.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT #3

The firm assigned a lot numbering system for the finished product which included an additional letter code to differentiate packaging configurations. In the case of Acyclovir Capsules, 200 mg Lot #PI96001, the 100 count was assigned the lot number of PI96001F, and the 400 count was assigned the lot number of PI96001L.

The firm's response to comment #3 is acceptable.

DEFICIENCY COMMENT #4:

Please submit dissolution data showing the dissolution behavior of the drug below the specification time point (30 minutes). For example, dissolution data for the drug at sampling time 10, 20 and 30 minutes, for both the test and reference products.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT #4

In vitro dissolution testing

Method:	FDA method
Apparatus:	Type #1 (Basket) at 100 rpm
Medium:	900 mL of water

Sampling Time: 10, 20, 30, 45 and 60 minutes.
Test Product: Stason's Acyclovir Capsules
200 mg, lot #PI96001
Reference Product: Glaxo Wellcome's Zovirax® Tablets
200 mg, lot #6N2235

Number of Units: 12 Capsules
The dissolution testing results are shown in the following table

Table. In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir Capsules
Dose Strength: 200 mg
ANDA No.: 75-090
Firm: Stason Industrial
Submission Date: January 19, 1998
File Name: 75090a.198

I. Conditions for Dissolution Testing:

USP 23 Basket:X Paddle: RPM: 100
No. Units Tested: 12
Medium: 900 mL water
Specifications: NLT —% in 30 minutes
Reference Drug: Zovirax®
Assay Methodology: UV

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #PI96001 Strength(mg) 200			Reference Product Lot #6N2235 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	87.5		4.1	74.9		4.2
20	96.8		2.1	92.7		3.4
30	98.5		1.9	97.8		3.4
45	98.9		2.0	100.3		3.5
60	99.8		1.6	101.9		2.4

1. The dissolution data for the test and reference listed products are acceptable.

2. There is no USP dissolution methodology for acyclovir. The firm conducted the dissolution testing according to the FDA

dissolution methodology.

The firm's response to comment #4 is acceptable.

NOTE: Subsequent to the OGD issuing the bioequivalency deficiency letter, the Pharmacopeial Forum, dated January-February 1998, published a dissolution method for Acyclovir Capsules.

REVIEWER'S COMMENTS:

1. The single-dose, fasting bioequivalence study (study #1782) and the single-dose non-fasting bioequivalence study (study #1783) conducted by Stason Industrial Corp., on the test product, Acyclovir 200 mg Capsule, lot #PI96001, comparing it with the reference listed drug Glaxo Wellcome's Zovirax® Capsule 200 mg, lot #6N2235 have been found acceptable. Under fasting conditions, the 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%. Under non-fasting conditions, the ratios of the test mean to the reference mean for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.

2. The dissolution testing data are acceptable.

RECOMMENDATIONS

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, conducted by Stason Industrial Corp. on its Acyclovir Capsule 200 mg, lot #PI96001, comparing it to the reference product Glaxo Wellcome's Zovirax® Capsule 200 mg, lot #6N2240, have been found acceptable by the Division of Bioequivalence. The two studies demonstrate that under fasting and non-fasting conditions, Stason's Acyclovir 200 mg Capsules are bioequivalent to Glaxo Wellcome's Zovirax® Capsules 200 mg.

2. The in vitro dissolution testing conducted by Stason Industrial Corp. on its Acyclovir Capsule 200 mg, lot #PI96001 has been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program according the Pharmacopeial Forum, dated January-February 1998. The dissolution testing should be conducted in 900 mL of 0.1 N

hydrochloric acid as the dissolution medium at 37 °C using USP Apparatus #1 (Basket) at 100 rpm. The test product should meet the following specifications:

> Not less than 75% (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the above recommendations.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED MMAKARY
FT INITIALLED MMAKARY Moheb H. Makary

Concur: Dale P. Conner Date: 5/29/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-090 APPLICANT: Stason Industrial Corp.

DRUG PRODUCT: Acyclovir Capsules, 200 mg

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

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

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program according the Pharmacopeial Forum, dated January-February 1998. The dissolution testing should be conducted in 900 mL of 0.1 N hydrochloric acid as the dissolution medium at 37 °C using USP Apparatus #1 (Basket) at 100 rpm. The test product should meet the following specifications:

> Not less than 75% (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-090
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Secretary - Bio Drug File
HFD-658/ Z. Wahba
HFD-655/ Bio Team Leader

Endorsements:
HFD-658/ Z. Wahba Z.W. 5/22/98
HFD-658/ M. Makary MHM 5/22/98
HFD-617/ N.Chamberlin
HFD-650/ D. Conner 5/29/98

X:\NEW\FIRMSNZ\STASON\LETRS&REV\75090A.198

BIOEQUIVALENCY - ACCEPTABLE

STUDY AMENDMENT dated January 19, 1998

Strength: 200 mg
Outcome: AC

OUTCOME DECISIONS: **AC** - Acceptable

WINBIO COMMENTS: Acceptable

APPEARS THIS WAY ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-090 SPONSOR: Stason Industrial Corp.
DRUG : Acyclovir
DOSAGE FORM: Capsules STRENGTH: 200 mg
REFERENCE PRODUCT: Glaxo Wellcome's Zovirax® Capsules, 200 mg.
TYPE OF STUDY: Two single dose studies under fasting conditions
Study Site:
Clinical, Analytical Statistical and Facilities

STUDY SUMMARY: The single-dose, fasting bioequivalence study (study #1782) and the single-dose non-fasting bioequivalence study (study #1783) conducted by Stason Industrial Corp., on the test product, Acyclovir 200 mg Capsule, comparing it with the reference listed drug Glaxo Wellcome's Zovirax® Capsule 200 mg, have been found acceptable. Under fasting conditions, the 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%. Under non-fasting conditions, the ratios of the test mean to the reference mean for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.

DISSOLUTION: The comparative dissolution testing data are acceptable.

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III
INITIAL: Z.W. DATE: 5/22/98

ACTING GROUP LEADER: Moheb Makary, Ph.D. BRANCH: III
INITIAL: MHM DATE: 5/22/98

ACTING DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL: DPC DATE: 5/29/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: _____ DATE: _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-090

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION/MEETING

I spoke with Harry Stason regarding the patent certifications. I advised him to amend the application with a Paragraph III certification only and to withdraw the Paragraph IV certification since the patent will expire at the end of next month. He promised to fax in the revised certification.

DATE

March 28, 1997

ANDA NUMBER

75-090

IND NUMBER

TELECON

INITIATED BY _ APPLICANT/ SPONSOR X FDA

MADE X BY TELE. _ IN PERSON

PRODUCT NAME

Acyclovir Capsules 200 mg

FIRM NAME

Stason Industrial

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Harry Stason

TELEPHONE NUMBER

(714) 380-4327

SIGNATURE

Ann Marie H. Wiebel

ANDA 75-090

RECORD OF TELEPHONE CONVERSATION

DATE: 11/3/97

PRODUCT NAME: Acyclovir Capsules, 200 mg

ANDA/AADA NUMBER: 75-090

FIRM NAME: Stason Industrial Corporation

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Monica Tinio, Reg. Aff. Manger
Giao Pham, Q.C. Manger
(714)380-4327

PARTICIPANT(S) TELEPHONE:
Mr. Norman R. Gregory, Review Chemist, Branch VI , OGD, CDER, FDA

MINUTES OF CONVERSATION:
I called the firm to clarify questions I asked in 10/23/97 major amendment. These are the responses to the firms questions:

1. The [redacted] a wish to see. The firm understands the question.

2. The firm has changed their specification for [redacted]. I asked the firm to lower their [redacted] specification from [redacted]% to at least [redacted]% based on their data and other Acyclovir ANDAs. They agreed.

NAME OF OGD REPRESENTATIVE: Norman R. Gregory

SIGNATURE OF OGD REPRESENTATIVE: [signature]

DIVISION/BRANCH: Office of Generic Drugs
Division II, Branch VI.

MINUTES PREPARED BY:

Mr. Norman R. Gregory, Review Chemist, Branch VI , OGD, CDER, FDA

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 24, 1998

FROM: Chemist, HFD-647

THRU: Ubrani Venkataram, Ph.D., Team Leader, HFD-647

SUBJECT: Methods Validation for ANDA 75-090

TO: Thomas Savage
Seattle District Laboratory, HFR-PA360
Food and Drug Administration
22201 23rd Drive, S.E.
P.O. Box 3012
Bothell, WA 98041-3012

Enclosed is one copy of the analytical methods for ANDA 75-090, Acyclovir Capsules, 200 mg as submitted in the original submission dated March 10, 1997, and MINOR amendment dated September 3, 1998. Since the finished drug product is not the subject of a USP monograph, satisfactory methods validation is needed for the approval of the ANDA. Also enclosed are copies of the components/composition statements, Certificates of Analysis, and Form 2871a.

The applicant is:

Stason Pharmaceuticals, Inc.
11 Morgan
Irvine, CA 92718-2005

The contact person at Stason Pharmaceuticals is:

Monica Tinio, Manager, Regulatory Affairs
Telephone: (714) 380-4327

Please comment on the suitability of the methods and procedures.

If you have any questions, please contact the undersigned at (301) 827-5803.

Robert C. Permisohn

RECORD OF TELEPHONE CONVERSATION

I called the firm and informed Monica Tinio of the firm that the insert is not acceptable because of the very poor readability due to small print size and photo copying. I directed her to increase the readability of the insert and submit original final printed copy, not photo copy as a telephone amendment to this application and she said she will do so.

Chan

DATE Nov. 4, 1998

ANDA 75-090

IND NUMBER

TELECON

INITIATED BY _ **APPLICANT/ SPONSOR** X **FDA**

MADE X **BY TELE.** _ **IN PERSON**

PRODUCT NAME
Acyclovir Capsules, 200 mg

FIRM NAME
Stason

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Monica M. Tinio

TELEPHONE NUMBER
949-380-4327 ext.235

SIGNATURE

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-090 Applicant Sfasen Pharmaceuticals, Inc.

Drug Acyclovir CAPSULES, USP

Strength 200 mg

APPROVAL ☑ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐

REVIEWER:

1. Tim Ames
Review Support Br

DRAFT RECEIPT
Date 12/9/98
Initials

FINAL ACTION
Date 12/22/98
Initials

Application Summary:

Original Rec'd date 13 MAR 97
Date Acceptable for Filing 08 MAY 97
Patent Certification (type) III paexp
Date of Office Bio Review 29 MAY 98
Methods Val. Samples Pending Yes ☐ No ☑
30 Day Clock Start NA End
Commitment rcd. from Firm Yes ☐ No ☐
First Generic Yes ☐ No ☑

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 1/11/99
Date Patent in effect EXP 12 APR 97
Citizens Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to Pet. Coord. notifying of pending approval)
Pediatric Exclusivity Tracking System
Date checked 09 DEC 98
Nothing Submitted ☑
Written request issued ☐
Study Submitted ☐

Comments:

2. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments: Chemistry is satisfactory

Date
Initials

Date 1/21/99
Initials BH for

3. Office Level Chem Review **(1st Generic Only)**
Chemistry Div. I or II
Comments: N/A Multiple ANDAs have been approved for this drug product. RLD

Date
Initials

Date
Initials

4. Pat Beers Block
Supv., Review Support Branch
Comments: RLD = 18828
• EER acceptable for all firms as of 1/11/99; no OAI alerts
• Final printed labels and labeling reviewed and found acceptable 12/1/98

Date 1/22/99
Initials PMBS

Date 1/25/99
Initials PMB

• Patent certification: Para. IV → Para. III; patent for RLD expired 4/12/97. No marketing exclusivity ~~applicable~~ for RLD. Firm ~~letter~~ submitted (9/3/98; 10/19/98) amended patent certification — Para. II (patent expired)
• No citizen's petitions or controlled correspondence about this ANDA.

x:\wpfile\branch7\ames\apsum.wpd

• Bioequivalence office level review/comparative dissol.: 1 (two) single dose study under fasting & non-fasting conditions were completed — and found acceptable 5/29/98

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
5. Peter Rickman	Date 1/25/99	Date 1/25/99
Supv., Reg. Support Branch	Initials 1/25/99	Initials
Contains certification Yes ☑ No ☐	Determ. of involvement? Yes ☐ No ☑	
(required by the GDEA if sub after 6/1/92)	Pediatric Exclusivity Tracking System	
Paragraph 4 Certification Yes ☐ No ☐	Date Checked 1/26/99	
NDA - 18-828	Nothing Submitted ☒	
No patent or exclusivity issues	Written request issued ☐	
multiple generics approved	Study Submitted ☐	
Comments: EER acceptable 1/11/99 per EES		
Office level Bio 5/29/98		
6. ~~Jerry Phillips~~	Date 1/26/99	Date 1/26/99
Dir. Div. Labeling & Prog. Support	Initials	Initials
Comments: Acceptable EES dated 1/11/99 (Verified 1/26/99) No O.A.I. alerts noted. Bioequivalence review (single dose fasting, multiple dose fasting) found acceptable 5/29/98. Office level bio endorsed 5/29/98. CMC review acceptable 12/21/98 Methods validation waived. No patent or exclusivity issues including pediatric exclusivity under FDAMA. FOI Acceptable 12/1/98		
7. Gordon Johnston	Date	Date 1/26/99
Deputy Director, OGD	Initials	Initials
Patent Cert - P_4 Yes ☐ No ☒	Petition Status N/A	
Pend. Legal Action Yes ☐ No ☒	No controlled correspondence or citizens petitions currently pending. AR letter to be revised.	
Comments: Recommend: Approval		
Doug Sporn	Date 1/26/99	Date 1/26/99
Dir., OGD	Initials	Initials
Comments:		
~~Roger Williams, M.D.~~	Date	Date
Dep.Dir., CDER	Initials	Initials
First Generic Approval ☐		
PD or Clinical for BE ☐		
Special Scientific or Reg.Issue ☐		
9. Tim Ames	Date	Date
Review Support Branch	Initials	Initials

N/A Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Applicant notification:

1/26/99 2:35p Time notified of approval by phone 2:38p Time approval letter faxed

FDA Notification:

26 JAN 99 Date e-mail message sent to "OGD approvals" account

26 JAN 99 Date Approval letter copied to "//cder/drugapp" directory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-090

CORRESPONDENCE

STASON INDUSTRIAL CORPORATION

11 MORGAN, IRVINE, CA 92718-2005, U.S.A.
TEL: (714)380-4327 FAX: (714)380-4345

RE: ANDA, Acyclovir 200 mg Capsules

Office of Generic Drug
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

March 10, 1997

Dear Sir:

Stason Industrial Corporation submits with this cover letter the ANDA package of Acyclovir capsules for your review and approval. The brand or reference drug is Zovirax® manufactured by Glaxo Wellcome, Inc., Research Triangle Park, NC.

The number of volumes submitted is 5.

Please let me know if any further information is needed.

Thank You.

Sincerely,

Harry Fan
Chief Operating Officer

RE: ANDA, Acyclovir 200 mg Capsules

Executive Summary

The Acyclovir Capsule ANDA package submitted for your review and approval contains 5 volumes. There is only one strength for the Acyclovir Capsule, 200 mg. A master blend was manufactured and encapsulated by using an encapsulation machine to fill in the empty capsules of size 1. The in vivo bioequivalence and in vitro dissolution testing were conducted according to the FDA Guidance on Acyclovir Capsules.

The formulation of the Stason Acyclovir Capsules contains the same excipients as those published in the "Physicians' Desk Reference." Stason's Acyclovir Capsules have the same size as that of the Zovirax® . All biolot capsules are manufactured and packaged by Stason Pharmaceuticals, Inc., a subsidiary of Stason Industrial Corporation, both located at 11 Morgan, Irvine, CA 92618. All raw material, intermediate products and finished products were tested and controlled by personnel in the laboratory and Quality Assurance Departments of Stason Pharmaceuticals, Inc.

The Bioequivalence (BE) study was carried out by [redacted] The Bioequivalence (BE) study was done in December 1996. Data and results of the recent study are submitted in this package.

The 3 months' accelerated stability study gave satisfactory results, which can justify being granted a two year's expiration dating period by FDA. A long term room temperature stability study is going on at this time.

Copies of the label draft for the single strength are included in this package. Inserts are also given in comparison with that of the brand drug.

APPEARS THIS WAY
ON ORIGINAL

75-090

STASON INDUSTRIAL CORPORATION

11 MORGAN, IRVINE, CA 92718-2005, U.S.A.
TEL: (714)380-4327 FAX: (714)380-4345

via facsimile (301)594-1174

March 28, 1997

Attention: Mr. Peter Rickman
Office of Generic Drug
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Re: Amendment to Acyclovir ANDA of Stason Industrial Corporation

This letter serves as amendment to Acyclovir ANDA submitted by Stason Industrial Corporation on March 10, 1997 that the following modification(s) be made:

Remove page 8: "PARAGRAPH IV CERTIFICATION" from the ANDA

Harry T. Fan
Chief Operating Officer

ANDA 75-090

Stason Industrial Corporation
Attention: Harry Fan
11 Morgan
Irvine, CA 92718-2005

MAY 1 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated March 10, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules, 200 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> The comparative dissolution data, as presented (Section XVI, p. 365), does not include all of the data necessary for a complete evaluation by the reviewer. A complete dissolution report should contain the individual data for twelve capsules, including means, range and relative standard deviation (RSD) at each time point, a description of the methodology being used, and the lot numbers being tested.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, please provide a hard copy of your March 28, 1997 fax correspondence regarding the revised patent certification.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions please call:

Anna Marie H. Weikel
Project Manager
(301) 827-5862

Sincerely yours,

Jerry Phillips 5/1/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-090
cc: DUP/Jacket
Division File
HFD-92
Field Copy
HFD-600/Reading File
HFD-610/JPhillips
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting [signature] date 5/1/97
HFD-615/AMWeikel, CSO [signature] date 4/28/97
HFD-647/Acting Chem Branch date
X:\WPFILE\ANNA\75S\75090.RTF
F/T File tdb 04-23-97
ANDA Refuse to File!

STASON INDUSTRIAL CORPORATION

11 MORGAN, IRVINE, CA 92718-2005, U.S.A.
TEL: (714)380-4327 FAX: (714)380-4345

NDA CHG AMENDMENT

N/AC

ANDA 75-090

May 7, 1997

505(j)(2)(a)(ok)
Anamarie H. Weikel
5/9/97

Office of Generic Drugs, CDER
Food and Drug Administration, HFD-650
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Sir,

Reference is made to the deficiency letter dated March 10, 1997 for ANDA 75-090 for Acyclovir 200 mg Capsules. Enclosed we have submitted our Amendment # 001 to resolve the deficiencies in the application as set forth in the deficiency letter.

Respectfully yours,

Harry Fan
Chief Operating Officer

RECEIVED
MAY 0 8 1997
GENERIC DRUGS

ANDA 75-090

Stason Industrial Corporation
Attention: Harry Fan
11 Morgan
Irvine, CA 92718-2005

MAY 16 [illegible]

Dear Sir:

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

Reference is also made to our "Refuse to File" letter dated May 1, 1997, and your amendment dated May 7, 1997.

NAME OF DRUG: Acyclovir Capsules 200 mg

DATE OF APPLICATION: March 10, 1997

DATE OF RECEIPT: May 8, 1997

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

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

5/16/97

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

cc: ANDA 75-090
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett
HFD-324/M.Lynch

Endorsement: HFD-615/PRickman, Chief, RSB _____ date 5/16/97
HFD-615/AMWeikel, CSO _____ date
HFD-647/SBasaran, Sup. Chem._____date
X:\NEW\FIRMSNZ\STASON\LTRS&REV\75090.ACK
F/T/njg/5/12/97
ANDA Acknowledgement Letter!

STASON INDUSTRIAL CORPORATION

11 MORGAN, IRVINE, CA 92718-2005, U.S.A.
TEL: (714)380-4327 FAX: (714)380-4345

NDA ORIG AMENDMENT

N/AC

ANDA 75-090

June 9, 1997

Office of Generic Drugs, CDER
Food and Drug Administration, HFD-650
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Sir,

Reference is made to the ANDA Receipt letter dated May 8, 1997, for ANDA 75-090 for Acyclovir 200 mg Capsules. Enclosed we have submitted our Amendment # 002 in response to the analytical method validation documents request.

Respectfully Yours,

Harry Fan
Chief Operating Officer

RECEIVED
JUN 11 1997
GENERIC DRUGS

MAJOR AMENDMENT

OCT 27 1997

ANDA: 75-090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT Taston Industrial Corp PHONE 714-380-4327
ATTN: Harry Fan FAX 714-380-4345

FROM: Timothy W. Ames, PROJECT MANAGER (301-827-5849)

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 3/10/97, submitted pursuant to Section ~~505(j)~~ of the Federal Food, Drug, and Cosmetic Act for Acyclovir Capsules, 200 mg.

Reference is also made to your amendment(s) dated 5/7/97, 6/9/97.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (15 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.mjr

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

10/27/1997 FDA FAX

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please be advised that the suitability of the proposed dissolution procedure and specification will be established upon completion of review by the Division of Bioequivalence.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

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.

Charlie Hoppes for

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

STASON PHARMACEUTICALS, INC.

11 MORGAN, IRVINE, CA 92718-2005, U.S.A.
TEL: (714)380-4327 FAX: (714)380-4345

November 20, 1997

ORIG AMENDMENT

N/A

Mr. Timothy W. Ames
Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

Major Amendment

Re: ANDA 75-090
Acyclovir Capsules, 200 mg

Dear Mr. Ames:

Reference is made to the FDA letter dated October 27, 1997, pertaining to the Acyclovir Capsules ANDA. This major amendment is being submitted to provide a complete response to the comments received. Our replies are given in the order in which the comments appear in the letter. Included in the submission are current patent certification and draft labeling.

Pursuant to the Final Rule published in the Federal Register dated September 8, 1993 and 21 CFR 314.94, Stason Pharmaceuticals, Inc. certify that a true copy of this amendment has been provided to the FDA Los Angeles District Office on the same date of this submission to the Office of Generic Drugs.

Please contact me at the letterhead address, call me at (714) 380-4327 ext. 235 or fax me at (714) 380-4327 if you require additional information.

Sincerely,

Monica M. Tinio
Manager, Regulatory Affairs
Stason Pharmaceuticals, Inc.

RECEIVED
NOV 24 1997
GENERIC DRUGS

S1:ANDA:ACY:MAJAM1

BIOEQUIVALENCY AMENDMENT

DEC 15 1997

ANDA 75-090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Stason Industrial Corp. PHONE: 714-380-4327

ATTN: Harry Fan FAX: 714-380-4345

FROM: Nancy Chamberlin PROJECT MANAGER (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on 3-10-97, 5-7-97, 6-9-97, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Acyclovir 200mg capsules.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached _____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

We note that this product is subject to the exception provisions of Section 125(d) (2) of Title 1 of the FDA Modernization Act of 1997.

X:\new\ogdadmin\glossary\biofax.frm

DEC 15 1997

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-090 APPLICANT: Stason Industrial Corp.

DRUG PRODUCT: Acyclovir 200 mg capsules

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. Please submit the analytical raw data for all subjects included in this study (under fasting and non-fasting conditions). In addition, you should provide a summary for the analytical methodology and its method of acyclovir plasma calculation accompanied by an example(s) of the calculation method.

2. Provide the recovery data for acyclovir plasma concentration in ng/mL, in addition to peak height measurements for the different concentration levels (low, medium and high). The mean and coefficient of variation (%CV) recovery for each concentration level (in ng/mL) should be separate from each other, not shown as overall results.

3. The lot number is given in two different ways #PI96001F and #PI96001, please provide clarification.

4. Please submit dissolution data showing the dissolution behavior of the drug below the specification time point (30 minutes). For example, dissolution data for the drug at sampling time 10, 20 and 30 minutes, for both the test and reference products.

Sincerely yours,

for Dale Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

STASON INDUSTRIAL CORPORATION

11 MORGAN, IRVINE, CA 92718-2005, U.S.A.
TEL: (714)380-4327 FAX: (714)380-4345

January 19, 1998

Archival Copy

Ms. Nancy Chamberlin
Project Manager
Division of Bioequivalence
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/R

RE: Acyclovir Capsules, 200 mg
ANDA 75-090

Dear Ms. Chamberlin:

BIOEQUIVALENCE INFORMATION

Pursuant to an FDA letter dated December 15, 1997, we are providing the following bioequivalence information for Acyclovir Capsules, 200 mg. Included in the submission are the analytical raw data provided by ———————— for all subjects who participated in the study under fasting and non-fasting conditions.

The responses are given in the order in which the comments appear in the FDA correspondence. Additionally, the request to show the dissolution behavior of the drug below the specification time point (30 minutes) has been acknowledged. The comparative dissolution testing was conducted at 10, 20, 30, 45, and 60 minutes.

Should you require additional information, please call me at (714) 380-4327 ext. 235 or fax me at (714) 380-4345. We hope to hear from you as soon as practical.

Sincerely,

Monica Tinio
Manager, Regulatory Affairs
Stason Industrial Corp.

RECEIVED
JAN 20 1998
GENERIC DRUGS

Si:Anda:Acy:biomajam

FACSIMILE AMENDMENT

JUN 9 1998

ANDA 75-090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Stason Industrial Corporation PHONE: 714-380-4327

ATTN: Monica Tinio FAX: 714-380-4345

FROM: Timothy Ames PROJECT MANAGER (301) 827–5798

Dear Madam:

This facsimile 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, 200 mg.

Reference is also made to your amendment(s) dated November 20, 1997.

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

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

SPECIAL INSTRUCTIONS:

CMC comments attached

Patti 6/9/98

X:\new\ogdadmin\macros\faxfax.frm

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

6/9/1998 FDA FAX

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please be advised that the suitability of the proposed dissolution procedure and specification will be established upon completion of review by the Division of Bioequivalence.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

STASON PHARMACEUTICALS, INC.

11 MORGAN, IRVINE, CA 92718-2005, U.S.A.
TEL: (714)380-4327 FAX: (714)380-4345

NEW CORRESP
NC / h.copy

ARCHIVAL COPY

June 26, 1998

Mr. Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Facsimile Amendment

RE: Acyclovir Capsules, 200 mg
ANDA 75-090

Dear Mr. Holcombe:

Stason Pharmaceuticals, Inc. submits herein a response to the referenced ANDA minor deficiency letter received from the agency via facsimile on June 9, 1998. Our replies are given in the order in which the comments appear in the letter. Included in the submission is the current patent certification for the drug product.

Pursuant to the Final Rule published in the Federal Register dated September 8, 1993 and 21 CFR 314.94, Stason Pharmaceuticals, Inc. certify that a true copy of this amendment has been provided to the FDA Los Angeles District Office on the same date of this submission to the Office of Generic Drugs.

Please contact me at the letterhead address, call me at (714) 380-4327 ext. 235 or fax me at (714) 380-4327 if you require additional information.

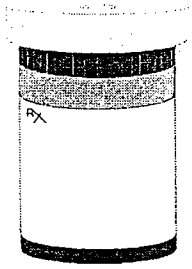
Sincerely,

Monica M. Tinio
Manager, Regulatory Affairs
Stason Pharmaceuticals, Inc.

FAX COVER SHEET

75090

Ms. Tino verified receipt 8/24/98



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: July 1998

TO: Monica M. Tino / Stason Pharmaceuticals, Inc.

Phone: 714 380-4327 **Fax:** 714 380-4345

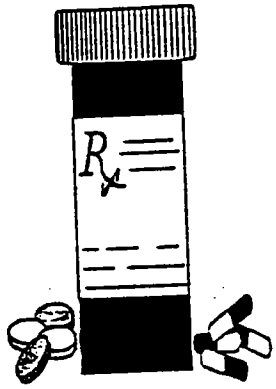
From: Labeling Review Branch

Phone: (301) 827-5846 **Fax:** (301) 443-3847

Number of Pages: 6
(Including Cover Sheet)

Comments:

See Labeling Review with
Date of Submission: November 20, 1997
for Deficiency Comments



Fax Cover Sheet

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: 8/5/98

To: Monica Tinio

Phone: 714-380-4327 *Fax:* 714-380-4345

From: Mark Anderson

Phone: (301) 827-5849 *Fax:* (301) 443-3839

Number of pages: 1
(Including Cover Sheet)

Comments: Bioequivalence acceptable comment for ANDA 75-090

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-090 APPLICANT: Stason Industrial Corp.

DRUG PRODUCT: Acyclovir Capsules, 200 mg

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

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

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program according the Pharmacopeial Forum, dated January-February 1998. The dissolution testing should be conducted in 900 mL of 0.1 N hydrochloric acid as the dissolution medium at 37 °C using USP Apparatus #1 (Basket) at 100 rpm. The test product should meet the following specifications:

> Not less than 75% (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FACSIMILE AMENDMENT

AUG 31 1998

ANDA 75-090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Stason Pharmaceuticals Inc. PHONE: 714-380-4327

ATTN: Monica M. Tinio FAX: 714-380-4345

FROM: Timothy Ames PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile 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 200mg.

Reference is also made to your amendment(s) dated June 26, 1998.

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

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

SPECIAL INSTRUCTIONS:

CMC and Bioequivalence comments are attached.

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of trade secret and/or

confidential commercial

information from

8/31/1998 FDA FAX

B. Labeling Deficiencies

Labels and labeling revisions are required as per our facsimile dated July 15, 1998.

C. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The evaluation of all firms involved in the manufacture and testing of the drug product with the current good manufacturing practices regulations will be undertaken by our Office of Compliance. A satisfactory evaluation is required prior to approval of this application.

2. Please provide any additional data for ongoing stability studies for the exhibit batch if available.

3. The evaluation of the analytical methods to be used for release and stability purposes will be undertaken by an FDA field laboratory at such time that the dissolution testing criteria have been finalized.

Sincerely yours,

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

STASON PHARMACEUTICALS, INC.

11 MORGAN, IRVINE, CA 92718-2005, U.S.A.
TEL: (714)380-4327 FAX: (714)380-4345

ARCHIVAL COPY

FPC
NEW CONREGP
NC

September 3, 1998

Mr. Timothy W. Ames
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

Facsimile Amendment

Re: ANDA 75-090
Acyclovir Capsules, 200 mg

FINAL PRINTED LABELING INCLUDED

Dear Mr. Ames:

Reference is made to the FDA facsimile letter dated August 31, 1998 pertaining to the Acyclovir Capsules ANDA. This facsimile amendment is being submitted to provide a complete response to the comments received. Our replies are given in the order in which the comments appear in the letter.

We have included twelve (12) final printed package inserts and container labels for your review; eleven (11) copies are in the archival copy and one (1) copy is in the review copy of this submission. Also, a current patent certification for the drug product is provided.

Pursuant to the Final Rule published in the Federal Register dated September 8, 1993 and 21 CFR 314.94, Stason Pharmaceuticals, Inc. certify that a true copy of this amendment has been provided to the FDA Los Angeles District Office on the same date of this submission to the Office of Generic Drugs.

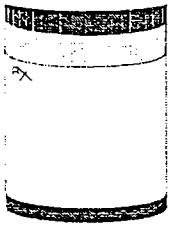
Please contact me at the letterhead address, call me at (714) 380-4327 ext. 235 or fax me at (714) 380-4327 if you require additional information.

Sincerely,

Monica M. Tinio
Manager, Regulatory Affairs
Stason Pharmaceuticals, Inc.

RECEIVED
SEP 10 1998
GENERIC DRUGS

FAX COVER SHEET



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: 9/23/98

TO: Monica Tinio 949

Phone: (714) 380-4327 Fax: (~~714~~) 380-4345

From: Charlie Hoppes

Phone: (301) 827-5846 Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments: Re: ANDA 75-090

3.1
Venlafaxine

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".

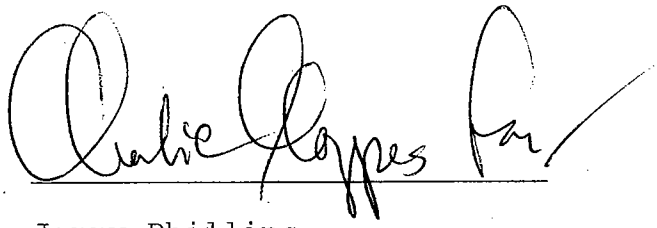
d. HOW SUPPLIED

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

ARCHIVAL COPY

STASON PHARMACEUTICALS, INC.

11 MORGAN, IRVINE, CA 92618-2005, U.S.A.
TEL: (949)380-4327 FAX: (949)380-4345

NDA ORIG AMENDMENT
FA

October 6, 1998

Mr. Charlie Hoppes
Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Acyclovir Capsules, 200 mg
75-090

Dear Mr. Hoppes:

Reference is made to your facsimile dated September 23, 1998 pertaining to Acyclovir Capsules package insert. The recommended changes have been made.

We have included twelve (12) final printed package inserts for your review; eleven (11) copies are in the archival copy and one (1) copy is in the review copy of this application.

If you need my assistance in the review of this submission, please call me at (949) 380-4327 ext. 235 or fax me at (949) 380-4345.

Sincerely,

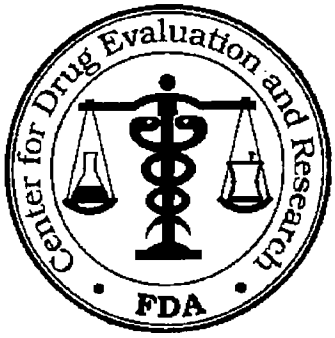
Monica M. Tinio
Manager, Regulatory Affairs
Stason Pharmaceuticals, Inc.

RECEIVED
OCT 07 1998
GENERIC DRUGS

FACSIMILE AMENDMENT

OCT 16 1998

ANDA 75-090



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Stason Pharmaceuticals, Inc. PHONE: 714-380-4327

ATTN: Monica Tinio FAX: 714-380-4345

FROM: Timothy Ames PROJECT MANAGER (301) 827–5798

Dear Madam:

This facsimile 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, 200 mg.

Reference is also made to your amendment(s)dated September 3, 1998.

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

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

SPECIAL INSTRUCTIONS:

CMC and labeling comments are attached. pmrg 10/15/98

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OCT 16 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-090 APPLICANT: Stason Pharmaceuticals, Inc.

DRUG PRODUCT: Acyclovir Capsules, 200 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Chemistry Deficiencies:

1. Regarding Laboratory Controls (Finished Dosage Form):

a. [redacted]

b. [redacted]

B. Labeling Deficiencies

1. CONTAINER: 100s and 400s

Satisfactory, however, at the time of the 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.

C. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

The evaluation of the analytical methods to be used for release and stability purposes will be undertaken by an FDA field laboratory. Samples will be requested in the near future.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

ARCHIVAL COPY

STASON PHARMACEUTICALS, INC.

11 MORGAN, IRVINE, CA 92618-2005, U.S.A.
TEL: (949)380-4327 FAX: (949)380-4345

NAI "hand carried"

NEW CORRESP.
NC to FA

October 19, 1998

Mr. Timothy Ames
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Facsimile Amendment

RE: ACYCLOVIR CAPSULES, 200 MG
ANDA 75-090

Dear Mr. Ames:

Stason Pharmaceuticals, Inc. submits herein a response to the referenced ANDA minor deficiency letter received from the agency via facsimile on October 16, 1998. Our replies are given in the order in which the comments appear in the letter. Included in the submission is the current patent certification for the drug product.

Pursuant to the Final Rule published in the Federal Register dated September 8, 1993 and 21 CFR 314.94, Stason Pharmaceuticals, Inc. certify that a true copy of this amendment has been provided to the FDA Los Angeles District Office on the same date of this submission to the Office of Generic Drugs.

Please contact me at the letterhead address, call me at (949) 380-4327 ext. 235 or fax me at (949) 380-4327 if you require additional information.

Sincerely,

Monica M. Tinio
Manager, Regulatory Affairs
Stason Pharmaceuticals, Inc.

RECEIVED
OCT 21 1998
GENERIC DRUGS

STASON PHARMACEUTICALS, INC.

FPL

11 MORGAN, IRVINE, CA 92618-2005, U.S.A.
TEL: (949)380-4327 FAX: (949)380-4345

ARCHIVAL COPY

November 5, 1998

Mr. Chan Park, Ph. D.
Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

RE: Acyclovir Capsules, 200 mg
ANDA 75-090

Dear Mr. Park:

Reference is made to our telephone conversation on November 4, 1998 pertaining to Acyclovir Capsules package insert. The recommended change in font size has been made to improve readability of the text. The change is from 5 pt. to 6 pt.

We have included twelve copies (12) of the package insert for your review; eleven (11) copies are in the archival copy and one (1) copy is in the review copy of this application.

Please contact me at the letterhead address, call me at (949) 380-4327 ext. 235 or fax me at (949) 380-4345, if you require additional information.

Sincerely,

Monica M. Tinio
Manager, Regulatory Affairs
Stason Pharmaceuticals, Inc.

NOV 0 6 1998