CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-382

Name: Acyclovir Tablets USP, 400 mg and 800 mg

Sponsor: Carlsbad Technology, Inc.

Approval Date: April 30, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-382

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-382

APPROVAL LETTER

ANDA 75-382

APR 30 1999

Carlsbad Technology Inc.
Attention: Simon Hsu
5923 Balfour Court
Carlsbad, CA 92008

Dear Sir:

This is in reference to your abbreviated new drug application dated May 7, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Tablets USP, 400 mg and 800 mg.

Reference is also made to your amendments dated August 20, and November 19, 1998; and February 22, and April 26, 1999.

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

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 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 4/30/99

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

cc: ANDA 75-352
Division File
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HFD-610/RLWest
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Endorsements:
HFD-643/V.Walton/2/22/99 V.Walton 3/19/99
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HFD-613/C.Hoppes (final only)/ C. Hoppes, 3/22/99

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F/T by: MDA/3/16/99

APPROVAL

Robert L. West
4/30/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-382

APPROVED LABELING

Acyclovir Tablets, USP

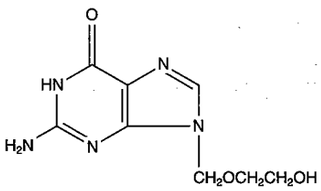
Rx only

DESCRIPTION: Acyclovir tablets are formulations of an antiviral drug for oral administration.

Each 800-mg tablet of acyclovir contains 800 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, corn starch, and sodium starch glycolate.

Each 400-mg tablet of acyclovir contains 400 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, corn starch, and sodium starch glycolate.

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



Acyclovir is a white to off-white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and 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 virus types 1 (HSV-1), 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 acyclovir 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 tablets 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 recommended 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/m² and 600 mg/m² 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 immunocompetent 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 5 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 is indicated for the acute treatment of herpes zoster (shingles).

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

Chickenpox: Acyclovir is 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 tablets are intended for oral ingestion only.

PRECAUTIONS: Dosage adjustment 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 six times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally six 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 five *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, weanling 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 nonsignificant increase in chromosomal damage

:HNOLOGY, INC.

ablets, USP

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 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 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 abnormalities, 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 number 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 decreased 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 acyclovir 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 (11.1%).

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 for 5 days.

Intravenous acyclovir is indicated for the treatment of varicella-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 initiated 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 tablets should be modified as shown in Table 3:

Table 3: Dosage Modification for Renal Impairment

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73 m²)	Adjusted Dosage Regimen Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

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

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 tablets (white to off-white, unscored, oval) containing 800 mg acyclovir and engraved with "CTI 113" - Bottle of 100 (NDC 61442-113-01), Bottle of 500 (NDC 61442-113-05), and unit dose pack of 100 (NDC 61442-113-11). Store between 15° and 25°C (59° and 77°F) and protect from moisture.

Acyclovir tablets (white to off-white, unscored, oval) containing 400 mg acyclovir and engraved with "CTI 112" - Bottle of 100 (NDC 61442-112-01), Bottle of 500 (NDC 61442-112-05), and unit dose pack of 100 (NDC 61442-112-11). Store between 15° and 25°C (59° and 77°F) and protect from moisture.

Made in U.S.A.

Manufactured by:
CARLSBAD TECHNOLOGY, INC.
5923 Balfour Court
Carlsbad, CA 92008

(Rev. 01/99)

100 Tablets

NDC 61442-112-11
Each tablet contains

ACYCLOVIR *Tablets, USP*

400mg

Unit Dose Pack **Rx Only**

PACKAGE NOT CHILD RESISTANT

(10 blisterpacks of 10 tablets each)

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

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

Made in U.S.A. Rev. 01/99

Carlsbad Technology, Inc.
Carlsbad, CA 92008

Lot
Exp

100 Tablets NDC 61442-112-01

ACYCLOVIR
Tablets, USP
Rx Only
Each tablet contains
400mg

Carlsbad Technology, Inc.
Carlsbad, CA 92008

Lot
Exp

For indications, dosage, precautions, etc., see accompanying package insert.
Store between 15° and 25°C (59° and 77°F) and protect from moisture.
Dispense in a tight, light-resistant container as defined in the USP.

Made in U.S.A.

Rev. 01/99

500 Tablets NDC 61442-112-05

ACYCLOVIR
Tablets, USP
Rx Only
Each tablet contains
400mg

Carlsbad Technology, Inc.
Carlsbad, CA 92008

Lot
Exp

For indications, dosage, precautions, etc., see accompanying package insert.
Store between 15° and 25°C (59° and 77°F) and protect from moisture.
Dispense in a tight, light-resistant container as defined in the USP.

Made in U.S.A.

Rev. 01/99

Carlsbad Technology, Inc. 5923 Balfour Ct. Carlsbad, CA 92008			
PACKAGING MATERIAL SPECIFICATIONS			
Label, Blister, VLT4-11			
Revision No	02	Document No	400605
Effective Date	JAN 12 1999	Page	2 of 2

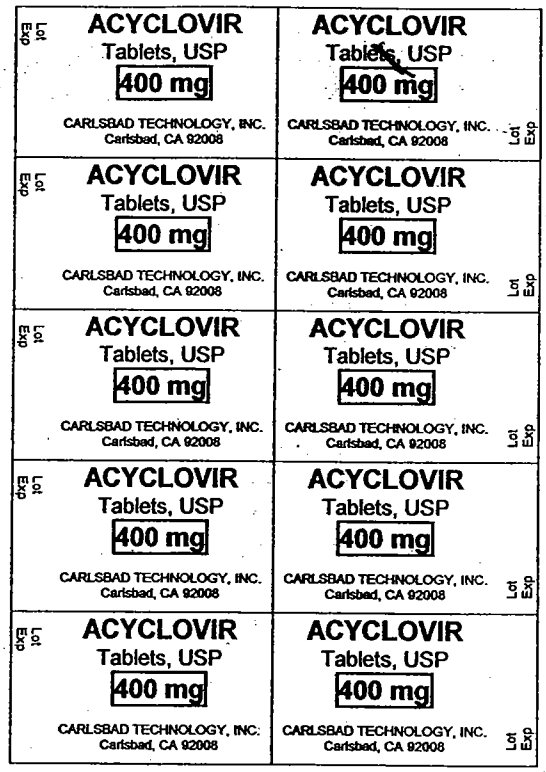
SPECIFICATIONS

Dimension of label : $1\frac{3}{8}$" (L) × $\frac{25}{32}$" (W)

Area reserved for printing Lot No. & Exp. Date

: Minimum $\frac{1}{5}$" (L) × $\frac{1}{2}$" (W)

LABEL CONTENT



** Please refer to the specifications above for actual label size.

100 Tablets NDC 61442-113-11
Each tablet contains

ACYCLOVIR *Tablets, USP* **800mg**

Unit Dose Pack **Rx Only**

PACKAGE NOT CHILD RESISTANT

(10 blisterpacks of 10 tablets each)

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

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

Made in U.S.A. Rev. 01/99

Carlsbad Technology, Inc.
Carlsbad, CA 92008

Lot
Exp

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100 Tablets NDC 61442-113-01

ACYCLOVIR
Tablets, USP
Rx Only
Each tablet contains
800mg

Carlsbad Technology, Inc.
Carlsbad, CA 92008

Lot
Exp

For indications, dosage, precautions, etc., see accompanying package insert.
Store between 15° and 25°C (59° and 77°F) and protect from moisture.
Dispense in a tight, light-resistant container as defined in the USP.

Made in U.S.A.

Rev. 01/99

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500 Tablets NDC 61442-113-05

ACYCLOVIR
Tablets, USP
Rx Only
Each tablet contains
800mg

Carlsbad Technology, Inc.
Carlsbad, CA 92008

Lot
Exp

For indications, dosage, precautions, etc., see accompanying package insert.
Store between 15° and 25°C (59° and 77°F) and protect from moisture.
Dispense in a tight, light-resistant container as defined in the USP.

Made in U.S.A.

Rev. 01/99

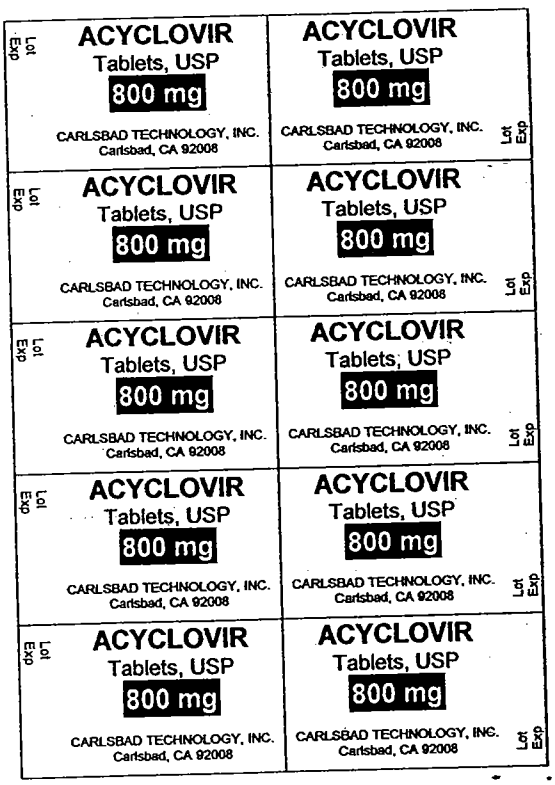
Carlsbad Technology, Inc. 5923 Balfour Ct. Carlsbad, CA 92008			
PACKAGING MATERIAL SPECIFICATIONS			
Label, Blister, VLT8-11			
Revision No	02	Document No	400705
Effective Date	JAN 1 2 1999	Page	2 of 2

SPECIFICATIONS

Dimension of label : $1\frac{3}{8}$" (L) × $\frac{25}{32}$" (W)

Area reserved for printing Lot No. & Exp. Date
: Minimum $\frac{1}{5}$" (L) × $\frac{1}{2}$" (W)

LABEL CONTENT



** Please refer to the specifications above for actual label size.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-382

LABELING REVIEW(S)

L. C. Hampton

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

ANDA Number: 75-382

Date of Submission: May 7, 1998

Applicant's Name: Carlsbad Technology Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

   Replace the "Caution: Federal law..." statement with "**Rx only**" or "**℞ only**" on labels and labeling. A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

2. CONTAINER:

   a. We encourage you to differentiate the different drug product strengths by boxing, contrasting colors, or some other means.

   b. 400 mg and 800 mg - 100s and 500s

      i. See GENERAL COMMENT.

      ii. Revise the storage statement to read as follows:

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

3. CARTON: 400 mg and 800 mg - unit dose 100s

   a. Please submit your proposed carton labeling for

our review and comment.

b. Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be with a child-resistant container, e.g.:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

[Note: The second sentnece is optional.]

c. Please note, your carton labeling should include the text found on your container labels.

4. INSERT

a. GENERAL COMMENTS

i. Revise your insert labeling to be in accord with the attached copy of the insert labeling of the reference listed drug Zovirax® (Glaxo Wellcome Inc.; revised March 1997 and approved May 29, 1997).

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

b. DESCRIPTION

Indicate the botanical source of starch.

c. HOW SUPPLIED

See comment 2(b) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

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

Attachment: Zovirax insert labeling.

Copy of Reference Listed Drug labeling removed.

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

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

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

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance? Yes No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:

Other Comments:

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?		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			
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: See comment above.

3. Patents/Exclusivity

   RLD patent expired on 4/22/97.

4. Components/Composition

   The firm's list of inactive ingredients in the DESCRIPTION section is consistent with the components and composition statements.
   [However, see comment above under DESCRIPTION regarding starach].
   [Vol. B1.1, p.2075, 2077 & 2078].

5. Manufacture:

   Carlsbad Technology Inc.
   Carlabad, CA
   [Vol. B1.1, p.2143]

10. Package size:

    RLD - 100s & unit-dose 100s
    ANDA - 100s, 500s & unit-dose 100s

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: 9/9/98

Primary Reviewer — Date: 9/23/98

* Jacqueline White, Pharm.D.

Team Leader — Date: 9/23/98

cc:

ANDA: 75-382
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes (no cc)
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Review

* Reviewed at different site.

Walker
1.1

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

ANDA Number: 75-382

Date of Submission: November 19, 1998 [document room date November 20, 1998]

Applicant's Name: Carlsbad Technology Inc.

Established Name: Acyclovir Tablets USP, 400 mg and 800 mg

Labeling Deficiencies:

1. CONTAINER: 400 mg and 800 mg

   Acyclovir tablets have become the subject of a USP monograph (See the 9th supplement to USP 23). We encourage you to include "USP" in the established name of your product where it appears on the principal display panel.

2. CARTON: 400 mg - 100s unit dose
   800 mg - 100s unit dose

   See comment under CONTAINER.

3. INSERT

   a. GENERAL

      i. Replace "ACYCLOVIR" with "acyclovir" (lower case lettering) where it appears throughout your insert labeling.

      ii. Italicize "*in vitro*" where it appears in the insert labeling.

   b. DESCRIPTION

      Revise the last paragraph to read as follows:

      ... white to off-white, ... weight of 225.21. The maximum ...

   c. CLINICAL PHARMACOLOGY

Pharmacokinetics (Table 2)

Include the data for the "200 mg" strength as seen in the reference listed drug.

d. PRECAUTIONS (Carcinogenesis, Mutagenesis, Impairment of Fertility)

Revise the first paragraph to read as follows:

... zoster) or 200 mg given orally six times a day (dosing appropriate for treatment of genital herpes). Plasma drug ... (See CLINICAL PHARMACOLOGY, Pharmacokinetics).

e. ADVERSE REACTIONS (Herpes Simplex)

i. Short-Term Administration

Revise to read as follows:

... with acyclovir 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting ...

ii. Long Term Administration

Revise to read as follows:

... 400 mg (two 200 mg capsules) two ...

f. DOSAGE AND ADMINISTRATION

i. Revise this section to read the same as the reference listed drug insert labeling, including all references to the 200 mg strength.

ii. Add the subsection "Bioequivalence of Dosage Forms" as the last subsection, as seen in the reference listed drug insert labeling.

g. HOW SUPPLIED

We encourage you to relocate "**℞ only**" to appear immediately following the Title/Established name. We refer you to A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was

revised July 1998 and posted at Internet site: http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

Please revise your labels and labeling, as instructed above, and submit final printed container labels, unit dose blister labels, carton labeling and 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 your last submission with all differences annotated and explained.

Robert West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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. USP 23/Suppl. 9	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?			
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?		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	-	-	-
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: Preserve in tight containers
   NDA: tight container
   ANDA:tight container

   -Storage recommendations:

   USP: Preserve in tight containers
   NDA: Store at 15° to 25°C(59° to 77°F) and protect from moisture.
   ANDA: See comment above.

3. Patents/Exclusivity

   RLD patent expired on 4/22/97.

4. Components/Composition

   The firm's list of inactive ingredients in the DESCRIPTION section is consistent with the components and composition statements.
   [However, see comment above under DESCRIPTION regarding starach].
   [Vol. B1.1, p.2075, 2077 & 2078].

5. Manufacture:

   Carlsbad Technology Inc.
   Carlabad, CA
   [Vol. B1.1, p.2143]

6 Package size:

   RLD - 100s & unit-dose 100s
   ANDA - 100s, 500s & unit-dose 100s

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: 12/8/98

Jacqueline White, Pharm.D. 12-8-98

Primary Reviewer Date

Jacqueline White, Pharm.D.

Team Leader 12/14/98

Date

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cc:

ANDA: 75-382
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes (no cc)
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Review

APPROVAL SUMMARY

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

ANDA Number: 75-382

Date of Submission: February 22, 1999

Applicant's Name: Carlsbad Technology Inc.

Established Name: Acyclovir Tablets USP, 400 mg and 800 mg

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

Do you have 12 Final Printed Labels and Labeling?
In the blue/A volume there are 9 of each piece, except for the unit dose blister. There is one draft copy of the unit dose 1x10 strip for each strength in the blue/A volume. In the red/B volume there are 3 of each piece, except for the unit dose blister. There are no copies of the unit dose blister in the red/B volume.

Container Labels:
400 mg and 800 mg – 100s, 500s
Satisfactory in final print as of the February 22, 1999 submission.

Unit Dose Blister Label:
400 mg and 800 mg -
Satisfactory as of the February 22, 1999 submission.

Unit Dose Carton
400 mg and 800 mg – 100 per carton
Satisfactory in final print as of the February 22, 1999 submission.

Professional Package Insert Labeling:
Satisfactory in final print as of the February 22, 1999 submission.

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: Acyclovir Tablets

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: S-11, approved 5/29/97, revised 3/97
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: Zovirax®
Basis of Approval for the Carton Labeling: Zovirax®

Other Comments:

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. USP 23/Suppl. 9	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?			
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?		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	-	-	-

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 ½ 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,		X	

briefly detail where/why.			
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].			

APPEARS THIS WAY
ON ORIGINAL

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: Preserve in tight containers
   NDA: tight container
   ANDA:tight container

   -Storage recommendations:

   USP: Preserve in tight containers
   NDA: Store at 15° to 25°C(59° to 77°F) and protect from moisture.
   ANDA: See comment above.

3. Patents/Exclusivity -none pending

4. Components/Composition

The firm's list of inactive ingredients in the DESCRIPTION section is consistent with the components and composition statements.
[Vol. B1.1, p.2075, 2077 & 2078].

5. Manufacture:

Carlsbad Technology Inc.
Carlabad, CA
[Vol. B1.1, p.2143]

6 Package size:

RLD - 100s & unit-dose 100s
ANDA - 100s, 500s & unit-dose 100s

7. Bioequivalence:

Fasting study 800 mg tablet

Pharmacokinetic parameter	ANDA	RLD
AUC(0-t)(ng.hr/mL)	3570.27 (34)	3763.41 (43.3)
AUCinf (ng.hr/mL)	4371.67 (27)	4452.42 (40.4)
Cmax (ng/mL)	743.21 (39)	745.46 (37.7)
Tmax (hr)	1.50	1.49
half-life (hr)	9.35	9.90

Non-fasting study 800 mg tablet

Pharmacokinetic parameter	ANDA	RLD	ANDA[fasting]
AUC(0-t)(ng.hr/mL)	6152.57	6351.49	4023.81
AUCinf(ng.hr/mL)	6555.71	6714.38	4542.70
Cmax (ng/mL)	1140.50	1223.00	778.81
Tmax (hr)	2.30	2.44	1.64
Half-life	7.51	7.01	8.82

The Cmax values are comparable to that listed in the insert labeling. The half-life values are not comparable to the insert labeling. The reported half-life in the insert labeling is 2.5 to 3.3 hours. The Tmax was not reported in insert labeling.

I sent an e-mail to the Bio. Reviewer. The Bio. Reviewer informed me that the data in the insert labeling was from a 200 mg strength and that the ANDA's study was done with a 800 mg strength. I was also shown another Bio. review for acyclovir from a different ANDA with similar half-live results, ~10 hours for the ANDA and RLD. Due to these findings will plan to send an e-mail to the new drug division requesting them to re-examine the pharmacokinetic parameters for this drug product including the 800 mg strength.

Food effect:

- half-life decreased
- tmax increased
- Cmax increased
- AUC increased

This is not consistent with the text found in the insert labeling, which reports that there is no effect of food on the absorption of acyclovir. This issue has been previously addressed. See FTR #8.

The Bio. Reviewer also mentioned the increase in the AUC and Cmax under nonfasting condition in the review.

The firm's *in vivo* bioequivalence studies conducted on the 800 mg strength under fasting and nonfasting were conditions were found to be acceptable.

A waiver of *in vivo* bioequivalence study requirements for the 400 mg has been granted.

Bio. Found acceptable on 8/21/98

8. 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: 3/2/99

Primary Reviewer
Jacqueline White, Pharm.D.

3-12-99
Date

Team Leader

3/12/99
Date

cc: Concur 3/12/1999

ANDA: 75-382
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes (no cc)
v:\new\...75382ap.1
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-382

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-382

3. NAME AND ADDRESS OF APPLICANT

Carlsbad Technology Inc.
5923 Balfour Court
Carlsbad, CA 92008

4. LEGAL BASIS OF SUBMISSION

The application is based on the reference listed drug Zovirax® 800 mg and 400 mg oral tablets manufactured by Glaxo Wellcome Inc. Pursuant to NDA 20-089.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir Tablets, 400 mg and 800 mg

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

9. AMENDMENTS AND OTHER DATES:

Date of Application: May 7, 1998

Date Acceptable for filing: May 12, 1998

New Corresp. Dated May 19, 1998: includes FDA form 356h, Patent certification, Exclusivity statement with original signatures and additional copies of the packaging labels and labeling insert.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 20-089 - Burroughs Wellcome (RLD - Zovirax®)
DMF#

13. DOSAGE FORM
Oral Tablets

14. POTENCY
400 mg
800 mg

15. CHEMICAL NAME AND STRUCTURE

9-[(2-Hydroxyethoxy)methyl]guanine.

$C_8H_{11}N_5O_3$
Molecular Weight: 225.21

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The application contains various deficiencies with respect to CMC and is Not Approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
Not-approvable.

19. REVIEWER: V.Walton

DATE COMPLETED: 9/4/98

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 75-382
DUP/Division File
FIELD COPY

Endorsements:
HFD-643/VWalton/9/4/98/ V.Walton 9-23-98
HFD-643/JHarrison/9/8/98/ J Harrison 9/23/98
HFD-617/MAnderson/9/22/98 Mark Anderson 9/24/98

F/T by tic 9/23/98
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CHEMISTRY FACSIMILE DEFICIENCY

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-382

3. NAME AND ADDRESS OF APPLICANT

Carlsbad Technology Inc.
5923 Balfour Court
Carlsbad, CA 92008

4. LEGAL BASIS OF SUBMISSION

The application is based on the reference listed drug Zovirax® 800 mg and 400 mg oral tablets manufactured by Glaxo Wellcome Inc. Pursuant to NDA 20-089.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir Tablets USP, 400 mg and 800 mg

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

9. AMENDMENTS AND OTHER DATES:

Date of Application: May 7, 1998

Date Acceptable for filing: May 12, 1998

New Corresp. Dated May 19, 1998: includes FDA form 356h, Patent certification, Exclusivity statement with original signatures and additional copies of the packaging labels and labeling insert.

New Corresp. (Facsimile Amendment) Dated November 19, 1998. Response to the deficiencies communicated to the applicant on October 26, 1998.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 20-089 - Burroughs Wellcome (RLD - Zovirax®)
DMF# [redacted]

13. DOSAGE FORM

Oral Tablets

14. POTENCY
400 mg and
800 mg

15. CHEMICAL NAME AND STRUCTURE

9-[(2-Hydroxyethoxy)methyl]guanine.

$C_8H_{11}N_5O_3$
Molecular Weight: 225.21

16. RECORDS AND REPORTS
N/A

17. COMMENTS

From the Chemistry and Manufacturing standpoint, the application is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable except for labeling.

19. REVIEWER:
V.Walton

DATE COMPLETED:
2/3/99

Redacted 15 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 75-382
DUP/Division File
FIELD COPY

Endorsements:
HFD-643/VWalton/2/3/99/ V. Walton 3/19/99
HFD-643/R.Adams/2/22/99 R. C. Adams, 3/19/99

FT:mda/3/13/99
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APPEARS THIS WAY
ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA: 75-382

DRUG PRODUCT: Acyclovir Tablets USP, 400 mg and 800 mg

FIRM: Carlsbad Technology Inc.

DOSAGE FORM: Tablets

STRENGTH: 400 mg and 800 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP Certification statement is included for Carlsbad Technology Inc., [redacted]

Inc.

BIO STUDY:

The bioequivalence studies are acceptable. See Bio review dated 8/21/98.

METHOD VALIDATION – (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
USP item method validation not necessary.

STABILITY – (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION):
The containers used in the stability study are identical to those in the container section.

LABELING: Satisfactory 3/12/99

STERILIZATION VALIDATION: n/a

SIZE OF STABILITY BATCHES – (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
The size of the stability batches is [redacted] tablets each. (Lot No. RB7003, 400 mg and Lot No. RB7002, 800 mg).

PROPOSED PRODUCTION BATCH – (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):
The proposed production batch size for the 400 mg tablet size is [redacted] tablets and [redacted] tablets for the 800 mg tablets. The manufacturing process is the same as that used to manufacture the stability samples.

CHEMIST: Vernon C. Walton 3/19/99

SUPERVISOR: Richard Adams

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-382

BIOEQUIVALENCE REVIEW(S)

Acyclovir	Carlsbad Technology, Inc.
400 mg and 800 Tablets	Carlsbad, CA
ANDA #75-382	Submission Date:
Reviewer: Moheb H. Makary	May 7, 1998
WP 75382SDW.598	August 20, 1998

Review of Two Bioequivalence Studies, Dissolution Data and a Waiver Request

I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions on its Acyclovir 800 mg tablets and dissolution data to compare the test product relative to Zovirax^{R} (Glaxo-Wellcome) 800 mg tablets for review. The firm has also requested a waiver of *in vivo* bioequivalence study requirements for its 400 mg strength. The formulations for the drug products Acyclovir 800 mg and 400 mg tablets were also submitted.

II. Background:

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside with antiviral activity against human herpes viruses, including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella zoster virus (VCV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). The viral inhibitory activity is highly selective, involving preferential uptake into virus-infected cells and requiring a virus-specific thymidine kinase for conversion to the monophosphate. Subsequent conversion to the triphosphate results in irreversible binding to DNA polymerase and termination of DNA replication. Acyclovir capsules, tablets and suspension are indicated for the treatment of initial episodes and management of recurrent episodes of genital herpes in certain patients and for the acute treatment of herpes zoster and chicken pox.

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

Pharmacokinetics

The oral absorption of acyclovir is slow, variable, and incomplete,

with absolute bioavailability estimated as 15-30% from different studies involving both normals and patients. Reported values for C_{max} and T_{max} in healthy subjects after a 200 mg capsule were 0.3 ± 0.1 mg/L and 1.5-2.5 hours, respectively. Several studies in healthy volunteers have demonstrated dose-dependent absorption: (1) fraction of the dose recovered unchanged in the urine decreased over the dosing range of 100-600 mg (13.2% of a 100 mg dose; 12.1%, 200 mg; 7.4%, 400 mg; 6%, 600 mg dose); (2) mean C_{MAX} was 0.58 mg/L after a single 600 mg dose and 0.50 mg/L after a single 200 mg dose; (3) mean AUC after a 600 mg dose given as divided doses every four hours, was about three times higher than after a single 600 mg dose; and (4) mean AUC from a 400 mg dose given as a duodenal infusion was about 1.7 times that from tablets, which suggested capacity-limited absorption. However, the results of one multiple dose study (200 mg q4h vs. 3 X 200 mg q4h) in immunocompromised patients suggested that net absorption of acyclovir is nearly proportional to dose in the 200-600 mg dose range.

Plasma elimination of acyclovir is biphasic with a beta phase half-life of 2-3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine. After an intravenous infusion of a ^{14}C tracer dose in patients, 71-99% of the dose was recovered in the urine. There is only one significant, inactive metabolite, 9-carboxymethoxymethyl guanine (CMMG), which accounts for 8-14% of a dose.

III. Study/Protocol #153-05-11138 For Single-dose Fasting Bioequivalence Study:

Study site: _____

_____

Principle Investigator:

_____, M.D.

Analytical site: _____

_____

Study design: A randomized, single-dose, open-label, 2-way crossover bioequivalence study under fasting conditions.

Study dates: Period I, December 22, 1997

Period II, December 29, 1997

Analytical dates: Sample analysis began on January 9, 1988 and was completed on February 3, 1998.

Subjects: Twenty-six (26) normal healthy subjects (8 female, 18 male) enrolled in the study. All met the selection criteria described in the protocol. They were judged to be healthy based on medical history, physical examination and clinical laboratory tests within 30 days prior to period 1 dosing. All subjects were within 18 to 46 years of age and the weight range was not more than ± 15% for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table. Two subjects failed to complete the study. Subject #14 withdrew from the study after completing period I for personal reasons, and subject #26 was withdrawn from the study because the toxicology report was not received in time for dosing for period II. Twenty-four (24) subjects completed the study.

Exclusion criteria: a. Volunteers with a recent history of drug or alcohol addiction or abuse.
b. Volunteers with the presence of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, herpes, or neurologic system or psychiatric disease.
c. Volunteers demonstrating a positive hepatitis B surface antigen screen HIV 1 & 2 antibody screen.
d. Volunteers with a history of allergic response to acyclovir or related drugs.
e. Any medication by prescription in past 14 days, except birth control pills.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug

treatments:

Test product: A. 1x800 mg Acyclovir Tablets (Carlsbad), lot #RB7002E, lot size ——— Tablets, Content uniformity and potency are 97.9% (%CV=1.5) and 97.9%, respectively.

Reference product: B. 1x800 mg Zovirax^{R} Tablets (Glaxo-Wellcome), lot #7B1371, Exp. 4/2001, potency 96.4%, content uniformity 97.1%.

Food and fluid intake: Following drug administration, the subjects remained fasting for 5 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. Water was permitted *ad lib.* except within 1 hour of drug administration.

Blood collection: Blood samples were obtained in heparinized Vacutainers prior to drug administration. Similarly, samples were drawn at the following times after dosing: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16 and 24 hours. Blood samples were centrifuged at 2500 RPM for 15 minutes.

Washout period: 7 days.

Assay Methodology: Plasma samples were analyzed for Acyclovir using ———————————————— ———.

Sensitivity: The lowest non-zero standard was — ng/mL for acyclovir. A sample value calculated to be below the LOQ was reported as zero.

Specificity: Human plasma used to prepare the standards and QCs was assayed before calibration sample preparation to show no interference of endogenous compounds at the retention time of acyclovir or the internal standard.

Precision: Between-run coefficient of variation from quality control samples ranged from [redacted]

Accuracy: The accuracy of the assay from quality control samples ranged from [redacted]% to [redacted]% for acyclovir.

Stability: Freeze and Thaw Stability: The stability of acyclovir was determined through three freeze and thaw cycles. These samples were analyzed against the standard curve prepared from the fresh stock. The percent change from theoretical following three freeze-thaw cycles was -0.3% and 6% for 1000 and 20.0 ng/mL, respectively.
Long-term stability of acyclovir in human plasma was evaluated by analysis of quality control samples stored under the same conditions as study samples (-20°C). Results indicated that acyclovir was stable up to 42 days.

Statistical Analysis:

AUC(0-t), AUCinf, Cmax, Kel, T1/2 and concentrations at each sampling time point were determined for acyclovir. ANOVA was performed at alpha level of 0.05 using the GLM procedure of SAS. The 90% confidence intervals were calculated for LnAUC(0-t), LnAUCinf and LnCmax.

IV. In Vivo Results:

Twenty-six (26) subjects enrolled and twenty-four (24) subjects completed the study. Six subjects reported fourteen adverse events (volume 1.1, Page #0096). All of the events were mild in severity, with the exception of one which was moderate in severity (experienced by subject #26).

The plasma concentrations and pharmacokinetic parameters for acyclovir are summarized below in Table I.

Table I

Mean Plasma Acyclovir Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x800 Acyclovir Tablet under Fasting Conditions

(N=24)

Time hr	Treatment A Carlsbad-Test Lot #RB7002E ng/mL	Treatment B Glaxo-Wellcome Lot #7B1371 ng/mL
0.0	0	0.45 (489.9)
0.33	149.00 (81.2)	154.77 (72.9)
0.67	450.84 (45.4)	483.44 (54.7)
1.00	597.54 (43.0)	571.75 (42.2)
1.33	668.04 (45.8)	633.04 (42.0)
1.67	647.21 (48.6)	639.13 (44.6)
2.00	625.29 (48.1)	624.42 (44.9)
2.50	557.71 (44.5)	570.04 (50.2)
3.00	478.25 (45.2)	517.96 (57.4)
3.50	405.00 (44.8)	441.08 (60.6)
4.00	339.75 (42.7)	383.75 (65.7)
5.00	261.50 (45.2)	292.13 (65.8)
6.00	195.88 (43.3)	213.80 (58.5)
8.00	124.27 (39.2)	133.25 (52.0)
10.00	82.15 (36.9)	88.58 (49.2)
12.00	56.88 (35.9)	63.85 (43.5)
14.00	44.22 (32.3)	49.20 (42.6)
16.00	39.29 (30.9)	41.83 (41.7)
24.00	32.48 (36.6)	32.86 (46.3)
AUC(0-t) (ng.hr/mL)	3570.27 (34)	3763.41 (43.3)
AUCinf (ng.hr/mL)	4371.67 (27)	4452.42 (40.4)
Cmax (ng/mL)	743.21 (39)	745.46 (37.7)
Tmax (hr)	1.50	1.49
half-life (hr)	9.35	9.90

	T/R	90% CI
LnAUC(0-t)	0.95	86.3-110.4%
LnAUCinf	0.98	86.4-114.9%
LnCmax	0.99	90.6-109.5%

1. For Acyclovir, the least squares means AUC(0-t), AUCinf and Cmax values were 5.13%, 3.82% and 0.3% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The Acyclovir mean plasma levels peaked at 1.33 and 1.67 hours for the test and the reference products, respectively, following their administration under fasting conditions.

V. Study #153-06-11139 For Single-dose Post-Prandial Bioequivalence Study of Acyclovir 800 mg Tablets

The objective of this study was to evaluate the effect of food on the rate and extent of absorption of a single dose of Acyclovir 800 mg Tablet (Carlsbad) relative to Zovirax^{R} 800 mg Tablets (Glaxo-Wellcome).

Study site: _____

_____

Principle Investigator:

_____ M.D.

Analytical site: _____

_____

Study design: Single-dose, three-way crossover, post-prandial bioequivalence study.

Study dates: Period I, November 24, 1997
Period II, December 1, 1997
Period III, December 8, 1997

Analytical dates: Sample analysis began on January 19, 1988 and was completed on February 12, 1998.

Subjects: Eighteen (18) normal healthy subjects (6

female, 12 male) enrolled in the study. All met the selection criteria described in the protocol. They were judged to be healthy based on medical history, physical examination and clinical laboratory tests within 30 days prior to period 1 dosing. All subjects were within 20 to 50 years of age and the weight range was not more than ± 15% for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table. One subject failed to complete the study. Subject #15 withdrew from the study after completing period I for personal reasons. Seventeen (17) subjects completed the study.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

A. 1x800 mg Acyclovir Tablet (Carlsbad), lot #RB7002E, administered after a high fat breakfast preceded by an overnight fast.

B. 1x800 mg Zovirax^{R} Tablet (Glaxo-Wellcome), lot #7B1371, administered after a high fat breakfast preceded by an overnight fast.

C. 1x800 mg Acyclovir Tablet (Carlsbad), lot #RB7002E, administered following an overnight fast.

Food and fluid intake: For treatments A and B, the subjects fasted for at least 10 hours prior to being served a high-fat meal. The subjects were instructed to consume their meal within 30 minutes. For treatment C, the subjects fasted for at least 10 hours prior to drug administration. Only fluids given with breakfast and water given with drug administration were allowed within one hour of dosing. Thereafter, water was allowed *ad lib*. Lunch was served to all subjects at 5 hours postdose. Following drug

administration, the subjects remained fasting for 5 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter.

Blood collection: Blood samples were obtained in heparinized Vacutainers prior to drug administration. Similarly, samples were drawn at the following times after dosing: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16 and 24 hours.

Washout period: One week.

Assay Methodology: Same as in Study #153-05-11138.

Statistical Analysis: Same as in Study #153-05-11138.

VI. In Vivo Results:

Eighteen (18) subjects enrolled and seventeen subjects completed the study. Plasma samples for subject #10, period III, could not be located for analysis, therefore, none of the samples for this subject were analyzed and no data are reported. Eight of the subjects experienced fourteen mild adverse events during the study. All the events were resolved, and none resulted in the withdrawal of any subject from the study.

The plasma concentrations and pharmacokinetic parameters for acyclovir are summarized below in Table II.

Table II

Mean Plasma Acyclovir Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 800 Acyclovir Tablet under Fasting and Nonfasting Conditions
(N=16)

Time hr	Treatment A Carlsbad-Test Lot #RB7002E Nonfasting ng/mL	Treatment B Glaxo Wellcome-Reference Lot #7B1371 Nonfasting ng/mL	Treatment C Carlsbad-Test Lot #RB7002E Fasting ng/mL
0	1.46 (400.0)	0	0
0.33	8.09 (157.5)	22.13 (310.9)	178.02 (68.1)
0.67	210.64 (107.8)	150.91 (171.6)	491.25 (43.2)
1.00	572.78 (68.9)	351.31 (102.8)	639.75 (28.9)
1.33	741.14 (58.1)	628.18 (68.7)	668.13 (26.5)
1.67	774.00 (53.9)	796.63 (46.6)	662.88 (31.5)
2.00	795.06 (49.3)	947.13 (33.9)	637.25 (36.7)
2.50	851.63 (39.0)	983.25 (35.4)	593.81 (48.8)
3.00	874.31 (42.4)	992.00 (47.0)	534.44 (55.5)
3.50	854.13 (47.9)	945.19 (48.7)	470.31 (55.2)
4.00	791.00 (53.0)	852.94 (48.3)	413.19 (54.7)
5.00	646.81 (58.0)	665.31 (53.5)	322.75 (53.4)
6.00	485.94 (60.3)	493.06 (56.2)	242.81 (54.4)
8.00	287.75 (58.5)	295.44 (57.2)	152.96 (56.3)
10.00	176.45 (55.8)	181.88 (55.4)	96.64 (51.3)
12.00	116.34 (48.9)	118.33 (48.4)	68.74 (39.4)
14.00	84.42 (42.4)	81.26 (44.4)	50.53 (35.7)
16.00	63.60 (38.6)	61.61 (37.3)	40.81 (31.0)
24.00	36.40 (25.0)	35.13 (22.3)	35.05 (30.5)

	A	B	C	A/B
AUC(0-t)(ng.hr/mL)	6152.57	6351.49	4023.81	0.97
AUCinf(ng.hr/mL)	6555.71	6714.38	4542.70	0.98
Cmax (ng/mL)	1140.50	1223.00	778.81	0.93
Tmax (hr)	2.30	2.44	1.64	
Half-life	7.51	7.01	8.82	

1. The acyclovir mean plasma levels peaked at 3 hours for both the test and the reference products, respectively, under nonfasting conditions and at 1.33 hours for the test product under fasting conditions.

2. For Carlsbad's test product, the Least Squares Means (LSM) AUC(0-t), AUCinf and Cmax values were 2.3%, 1.5% and 6.2% lower, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic LSM to the reference arithmetic LSM are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax.

3. For the comparison of the test product under fasting and nonfasting conditions, the mean AUC(0-t) and Cmax values under nonfasting conditions were 53% and 46.4% higher than the respective means under fasting conditions.

VII. Formulations:

Carlsbad's formulations for its Acyclovir 400 mg and 800 mg Tablets are shown in Table III.

Table III

Ingredient	800 mg Tablet mg/Tablet	400 mg Tablet mg/Tablet
Acyclovir	800.00	400.00
Magnesium Stearate, NF		
Microcrystalline Cellulose, NF		
Sodium starch glycolate, NF		
Starch ——, NF		
———————*		
Total	1050.00 mg	525.00 mg

*estimated quantity, removed during processing

VIII. In Vitro Dissolution Testing (FDA Method)

Method: USP 23 apparatus 2 (paddle) at 50 rpm
Medium: 900 mL of water
Sampling Time: 5, 10, 20, 30, 45 and 70 minutes.

Test Product: Carlsbad's Acyclovir Tablets
400 mg, lot #RB7003
800 mg, lot #RB7002

Reference
Product: Glaxo-Wellcome's Zovirax Tablets
400 mg, lot #7B1372
800 mg, lot #7B1371

Number of
Tablets: 12

Specification: NLT 80% (Q) in 45 minutes

The dissolution testing results are shown in Table IV.

IX. Comments:

1. The firm's *in vivo* bioequivalence studies conducted on the 800 mg strength under fasting and nonfasting conditions are acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions. The ratios of the test mean to the reference mean for AUC(0-t), AUCinf and Cmax are within the acceptable range of 0.8-1.2 under nonfasting conditions.

2. The *in vitro* dissolution testing submitted by the firm on its Acyclovir Tablets, 400 mg and 800 mg is acceptable.

3. The formulation for Acyclovir Tablet, 400 mg, is proportionally similar to the 800 mg strength.

X. Recommendations:

1. The bioequivalence studies conducted by Carlsbad Technology, Inc., under fasting and nonfasting conditions on its Acyclovir, 800 mg Tablet, lot #RB7002E, comparing it to Glaxo-Wellcome's Zovirax^{R} 800 mg Tablet have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Carlsbad's Acyclovir Tablet, 800 mg, is bioequivalent to Glaxo-Wellcome's Zovirax^{R} 800 mg Tablet.

2. The dissolution testing conducting by Carlsbad Technology, Inc., on its Acyclovir, 400 mg and 800 mg Tablets, lot #RB7003 and lot

#RB7002, respectively, has been found acceptable by the Division of Bioequivalence. The formulation for the 400 mg strength is proportionally similar to the 800 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of *in vivo* bioequivalence study requirements for the 400 mg tablet of the test product is granted. The Division of Bioequivalence deems Acyclovir Tablet, 400 mg, manufactured by Carlsbad Technology, Inc., to be bioequivalent to Zovirax[R] Tablet, 400 mg, manufactured by Glaxo-Wellcome.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than 80% (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.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT BMD 8/21/98)
FT INITIALLED BDAVIT Barbara M Davit Date: 8/21/98)

Concur: Dale P. Conner Date: 8/24/98

Dale Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/8-21-98, wp 75382SDW.598
cc: ANDA #75-382,original, HFD-658 (Makary), Drug File, Division File.

Table IV. In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir Tablets
Dose Strength: 400 mg and 800 mg
ANDA No.: 75-382
Firm: Carlsbad
Submission Date: May 7, 1998
File Name: 75382SDW.598

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM: 50
No. Units Tested: 12
Medium: 900 mL of water
Specifications: NLT 80% (Q) in 45 minutes
Reference Drug: Zovirax
Assay Methodology: UV

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #RB7002 Tablet Strength(mg) 800			Reference Product Lot #7B1371 Tablet Strength(mg) 800		
	Mean %	Range	%CV	Mean %	Range	%CV
5	45.8	41.0-62.3	12.5	46.5	34.9-56.5	13.5
10	73.4	66.3-77.7	5.1	79.4	71.9-83.5	3.8
20	86.5	78.6-90.0	4.4	90.1	83.5-97.4	5.0
30	91.5	85.6-96.5	3.8	91.1	86.2-95.0	3.1
45	93.2	88.3-97.9	3.3	92.5	87.4-99.2	4.3
70	93.4	87.6-97.9	3.3	94.1	89.0-100.9	4.4
Sampling Times (Minutes)	Test Product Lot #RB7003 Tablet Strength(mg) 400			Reference Product Lot #7B1372 Tablet Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
5	72.5	65.1-80.6	6.8	61.8	53.7-72.2	10.4
10	84.6	79.7-90.0	4.3	76.9	73.4-79.2	2.5
20	93.5	91.6-96.1	1.6	84.9	81.8-89.3	2.7

30	96.2	94.0-98.9	1.4	88.6	85.8-92.2	2.5
45	97.8	96.0-100.6	1.3	90.7	88.6-93.7	1.8
70	97.8	96.2-100.1	1.1	91.9	89.8-94.2	1.6

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-382 APPLICANT: Carlsbad Technology, Inc.

DRUG PRODUCT: Acyclovir Tablets, 400 mg and 800 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 conducted in 900 mL of water, at 37 °C using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than 80 %(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, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-382
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M Makary

X:\NEW\FIRMS\Carlsbad\ltrs&rev\75382sdw.598
Printed in final on 8/21/1998

Endorsements: (Final with Dates)
HFD-658/ Reviewer M Makary MM
HFD-658/ Bio team Leader B Davit BD
HFD-650/ D. Conner DB 8/24/98

BIOEQUIVALENCY - ACCEPTABLE

submission date: May 7, 1998
August 20, 1998

1. **FASTING STUDY** (STF)
Clinical: ————————
Analytical: ————————
Strengths: 800 mg
Outcome: AC

2. **FOOD STUDY** (STP)
Clinical: ————————
Analytical: ————————
Strengths: 800 mg
Outcome: AC

3. **DISSOLUTION WAIVER** (DIW)
Strengths: 400 mg
Outcome: AC

4. **STUDY AMENDMENT** (STA)
Strengths: 800 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-382 SPONSOR: Carlsbad Techology, Inc
DRUG: Acyclovir
DOSAGE FORM: Tablets
STRENGTH(s): 800 mg and 400 mg
TYPE OF STUDY: Single/Multiple Fasting/Fed
STUDY SITE: [ ]

STUDY SUMMARY: The bioequivalence studies conducted by Carlsbad under fasting and nonfasting conditions on its Acyclovir, 800 mg Tablets are acceptable.

DISSOLUTION: Dissolution testing conducted by the firm on its Acyclovir Tablets, 800 mg and 400 mg, is acceptable. Waiver is granted for the 400 mg strength.

PRIMARY REVIEWER: Mohib H. Makary BRANCH: III

INITIAL: MHM DATE: 8/21/98

BRANCH CHIEF: Barbara M Davit BRANCH: III

INITIAL: BMD DATE: 8/21/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DB DATE: 8/24/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-382

ADMINISTRATIVE DOCUMENTS

File 75-382

RECORD OF TELEPHONE CONVERSATION

Mr. Harrison and I spoke with Mr. Lu and 2 associates about questions they had regarding our deficiency comments.

Regarding #3, they questioned the need for an additional identification test such as a chromatographic procedure. They stated this was not a USP requirement and that IR spectrocopy is usually only used for pure raw material and not for finished dosage form. They claimed that excipients in finished dosage form could affect results.

Mr. Harrison told firm to make this justification and reference to USP and we would consider their position.

Regarding #4: they questioned the need for conducting moisture permeability testing for unit dose packaging. They pointed out that they conducted 3 month accelerated stability testing at 40 C, 75% RH which they feel is a more stringent test of container than doing permeability testing.

Mr. Harrison told firm to make this justification in response and we will consider.

X:\new\firmsam\carlsbad\telecons\75382.001

DATE
11/17/98

APPLICATION NUMBER
75-382

TELECON

INITIATED BY APPLICANT

PRODUCT NAME
Acyclovir Tablets 400 mg and 800 mg

FIRM NAME
Carlsbad Technology

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Bruce LU

TELEPHONE NUMBER
760-431-8284 Ext 116

SIGNATURE
Mark Anderson

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-382 Applicant Carlsbad Technology Inc
Drug Acyclovir Tablets USP
Strength 400mg and 800 mg

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

REVIEWER:

1. Project Manager Mark Anderson
Review Support Br

DRAFT RECEIPT Date 3/12/99 Initials MA

FINAL ACTION Date 3/22/99 Initials MA

Application Summary:
Original Rec'd date 5/12/98
Date Acceptable for Filing 5/12/98
Patent Certification (type) II
Date of Office Bio Review 8/28/98
Methods Val. Samples Pending Yes ☐ No X
30 Day Clock Start N/A End ____
Commitment rcd. from Firm N/A Yes ☐ No ☐
First Generic Yes ☐ No X

EER Status Pending ☐ Acceptable X OAI ☐
Date of EER Status 8/24/98
Date Patent in effect N/A
Citizens Petition/Legal Case Yes ☐ No X
(If YES, attach email from PM to Pet. Coord. notifying of pending approval)
Pediatric Exclusivity Tracking System
Date checked ____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Comments:
Previously reviewed and tentatively approved NO ☐ Date ____
Previously reviewed and CGMP def./N/A Minor issued NO ☐ Date ____

2. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Date 3/22/99 Initials [illegible]
Date 4/26/99 Initials [illegible]
Comments:
3/26/99 Called Aimen How regarding particle size spec. for the drug substance
4/26/99 Amendment - method & spec submitted
Chemistry is satisfactory

3. Office Level Chem Review (1st Generic Only) Date ____ Initials ____
Chemistry Div. I or II
Date ____ Initials ____
Comments:
Multiple ANDAs approved for this drug product. [illegible] 4/30/99

4. Pat Beers Block
Supv., Review Support Branch
Date 4/28/99 Initials [illegible]
Date ____ Initials ____
Comments: Refer to DCRS REVIEW.
[illegible] 4/30/99

REVIEWER: **DRAFT RECEIPT** **FINAL ACTION**

5. Peter Rickman
Supv., Reg. Support Branch
Contains certification Yes ☑ No ☐
(required by the GDEA if sub after 6/1/92)
Paragraph 4 Certification Yes ☐ No ☒
Comments:

Date 4/30/99 Initials RW
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity Tracking System
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Date 4/30/99 Initials Request for RW

RLD = NDA 20-089 Zovirax Tablets Glaxo Wellcome.

No unexpired patents or exclusivity.

6. ~~Jerry Phillips~~
Dir. Div. Labeling & Prog. Support
Comments: Acceptable, ES dated 8/24/98 (Verified 4/30/99). No ONE shots noted. Bioequivalence studies (fasting, fed, dissolution) found acceptable on 400mg tablet. Waiver granted to 400mg strength due to proportionality. Office Overbio endorsed 9/24/98. Bio studies conducted at _____. CMC Acceptable 3/19/99. Methods validation waived. FPL Acceptable for approval 5/1/1999.

Date 4/30/99 Initials RW

Date 4/30/99 Initials Robert Request for

Recommend: Approval

7. ~~Gordon Johnston~~
Deputy Director, OGD
Patent Cert - P_4 Yes ☐ No ☒
Pend. Legal Action Yes ☐ No ☒
Comments: No controlled correspondence or Citizens Petitions currently pending. No pediatric exclusivity issues under FDAMA. No unexpired patents or exclusivity. OK to approve.

Date 4/30/99 Initials RW
Petition Status None

Date 4/30/99 Initials Request for RW

Doug Sporn
Dir., OGD
Comments:

Date 4/30/99 Initials DS

Date 4/30/99 Initials DS

Roger Williams, M.D.
Dep.Dir., CDER

Date _____ Initials _____

Date _____ Initials _____

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Mark Anderson
Review Support Branch
N/A Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Date _____ Initials _____

Date _____ Initials _____

Applicant notification:
11:56am 5/3/99 Time notified of approval by phone 12:00 (noon) Time approval letter faxed

FDA Notification:
5/3/99 Date e-mail message sent to "OGD approvals" account
_____ Date Approval letter copied to "//cder/drugapp" directory

x:\wpfile\beersbl\aprovrou.wp

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-382

CORRESPONDENCE

CARLSBAD TECHNOLOGY INC.

5923 Balfour Court, Carlsbad, CA, 92008, USA
Tel: (760) 431-8284 Fax: (760) 431-7507

May 7, 1998

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food & Drug Administration
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

Re: ANDA for Acyclovir 800 mg and 400 mg Oral Tablet, archival copy

Dear Mr. Sporn:

Carlsbad Technology, Inc. ("CTI") submits today an original abbreviated new drug application ("ANDA") seeking approval to market a 800 mg *Acyclovir* tablet and a 400 mg *Acyclovir* tablet that are bioequivalent to the listed drug, *Zovirax*® 800 mg and 400 mg oral tablets, manufactured by Glaxo Wellcome Inc. pursuant to NDA # N20089.

This ANDA consists of eight volumes. CTI is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence Section (VI). A separate copy of the Bioequivalence Section is provided in orange folders. For more detailed information on the organization of this ANDA, please refer to Page v of the ANDA, "Executive Summary -- Organization of the ANDA."

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 760-431-8284 and 760-431-7507 (fax).

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our local district office. This "field copy" was contained in burgundy folders.

Thank you for your prompt handling of this submission.

Sincerely,

Simon Hsu

Simon Hsu, Ph.D.
Regulatory Affairs

CARLSBAD TECHNOLOGY INC.
5923 Balfour Court, Carlsbad, CA. 92008. USA
Tel: (760) 431-8284 Fax: (760) 431-7507

May 19, 1998

NEW CORRESP

Sandra Middleton
Office of Generic Drugs
CDER, Food & Drug Administration
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

Re: ANDA #75-382

Dear Ms. Middleton:

In response to your recent request, I am sending FDA form 356h, Patent certification, Exclusivity statement, and cGMP statement with original signatures. I am also sending the additional copies of the packaging labels and labeling insert, as requested. I apologize for any inconvenience.

Please let me know if you need any further assistance. I can be reached at (760) 431-8284 ext. 117.

Sincerely,

Simon Hsu

Simon Hsu,
Regulatory Affairs

SH/dw

ANDA 75-382

Carlsbad Technology Inc.
Attention: Simon Hsu, Ph.D.
5923 Balfour Court
Carlsbad, CA 92008

JUN 10 1998

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 the telephone conversation dated May 18, 1998 and your correspondence dated May 19, 1998.

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

DATE OF APPLICATION: May 7, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 12, 1998

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

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

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

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

CARLSBAD TECHNOLOGY INC.
5923 Balfour Court, Carlsbad, CA, 92008, USA
Tel: (760) 431-8284 Fax: (760) 431-7507

August 20, 1998

AMENDMENT
N / AB

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **Telephone Amendment** for Acyclovir Tablets, ANDA #75-382

Dear Dr. Conner:

This attached information provided is in reference to a telephone request from Ms. Nancy Chamberlain dated August 19, 1998. Pursuant to 21CFR314.96(3), we wish to provide additional information for Bio-session, ANDA 75-382. Your review and consideration of our submitted information is greatly appreciated.

Should you have any further comments, please direct any questions regarding this information to me at the above address. If you need to contact me, my phone number is 760-431-8284 Ext. 116 and 760-431-7507 (fax).

Thank you for your prompt handling of this information.

Sincerely yours,

Bruce J.C. Lu
Director
Regulatory and Compliance

Enclosure:
1. Assay and Content Uniformity Testing Result for reference drug Acyclovir 800 mg Tablets, Lot #7B1371
2. Assay and Content Uniformity Testing Result for reference drug Acyclovir 400 mg Tablets, Lot #7B1372
3. Assay and Content Uniformity Testing Result for testing drug Acyclovir 800 mg Tablets, Lot #RB7002
4. Assay and Content Uniformity Testing Result for testing drug Acyclovir 400 mg Tablets, Lot #RB7003
5. Batch Size of testing products, Acyclovir 800mg and 400mg Tablets

Two copies follow by Certified Mail
Return Receipt Requested

RECEIVED
AUG 25 1998
GENERIC DRUGS

FACSIMILE AMENDMENT

OCT 2 6 1998

ANDA 75-382

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: Carlsbad Technology, Inc. PHONE: 760-431-8284 Ext 116

ATTN: Bruce Lu FAX: 760-431-7507

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 7, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Acyclovir Tablets, 400 mg and 800 mg.

Attached are 6 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, labeling and Bioequivalence comments are attached.

AMB 10/26/98

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

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

10/26/1998 FDA FAX

5. Please provide USP 23 <671> moisture permeability test data for the unit dose packaging system.

Sincerely yours,

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

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

ANDA Number: 75-382

Date of Submission: May 7, 1998

Applicant's Name: Carlsbad Technology Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

   Replace the "Caution: Federal law..." statement with "**Rx only**" or "**℞ only**" on labels and labeling. A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

2. CONTAINER:

   a. We encourage you to differentiate the different drug product strengths by boxing, contrasting colors, or some other means.

   b. 400 mg and 800 mg - 100s and 500s

      i. See GENERAL COMMENT.

      ii. Revise the storage statement to read as follows:

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

3. CARTON: 400 mg and 800 mg - unit dose 100s

   a. Please submit your proposed carton labeling for

our review and comment.

b. Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be with a child-resistant container, e.g.:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

[Note: The second sentnece is optional.]

c. Please note, your carton labeling should include the text found on your container labels.

4. INSERT

a. GENERAL COMMENTS

i. Revise your insert labeling to be in accord with the attached copy of the insert labeling of the reference listed drug Zovirax® (Glaxo Wellcome Inc.; revised March 1997 and approved May 29, 1997).

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

b. DESCRIPTION

Indicate the botanical source of starch.

c. HOW SUPPLIED

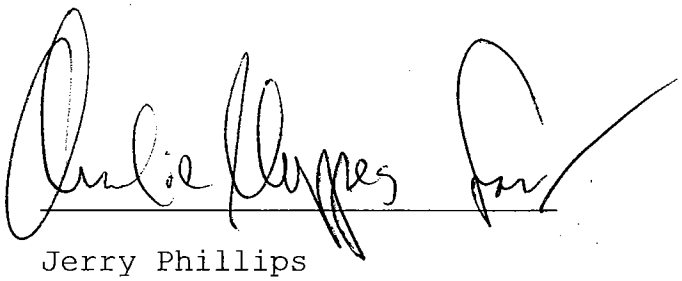
See comment 2(b) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

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

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-382 APPLICANT: Carlsbad Technology, Inc.

DRUG PRODUCT: Acyclovir Tablets, 400 mg and 800 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 conducted in 900 mL of water, at 37 °C using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than 80 %(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, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CARLSBAD TECHNOLOGY INC.

5923 Balfour Court, Carlsbad, CA, 92008, USA
Tel: (760) 431-8284 Fax: (760) 431-7507

COPY 1

November 19, 1998

NEW CORRESP
NC

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax #: 301-827-4337

RE: **Facsimile Amendment** to Acyclovir Tablets, 400 mg and 800 mg, ANDA #75-382

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(3), we wish to amend ANDA #75-382. Reference is made to your chemistry, labeling and Bioequivalency comments dated on Oct 26, 1998. Your review and consideration of our response is greatly appreciated.

For ease of review, each deficiency is stated and followed by our response.

For Chemistry Deficiencies:

Chemistry Deficiency #1:

[redacted]

Response:

[redacted]

submission, Vol. 7 of 8, page 2087.

RECEIVED

NOV 23 1998

GENERIC DRUGS

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

11/19/1998 CARLSBAD LETTER

Sincerely yours,

Bruce J.C. Lu
Director
Regulatory and Compliance

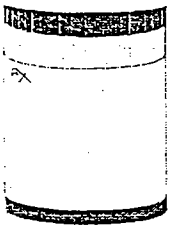
Enclosure:

Attachment 1
Attachment 2
Attachment 3
Attachment 4
Attachment 5

APPEARS THIS WAY
ON ORIGINAL

Certified Mail with Return Receipt Requested

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: December 14 1998

TO: Simon Hsu

Phone: (760) 431-8284 Fax: (760) 431-7507

From: Merle Apples

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

Number of Pages: 4
(Including Cover Sheet)

Comments: Labeling Comments to the 11/19/98 Submission for ANDA 75-382

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

ANDA Number: 75-382

Date of Submission: November 19, 1998 [document room date November 20, 1998]

Applicant's Name: Carlsbad Technology Inc.

Established Name: Acyclovir Tablets USP, 400 mg and 800 mg

Labeling Deficiencies:

1. CONTAINER: 400 mg and 800 mg

   Acyclovir tablets have become the subject of a USP monograph (See the 9th supplement to USP 23). We encourage you to include "USP" in the established name of your product where it appears on the principal display panel.

2. CARTON: 400 mg - 100s unit dose
   800 mg - 100s unit dose

   See comment under CONTAINER.

3. INSERT

   a. GENERAL

      i. Replace "ACYCLOVIR" with "acyclovir" (lower case lettering) where it appears throughout your insert labeling.

      ii. Italicize "*in vitro*" where it appears in the insert labeling.

   b. DESCRIPTION

      Revise the last paragraph to read as follows:

      ... white to off-white, ... weight of 225.21. The maximum ...

   c. CLINICAL PHARMACOLOGY

Pharmacokinetics (Table 2)

Include the data for the "200 mg" strength as seen in the reference listed drug.

d. PRECAUTIONS (Carcinogenesis, Mutagenesis, Impairment of Fertility)

Revise the first paragraph to read as follows:

... zoster) or 200 mg given orally six times a day (dosing appropriate for treatment of genital herpes). Plasma drug ... (See CLINICAL PHARMACOLOGY, Pharmacokinetics).

e. ADVERSE REACTIONS (Herpes Simplex)

i. Short-Term Administration

Revise to read as follows:

... with acyclovir 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting ...

ii. Long Term Administration

Revise to read as follows:

... 400 mg (two 200 mg capsules) two ...

f. DOSAGE AND ADMINISTRATION

i. Revise this section to read the same as the reference listed drug insert labeling, including all references to the 200 mg strength.

ii. Add the subsection "Bioequivalence of Dosage Forms" as the last subsection, as seen in the reference listed drug insert labeling.

g. HOW SUPPLIED

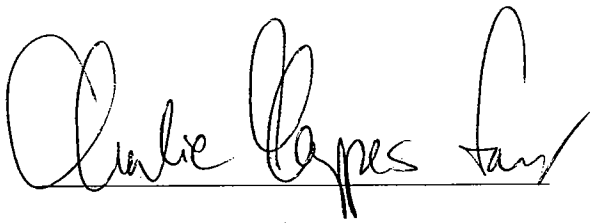
We encourage you to relocate "**℞ only**" to appear immediately following the Title/Established name. We refer you to A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was

revised July 1998 and posted at Internet site: http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

Please revise your labels and labeling, as instructed above, and submit final printed container labels, unit dose blister labels, carton labeling and 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 your last submission with all differences annotated and explained.



Robert West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CARLSBAD TECHNOLOGY INC.
5923 Balfour Court, Carlsbad, CA, 92008, USA
Tel: (760) 431-8284 Fax: (760) 431-7507

bruary 22, 1999

NDA ORIG AMENDMENT
FA

uglas Sporn, Director
ffice of Generic Drugs
DER, Food & Drug Administration
etro Park North II, HFD-600
00 Standish Place, Room 150
ckville, MD 20855-2773

x #: (301) 827-4337

: Facsimile Amendment to Acyclovir Tablets, 400 mg and 800 mg, ANDA #75-382

ear Mr. Sporn:

rsuant to 21 CFR 314.96(3), we wish to amend ANDA #75-382. Reference is made to the csimile labeling deficiencies dated December 14, 1998. Your review and comments of our vised labeling is greatly appreciated.

e have revised our container, carton and package insert labeling as recommended. We are bmitting 12 copies of final printed labeling of each container labeling, carton labeling for unit se, package insert labeling and draft unit dose labeling for your comments and consideration. o facilitate your review of our submission in accordance with 21 CFR 314.94(a)(8)(iv), we ve also provided a side-by-side comparison of our proposed labeling and the labeling of our st submission with all the differences annotated and explained.

lease direct any written communication regarding this ANDA to me at the above address. If ou have any questions or concerns, please contact me at 760-431-8284 ext. 116 (phone) and 60-431-7507 (fax).

hank you,
arlsbad Technology Inc.

Simon Hsu

mon Hsu, Ph.D.
irector
egulatory & Compliance

gdr

ttachments

CARLSBAD TECHNOLOGY INC.
5923 Balfour Court, Carlsbad, CA, 92008, USA
Tel: (760) 431-8284 Fax: (760) 431-7507

April 26, 1999

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/FA

RE: **Telephone Amendment** for Acyclovir Tablets, 800mg and 400 mg, ANDA # 75-382

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(3), we with to amend ANDA # 75-382. Reference is made to the telephone comments made by your chemistry reviewer dated on March 29, 1999. Your review and consideration of our comments are greatly appreciated.

For easy of review, I have repeated each of the deficiencies followed by our response.

Deficiency #1: CTI needs to include particle size distribution specification for its active drug substance acyclovir. Testing should be performed on the lot which was used in CTI's Biolot.
CTI Response: Testing has been done on acyclovir Lot No ACV O003. A copy of the testing results and our modified specification is attached.

Deficiency #2: In CTI's amendment dated on November 19, 1998, changes are made to its

[redacted]

CTI Response: [redacted] in percentage to be able to compare to the specification.

Deficiency #3: Limit of guanine is 2% in CTI's finished product. It should be lowered to 1%.
CTI Response: CTI's specification for Acyclovir Tablets complies with the official monograph found in the Ninth Supplement, USP 23. Under the section "Related Compounds" it is read "... not more than 2.0% of guanine is found. and not more than 0.5% of any other impurity is found."

Should you have any further comments, please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number are 760-431-8284, ext. 116 and 760-431-7507 (fax).

RECEIVED
APR 27 1999
GENERIC DRUGS

CARLSBAD TECHNOLOGY INC.
5923 Balfour Court, Carlsbad, CA, 92008, USA
Tel: (760) 431-8284 Fax: (760) 431-7507

Thank you for your prompt handling of this submission.

Sincerely,

Simon Hsu, Ph.D.
Regulatory & Compliance

CERTIFIED MAIL
Return Receipt requested

APPEARS THIS WAY
ON ORIGINAL