

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**74975**

**APPROVAL LETTER**

SEP 30 1996

Ranbaxy Pharmaceuticals Inc.  
Attention: Shirley Ternyik  
U.S. Agent for: Ranbaxy Laboratories Limited  
600 College Road East  
Princeton, NJ 08540



Dear Madam:

This is in reference to your abbreviated new drug application dated October 9, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

Reference is also made to your amendments dated October 21, and November 25, 1996; May 23, and May 26, 1997; and January 9, March 26, July 22 and August 24, 1998.

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

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

*for 9-30-98*

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**74975**

**DRAFT FINAL PRINTED LABELING**



PV 3112 UFP

**ACYCLOVIR**  
CAPSULES AND TABLETS

30

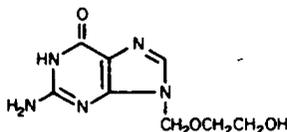
APPROVED

**Description:** Acyclovir is an antiviral drug. Acyclovir capsules and tablets are formulations for oral administration. Each capsule of acyclovir contains 200 mg of acyclovir and the inactive ingredients lactose monohydrate, pregelatinized starch, magnesium stearate, cetyl alcohol, dimethicone, ethylparaben, glycerin, sodium lauryl sulfate, stearyl alcohol and white wax. The capsule shell consists of gelatin, sodium lauryl sulfate and titanium dioxide. Printed with edible black ink.

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

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

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



Acyclovir is a white to off-white crystalline powder with a molecular weight of 225.21, and formula  $C_8H_{11}N_5O_3$ . 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<sub>50</sub>), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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 <sub>max</sub> <sup>ss</sup>	0.83 mcg/mL	1.21 mcg/mL	1.61 mcg/mL
C <sub>trough</sub> <sup>ss</sup>	0.46 mcg/mL	0.63 mcg/mL	0.83 mcg/mL

There was no effect of food on the absorption of acyclovir (n=6); therefore, acyclovir capsules and 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/m<sup>2</sup> and 600 mg/m<sup>2</sup> 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 capsules and 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 a 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 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 non-significant increase in chromosomal damage at 62 to 125 times human levels. No activity was observed in a dominant lethal study in mice at 36 to 73 times human levels.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study, they were 8 to 15 times human levels. At 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 corpora 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 numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of 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 capsules and tablets should be modified as shown in Table 3:

**Table 3: Dosage Modification for Renal Impairment**

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m <sup>2</sup> )	Adjusted Dose 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 capsules (white, opaque cap and body) containing 200 mg acyclovir and printed with "RX 652" on both the cap and the body - Bottle of 100 (NDC 66304-652-01) and bottle of 500 (NDC 63304-652-05).

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

Acyclovir tablets (white, oval-shaped, unscored) containing 800 mg acyclovir and debossed with "RX 505" on one side - Bottle of 100 (NDC 63304-505-01) and unit dose pack of 100 (NDC 63304-505-80).

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

Acyclovir tablets (white, oval-shaped, unscored) containing 400 mg acyclovir and debossed with "RX 504" on one side - Bottle of 100 (NDC 63304-504-01).

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

Rx only

Manufactured by Eli Lilly and Company  
Indianapolis, IN 46285, USA  
for Ranbaxy Pharmaceuticals Inc.  
Princeton, NJ 08540, USA

PV 3112 UFP

Merl

ANDA 74-975

30

APPROVED



UF 0001  
Lot/Exp:

**R RANBAXY**  
NDC 63304-652-05

**ACYCLOVIR**  
Capsules

**200 mg**

Rx only

---

**500 Capsules**

Dispense in a tight, light-resistant container.  
Manufactured by Eli Lilly and Company  
Indianapolis, IN 46285, USA  
for Ranbaxy Pharmaceuticals Inc.  
Princeton, NJ 08540, USA

Each capsule contains:  
Acyclovir USP 200 mg

Store at 15° to 25°C (59° to 77° F) and protect from moisture.  
For indications, dosage, precautions, etc., see accompanying  
package insert.

WW 567Z UFX



3 63304-652-05 5

Margo

ANDA 74-975

**R** **RANBAXY**  
NDC 63304-652-01

**ACYCLOVIR**  
Capsules  
**200 mg**

Rx only

**100 Capsules**

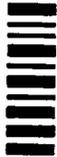
Dispense in a tight, light-resistant container.  
Manufactured by Eli Lilly and Company  
Indianapolis, IN 46285, USA  
for Ranbaxy Pharmaceuticals Inc.  
Princeton, NJ 08540, USA

Each capsule contains  
Acyclovir USP 200 mg

Store at 15° to 25°C (59° to 77° F) and protect  
from moisture.  
For indications, dosage, precautions, etc., see  
accompanying package insert.

UV 5662 UFX

UF 0001  
Lot/Exp:



3 63304-652-01 7

30

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**74975**

**CHEMISTRY REVIEW(S)**

**DIVISION REVIEW SUMMARY**

**ANDA 74-975**

**DRUG PRODUCT: Acyclovir**

**FIRM: Ranbaxy Pharmaceuticals, Inc.**

**U.S. Agent for: Ranbaxy Laboratories Limited**

**DOSAGE FORM: Capsules (Oral)**

**STRENGTH: 200 mg**

**CGMP STATEMENT/EIR UPDATE STATUS: ACCEPTABLE -**

An **ESTABLISHMENT EVALUATION REQUEST** issued 10/10/96 to the Division of Compliance has found the CGMP status of the facilities acceptable, dated 12/17/97.

**BIO INFORMATION: Satisfactory -**

The Division of Bioequivalence has found the bio study acceptable. See review of bio amendment dated May 1, 1998.

**VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):** Pending - Methods validation is required on the drug product because it is a non compendial item. Methods validation is not required for the drug substance. Methods validation found acceptable dated 7/7/98, as for the Detroit District Laboratory.

**STABILITY: Satisfactory -**

Accelerated (40°C/75% RH) stability data are provided from lot no. D20511 tested initially, 1, 2 and 3 months. The lot was packaged in 100 count (lot #D20511M) and 500 count (lot #20511N) bottles in the final marketed container/closure systems. The data are adequate and within the specified limits. The revised stability protocol is adequate and provides the requested information. The container/closure systems used in the stability studies are the same as those in the container section of the application. An expiration dating of 24 month has been granted.

**LABELING: Acceptable**

See review of professional labeling conducted by Chan Park, concurred by Charlie Hoppes, dated 8/21/98.

**STERILIZATION VALIDATION: N/A**

**SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Satisfactory -**

Lot #D20511 (RANBAXY LABORATORIES LIMITED NDS lot #DAC-00295) is a capsules (theoretical) production batch, actual yield capsules. DMF was found satisfactory, dated 8/27/98.

**SIZE OF STABILITY BATCHES - Satisfactory -**

Lot no. D20511, theoretical production batch size \_\_\_\_\_ capsules, actual yield \_\_\_\_\_ capsules. Total packaged: \_\_\_\_\_ capsules. From the batch \_\_\_\_\_ capsules were packaged in blister pak of 10s. Applicant does not intend to market this package size. The packaging reconciliation for batch = \_\_\_\_\_ % (pp 007-035). The entire batch was packaged. The batch was manufactured using production scale equipment under production conditions. The batch size meets the Office of Generic Drug policy #22-90 which requires a minimum \_\_\_\_\_ units batch or \_\_\_\_\_ % of the proposed production batch size, whichever is greater.

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

The proposed production batch size is \_\_\_\_\_ capsules (Sec. XI, pp. 007-035). The manufacturing process is the same as for lot #D20511.

**RECOMMENDATION:  
APPROVE**

1. CHEMIST'S REVIEW NO. 2
2. ANDA 74-975
3. NAME AND ADDRESS OF APPLICANT  
Ranbaxy Laboratories Limited  
19 Nehru Place, New Delhi, India

U.S. Agent:  
Shirley Terynik  
600 College Road East  
Princeton, NJ 08540

4. LEGAL BASIS FOR ANDA SUBMISSION  
Generic version of Burroughs Wellcome's ZOVIRAX®  
(NDA 18-828). Patent certification and exclusivity  
statement are provided (Vol. 1.1, Section III, pp. 001-007).

Final approval date is January 25, 1985.

U.S. Patent No. 4,199,574 expired April 22, 1997

5. SUPPLEMENT(s) N/A
6. ESTABLISHED NAME  
**Acyclovir Capsules**
7. PROPRIETARY NAME  
Zovirax®

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

<u>Firm</u>		<u>FDA</u>
Orig. submission	10/09/96	Acknowledgment letter
	12/04/96	
New Correspondence	10/21/96	CSO review
	11/19/96	
New correspondence	11/25/96	Labeling review
	01/29/97	
		Bioequivalency
	03/25/97	
		Bio deficiency letter
		04/03/97
New Correspondence	5/23/97	Method validation
	07/07/97	

New correspondence	5/26/97	Deficiency letter 06/09/97
Amendment (Bio) 05/19/98	1/9/98	Bio review
Amendment (Chem)	3/26/98	Labeling review 09/08/98
Fax Amendment (labeling)	7/22/98	
Fax Amendment	8/24/98	

**This review covers submission dated March 26, 1998.**

10. PHARMACOLOGICAL CATEGORY

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 (shingles) and chickenpox (varicella).

11. Rx or OTC

**R**

12. RELATED DMF(s)

**DMF**

13. DOSAGE FORM

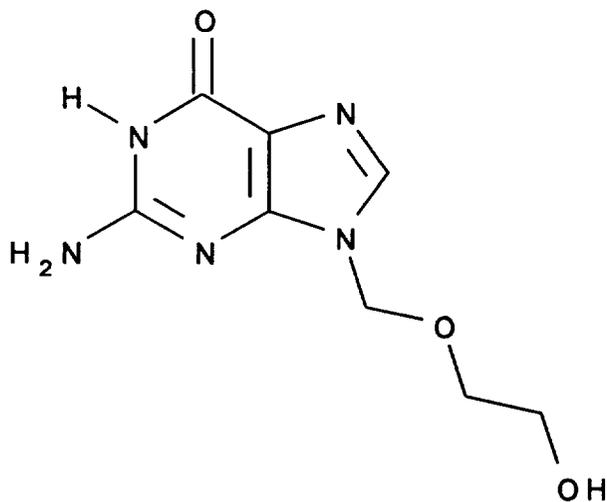
Capsules (GELATIN)

14. STRENGTH

200 mg

15. CHEMICAL NAME AND STRUCTURE

## Acyclovir USP

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

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

**Drug substance is an official USP 23 item. Drug product is not an official USP 23 item.**

16. RECORDS AND REPORTS None

17. COMMENTS

- a. Application is satisfactory for approval
- b. Labeling is **Acceptable** dated 8/21/98.
- c. Bio is **ACCEPTABLE**, dated 5/19/98
- d. DMF is **ADEQUATE**, dated 8/27/98.
- e. Methods validation for drug product has been submitted to the Detroit Regional Laboratory, dated 3/26/97, and found acceptable 7/7/97.
- f. Drug Substance does not require Methods validation
- g. Establishment evaluation submitted to compliance, dated 10/31/96, and found acceptable 12/17/97.

18. CONCLUSIONS AND RECOMMENDATIONS

**APPROVE**

19. REVIEWER:

Raymond Brown

DATE COMPLETED:

June 16, 1998

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**74975**

**BIOEQUIVALENCY REVIEW(S)**

Acyclovir  
200 mg capsule  
ANDA 74-975  
Reviewer: Pradeep M. Sathe, Ph.D.  
WP # 74975D.198

Ranbaxy Laboratories Ltd.  
New Delhi, India-110019  
Submission Date:  
January 09, 1998

## REVIEW OF AN AMENDMENT

I.BACKGROUND : The firm had submitted an application on October 9, 1996, which consisted of two bio-studies and the dissolution. The application was found to be deficient primarily with respect to the dissolution testing. In a letter dated March 18, 1997, the Division conveyed to the firm the deficiencies. The current application consists of the firm's responses to the cited deficiencies.

## II.DIVISION CITED DEFICIENCIES AND THE FIRM'S RESPONSE:

### Deficiency:

1. The firm should conduct the dissolution using the following FDA recommended dissolution methodology and specifications:

Apparatus: U.S.P. XXIII Apparatus I (basket)

Speed: 100 rpm

Medium: Deaerated water

Volume: 900 ml

FDA dissolution handbook recommended 'Q': NLT % in 30 minutes.

Comparative dissolution should be conducted on 12 units of the test and reference bio-study lots. The results should be reported in terms of the mean, range and percent coefficient of variation.

### Firm's Response:

"Subsequent to you issuing the Bioequivalence deficiency letter, the Pharmacopeial Forum, dated September-October 1997, published a revised dissolution method. Upon the advise of the Bioequivalence Project Manager, Lilly (the manufacturer), has performed, for Ranbaxy comparative dissolution studies using both the FDA requested method and the new Pharmacopeial Forum method.

Attached are comparative dissolution summaries from the above FDA requested method

and the method listed in September-October 1997 Pharmacopeial Forum, volume 23, number 5".

**Division Comment:**

The Sept-Oct 1997 Pharmacopeial Forum (volume 23, number 5), lists the following dissolution method:

Apparatus: USP Apparatus I (basket)  
Speed: 100 rpm  
Medium: 0.1 N HCL  
Volume: 900 ml  
'Q': NLT % dissolved in 45 minutes.

The new dissolution data using the Pharmacopeial Forum recommended method is given in Table I. The firm has reported set-up 1 (10/15/97), set-up 2 (10/17/97) and set-up 3 (10/21/97) results. For convenience, the reviewer has evaluated the latest (i.e. of 10/21/97) results. Based on the reported study data, the dissolution testing method and results are acceptable.

**Deficiency:**

2. The dissolution has been conducted on the test lot CT04826. The relationship between CT04826 and the number used in the study CT04799 should be clarified.

**Firm's Response**

"Lilly assigns different numbers at different stages of their manufacturing operations. The attached documents from Lilly's files indicate the CT04826 was the bulk drug product assigned to capsules from Lot D20511M, Acyclovir capsules. This lot of bulk product was then packaged as CT04799 and labeled as such".

**Division Comment:**

Firm's response is acceptable.

**Division Deficiency:**

3. The firm has stated that "one of the extracted blanks had an interference at the retention time of the analyte approximately % of the LOQ". Since no other statement

was made in relation to specificity, please provide the chromatogram of that sample.

**Firm's Response:**

“Please find the attached chromatogram of the pre-dose for subject 10, period 2 (figure 1) along with the lowest standard (STD B) extracted with the batch (figure 2). The retention time of Acyclovir is indicated on the chromatogram.

Since the reported concentration of the pre-dose for subject 10, period 2 is below the limit of quantitation, no statement can be made as to the impact on the reported subject sample concentrations. The data for this sample was obtained from an analytical batch that met acceptance criteria for interference in the control blanks. In such an instance, it is the general practice at [redacted] to list the patient pre-dose samples and the percent observed interference, which in this case was 40.1% of the LOQ. The analytical department cannot make any further comment since the interference is not quantifiable”.

**Division Comment:**

The firm's response is acceptable.

**III.RECOMMENDATIONS :**

1. The bioequivalence studies conducted by Ranbaxy Labs. on its 200 mg acyclovir capsule lot #CT04799, comparing it to Zovirax<sup>R</sup> 200 mg capsule have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Ranbaxy Labs' acyclovir 200 mg capsule is bioequivalent to the reference product, Zovirax<sup>R</sup> 200 mg acyclovir capsule manufactured by Burroughs Wellcome.

2. The dissolution testing conducted by Ranbaxy Labs on its Acyclovir, 200 mg capsule, lot #CT04826, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing, controls and stability program. The dissolution should be conducted in 900 ml of 0.1 N HCL, using USP XXIII apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than [redacted] % of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

3. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and in-vitro dissolution testing and the application is acceptable.

**/S/**

*Pr/AC* 5/1/98

Pradeep M. Sathe, Ph.D.  
Division of Bioequivalence,  
Review Branch I.

RD INITIALED BY YCHUANG  
FT INITIALED BY YCHUANG\_

**/S/**

5/1/98

Concur **/S/** Date: 5/1/98

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence

cc: ANDA #74-975 (Original, Duplicate), HFD-650 (Director), HFD-652 (Sathe), Drug File, Division File.

**Table I. *In-Vitro* Dissolution Testing**

Drug (Generic Name): Acyclovir  
 Dose Strength: 200 mg capsule  
 ANDA No.: 74-975  
 Firm: Ranbaxy labs  
 Submission Date: January 9, 1998

**I. Conditions for Dissolution Testing:**

U.S.P. XXIII (Basket) RPM: 100  
 No. Units Tested: 12  
 Medium: 0.1N HCl Volume: 900 ml  
 Firm's Specification: NLT % dissolved in 45 minutes.  
 Reference Drug: Zovirax<sup>R</sup> by Burroughs Wellcome  
 Assay Methodology:

**II. Results of *In-Vitro* Dissolution Testing (10/21/97 results):**

Sampling Times (Minutes)	Test Product: Acyclovir capsule Lot #CT04799 Strength (200 mg)			Reference Product: Zovirax Lot # 5O2064 Strength (200 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	101		1.2	100		1.8
20	102		0.9	102		0.8
30	102		0.7	103		0.7
45	103		0.5	103		0.8

JUN 17 1998

2.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:74975

APPLICANT: Ranbaxy laboratories Ltd.

DRUG PRODUCT:Acyclovir Capsule, 200 mg

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

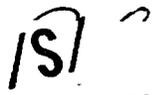
The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl, using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than % (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

MAR 12 1997

Acyclovir  
200 mg capsule  
ANDA 74-975  
Reviewer: Pradeep M. Sathe, Ph.D.  
WP # 74975SD.O96

Ranbaxy Laboratories Ltd.  
New Delhi, India-110019  
Submission Date:  
October 9, 1996

## REVIEW OF TWO BIO-STUDIES AND DISSOLUTION

I.INTRODUCTION : Acyclovir is a synthetic purine nucleoside analog, 9-[(2-hydroxyethoxy)methyl]guanine, in which a linear side chain has been substituted for the cyclic sugar of the naturally occurring guanosine molecule. It is a white crystalline powder with a molecular weight of 225.21 Daltons with a maximum water solubility of 2.5 mg/ml at 37°C. Acyclovir is used as an anti-viral agent in the treatment of human herpes viruses, including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella zoster virus (VZV), Epstein Barr virus (EBV) and cytomegalovirus (CMV). In cell culture Acyclovir has highest anti-viral activity against HSV-1, followed by HSV-2, VZV, EBV and CMV in that order. The mechanism of action includes inhibition of DNA synthesis resulting in inhibition of viral replication. In order to inhibit DNA synthesis, Acyclovir must be phosphorylated first by viral thymidine kinase. The affinity of Acyclovir for herpes-virus encoded thymidine kinase is 200 times greater than for the mammalian enzyme, and phosphorylation of Acyclovir by mammalian enzyme proceeds at a negligible rate. After synthesis of Acyclovir monophosphate (acyclo-GMP) in virally infected cells, normal cellular enzymes catalyze the sequential synthesis of acyclo-GDP and acyclo-GTP. The amount of acyclo-GTP formed in a herpes virus infected cell is 40 to 100 times greater than in uninfected cells. Acyclo-GTP then selectively inhibits the viral DNA polymerase by competing with deoxoguanosine triphosphate and to a much lesser extent, the cellular polymerase. In addition acyclo-GTP is incorporated into the elongating viral DNA, where it causes termination of biosynthesis of the viral DNA strand.

The oral availability of the drug is about 15-30% and decreases with increasing doses. Protein binding is about 15%. The drug is primarily cleared by renal route by glomerular filtration and tubular secretion. The urinary excretion accounts for upto 75% of the drug clearance, while 15% of the drug is recovered as an inactive metabolite, 9-carboxy methoxy guanine. In patients with normal renal function, mean volume of distribution and half-life are about 0.69 liters/kg, and 2.4 hours respectively. The normal dosage regimen is 200 mg every four hours, five times daily for 10 days. The draft labeling states that "in the study in six volunteers, the influence of food on the absorption of Acyclovir was not apparent." The above information suggests the conduct of a food challenge study.

**II. THE SUBMISSION:** The application consists of A] a single dose fasting bio-equivalence study, B] a single dose 'food challenge' bio-equivalence study, and C] Dissolution testing methodology and data comparing 200 mg test (Ranbaxy) and reference (Burroughs Wellcome's Zovirax<sup>R</sup>) capsule formulations.

As per the orange book, Burroughs Wellcome's Zovirax<sup>R</sup> capsule is the reference formulation. Recently, the Division approved ESI Lederle's bio-study/ies and dissolution for the 200 mg Acyclovir capsule formulation.

**III. TEST FORMULATION:**

Ingredient	Quantity per Capsule	Percent W/W
Acyclovir, U.S.P*.	200.0 mg	50%
Pregelatinized Starch**	mg	%
Lactose, NF	mg	%
Magnesium Stearate	mg	%
<b>Theoretical Total Weight</b>	<b>mg</b>	<b>%</b>

\* = Equivalent to 200mg acyclovir calculated on anhydrous basis

\*\* = Figured with acyclovir to provide a total of mg combined weight

Besides acyclovir, the active ingredient, lactose and starch are diluents and magnesium stearate is the lubricant. The firm is planning a batch size of kgs consisting of approximately capsules.

**IV. BIO-STUDY REPORT No.960902. FASTING BIOEQUIVALENCE STUDY:**

A. TITLE: A comparative, randomized, single dose, two way crossover bioavailability study of Ranbaxy and Glaxo-Wellcome (Zovirax<sup>R</sup>) 200 mg Acyclovir capsules in healthy adult males under fasting conditions.

**B. STUDY INVESTIGATORS AND CONTRACT LABORATORY:**

1. Principal Investigator:

2. Bio-Study Site:

3. Analytical Lab:

4. Analytical Investigator:

5. Study dates: May 96  
Analysis dates: May, June 96  
Duration of sample storage: 38 days

C. STUDY OBJECTIVE: To compare the single-dose bioavailability of Ranbaxy and Glaxo-Wellcome (Zovirax<sup>R</sup>) 200 mg Acyclovir capsules under fasting conditions.

D. STUDY DESIGN AND NUMBER OF SUBJECTS: This was an open label, comparative, randomized, single dose two-way crossover bioavailability study. Thirty-eight (38) adult male volunteers were enrolled in the study. Four (4) volunteers did not complete the crossover. Subjects 6, 23, 34 and 35 withdrew for personal reasons and did not return prior to period 2 dosing. Thus a total of thirty-four (34) subjects completed the crossover study. As per protocol samples from 34 subjects were analyzed. There was a seven-day washout period between the two study phases.

E. SUBJECT SELECTION/EXCLUSION CRITERIA: Volunteers were included in the study if they met the following criteria:

1. Male volunteers between ages 18-45 years, weighing at least 60 kgs and who are within 15% of their ideal weight based on the table of "desirable weights of adults" by Metropolitan Life Insurance Company, 1983.
2. Bases on the medical histories and demographic data, medically healthy subjects with clinically normal laboratory profiles as judged by the following tests:
  - a. Hematology: Hemoglobin, Hematocrit, Total and differential leucocyte count, Red blood cell count, Platelet counts
  - b. Serum Chemistry: BUN, Creatinine, Total bilirubin, Alkaline phosphatase, SGOT, SGPT, Potassium, Sodium.
  - c. Urinalysis: pH, Specific gravity, Proteins, Glucose, Ketones, Bilirubin, Blood, Nitrite, Urobilinogen, Microscopic examination
  - d. An HIV-AIDS test
  - e. A urine 'drug' screen

Volunteers were excluded from the study if they met the following:

1. History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease
2. History or presence of alcoholism or drug abuse or hypersensitivity or idiosyncratic reaction to acyclovir.
3. Abnormal diet during the four weeks preceding the study
4. Subjects who would have participated in another clinical trial within 28 days of the study start.
5. Subjects who through completion of the study, would have donated in excess of 500 ml of blood in 14 days, 750 ml in three months, 1000 ml in six months, 1500 ml in nine months or 2000 ml in 1 year.

F. SUBJECT RESTRICTIONS: The following restrictions were put on the subjects throughout the study:

1. No other medication including over the counter medication for seven days preceding the study. This prohibition does not include vitamins taken as nutritional supplement in a non therapeutic doses, as judged by the attending physician.
2. No consumption of alcohol or xanthine-containing beverages and foods. The prohibition will be applicable for 24 hours before dosing and throughout the period of sample collection.
3. If drug therapy other than that specified in the protocol is required during the time of sample collection, or during the washout period between drug administrations, a decision to continue or discontinue the subject will be made based on the time the medication was administered and its pharmacology and pharmacokinetics.

G. STUDY SCHEDULES:

1. **Methods**: Study subjects were required to fast overnight before dosing and for 4 hours thereafter. After a supervised overnight fast, subjects were administered an oral dose of the assigned test or reference formulation, with 240 ml of water at ambient temperature, according to the randomization schedule. Water was not permitted for 1 hour before and 1 hour after dosing. Standard meals were provided at 4 and approximately 9 hours after dosing and at appropriate times thereafter. During dosing post-dose meal plans were identical for both periods.

## 2. Randomization Schedule:

Treatment		Volunteer Number
Phase I	Phase II	
A	B	1, 3, 6, 8, 10, 11, 13, 14, 17, 19, 21, 22, 24, 26, 27, 28, 31, 33, 37
B	A	2, 4, 5, 7, 9, 12, 15, 16, 18, 20, 23, 25, 29, 30, 32, 34, 35, 36, 38

## 3. Drug Treatments:

i. REGIMEN A (TEST PRODUCT): Acyclovir capsule, 200 mg (Eli Lilly & Company), Lot #CT04826 (traceable back to D20511 exhibit lot), Assay Potency %, Batch Size capsules, Expiry Date: 06/96

ii. REGIMEN B (REFERENCE PRODUCT): Zovirax<sup>R</sup> Capsules, 200 mg (Burroughs Wellcome), Lot #5O2064, Assay Potency %, Expiry date: 05/98

4. **Blood Sampling**: Samples (1\*7 ml) were collected before dosing (0hr) and at following times after dosing 0.33, 0.5, 0.67, 0.83, 1.0, 1.17, 1.33, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 16.0 hours. The samples were collected in tubes containing EDTA anticoagulant, centrifuged under refrigeration, plasma samples separated and stored at -12°C until analysis.

## H. ASSAY METHODOLOGY:

#### **4. Analytical Validation:**

--

.....

I. PHARMACOKINETICS AND STATISTICS: Following pharmacokinetic parameters were calculated and evaluated: Area under the curve from time 0 to last measurable concentration  $AUC_t$ , area under the plasma concentration time curve from time 0 to infinity, calculated as  $AUC_t + C_t/K_{el}$  where  $C_t$  is the last measurable concentration and  $K_{el}$  is the terminal elimination rate constant, maximum measurable concentration  $C_{max}$ , time of the maximum measured concentration  $T_{max}$ , terminal elimination rate constant  $K_{el}$ , terminal half-life  $T_{1/2}$  and ratio of  $AUC_t/AUC_{inf}$ . Analysis of variance was performed and  $AUC_t$ ,  $AUC_{inf}$  and  $C_{max}$  were evaluated using two one-sided test with and without logarithmic transformation.

J. RESULTS OF THE BIOEQUIVALENCE STUDY: The mean plasma level time data corresponding to the test (Ranbaxy) and reference (Burroughs Wellcome) is given in Table 1.1. The mean pharmacokinetic parameters and the relevant confidence intervals are given in Table 1.2. The plasma level time profiles are given in Attachment I. Bar graphs of the mean levels and their ratios are given in Figure 1. The ratio scale is from 0 to 1. Plasma levels including the parameter  $C_{max}$  were reported as ng/ml,  $T_{max}$  and  $T_{1/2}$  as hours, AUC's as ng/ml\*hr.

Table 1.1: Acyclovir mean (n=34) concentrations (ng/ml) with (%CV)

Time (hr)	Test (T)	Ref.(R)	(T/R)*100
0.0	0.0	0.0	-----
0.33	17.10 (130.7)	16.74 (139.7)	102.2
0.5	100.35 (75.4)	85.25 (76.6)	117.7
0.67	176.12 (50.9)	169.21 (41.7)	104.1
0.83	247.53 (50.7)	241.45 (32.7)	102.5
1.0	294.81 (45.6)	279.77 (27.7)	105.4
1.17	315.12 (41.0)	301.21 (26.1)	104.6
1.33	317.99 (32.2)	316.83 (34.7)	100.4
1.5	320.86 (32.9)	318.34 (37.2)	100.8
1.75	324.16 (33.8)	326.16 (39.4)	99.4
2.0	319.03 (34.4)	318.72 (40.9)	100.1
2.5	286.43 (37.5)	285.54 (43.4)	100.3
3.0	264.93 (37.5)	245.22 (40.8)	108.0
4.0	213.18 (42.3)	188.58 (44.4)	113.0
6.0	118.28 (42.6)	106.22 (55.5)	111.4
8.0	70.28 (36.8)	66.47 (48.1)	105.7
10.0	45.81 (36.8)	44.50 (45.2)	102.9
12.0	30.09 (33.8)	30.26 (43.1)	99.4
16.0	16.40 (49.5)	17.91 (47.8)	91.6

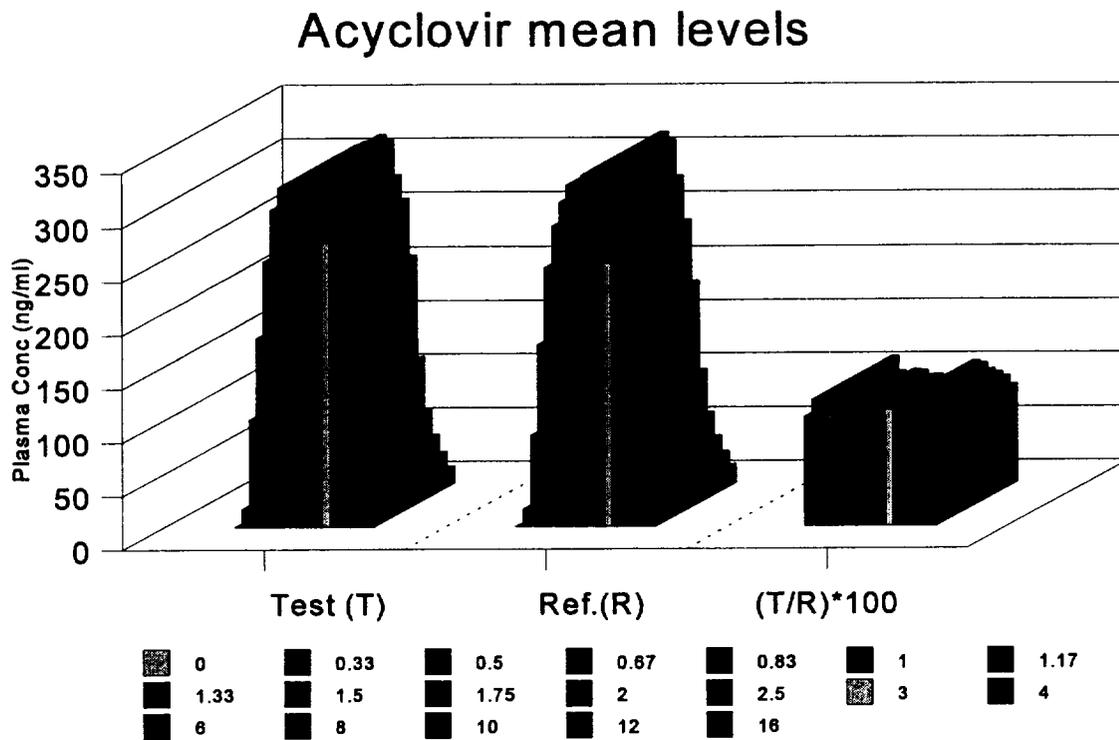


Figure 1. Acyclovir mean levels for test and reference formulation, bar graph

Table 1.2: LSMEAN pharmacokinetic parameters

Parameter	Test(T)	Reference(R)	%Ratio (T/R)	90% Con.Int.
LnAUCt*	1665.68	1587.14	104.9	96.5-114.2
LnAUCinf*	1775.46	1699.11	104.5	96.6-113.0
LnCmax*	362.542	355.779	101.9	94.2-110.2
Tmax	1.45	1.47	99	-----
T <sub>1/2</sub>	3.8	4.1	93	-----
AUCt	1760.7	1677.6	105	95.5-114.5
AUCinf	1866.5	1791.7	104.2	95.4-113
Cmax	379.52	369.52	102.7	94.8-110.6

\* : For Ln parameters Antilog of geometric mean is reported.

K. ADVERSE EFFECTS: A total of six and seven medical events were reported for treatments A and B in five and six subjects respectively. All events were of mild to moderate intensity and occurred randomly. The events were mainly headache, lightheadedness and were possibly or probably related to drug treatments.

L. COMMENTS ON THE FASTING BIOEQUIVALENCE STUDY:

1. From Tables 1.1 it is evident that the test and reference mean levels and their coefficients of variation are comparable, and mean ratios are close to 1.0 for all measurement points. Table 1.2 indicates that 90% confidence intervals of all pharmacokinetic mean parameter ratios (ln transformed data) are within the regulatory limits of 80-125%. Parameters T<sub>max</sub> and T<sub>1/2</sub>, are comparable. The area under the curve from zero to last measurable sample point AUC<sub>t</sub>, is more than 93% of AUC<sub>inf</sub>, indicating adequacy of sampling duration.

2. Considering the detectable levels at 16 hr sample point, in almost all subjects in the fasting study, the firm correctly appears to have extended the sample scheme to up to 24 hr in the 'food challenge' study.

V. BIO-STUDY NO.951321, POST PRANDIAL STUDY

A. TITLE: A comparative, randomized, single dose, three way crossover bioavailability study of Ranbaxy and Burroughs Wellcome (Zovirax) 200 mg Acyclovir capsules in healthy males under fed and fasting conditions.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

1. Principal Investigator:

2. Bio-Study Site:

3. Analytical Site:

4. Analytical Investigator:

C. STUDY OBJECTIVE: To compare the bioavailability of Ranbaxy and Burroughs Wellcome (Zovirax) 200 mg acyclovir capsules under fed conditions. In addition, the bioavailability of the Ranbaxy product was compared under fed and fasting conditions.

D. STUDY DESIGN: This was an open label, randomized, comparative, 3-way crossover design with a seven day washout period between the two study phases. Eighteen (18) healthy adult male volunteers enrolled in the study, one did not complete the crossover. Subject #11, elected to withdraw from the study for personal reasons 6.4 days after Period 1 dosing. The study was completed by remaining seventeen (17) subjects.

E. SUBJECT SELECTION/EXCLUSION CRITERIA: Similar to the previous study.

F. SUBJECT RESTRICTIONS: Similar to the fasting study.

G. STUDY SCHEDULES:

1. **Methods**: After a supervised overnight fast, subjects were administered an oral dose of the assigned formulation, with 240 ml water at ambient temperature. The treatments were assigned according to the randomization scheme. For treatments B and C which included administration of a standard breakfast, the following breakfast was administered, following a supervised overnight fast: 1 buttered English muffin, 1 fried egg, a slice of American cheese, 1 rasher of Canadian bacon, hash brown potatoes, 180 ml of orange juice and 240 ml of whole milk. The breakfast was administered 30 minutes prior to dosing.

2. **Randomization Schedule**:

Treatments			Volunteer Number
Phase I	Phase II	Phase III	
A	B	C	1, 2, 7,
B	C	A	4, 5, 11
C	A	B	10, 13, 16
B	A	C	3, 6, 18
C	B	A	8, 9, 12
A	C	B	14, 15, 17

3. **Drug treatments**:

i. REGIMEN A: Acyclovir Capsule, 200 mg (Ranbaxy, Manufactured by Eli Lilly and Company) fasting, Lot #CT04799, Assay Potency %, Batch Size capsules.

ii. REGIMEN B: Acyclovir Capsule, 200 mg (Ranbaxy, Manufactured by Eli Lilly and Company) fed, Lot #CT04799, Assay Potency %, Batch Size: capsules.

iii. REGIMEN C: Zovirax<sup>R</sup> Capsule, 200 mg (Burroughs Wellcome) fed, Lot #5O2064, Assay Potency %, Expiry date: 05/98

4. **Blood Sampling**: Samples were collected before dosing (0 hr) and at the following times after dosing: 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours. The samples were collected in tubes containing EDTA anticoagulant, centrifuged under refrigeration, plasma samples separated and stored at -12°C until analysis.

H. ASSAY METHODOLOGY: Similar to the fasting study.

I. PHARMACOKINETICS AND STATISTICS: The parameter estimation was similar to the previous study. The evaluation of pharmacokinetic parameters was done by using point estimates.

J. RESULTS OF THE POST PRANDIAL BIO-STUDY: Tables 2.1 and 2.2 give the plasma concentration time data and the mean pharmacokinetic parameters for the three treatments. The bar graph shown in Figure 2 gives test/reference mean level ratios for the fed treatments. The ratio scale is 0 to 1. Plasma levels including the parameter C<sub>max</sub> were expressed as ng/ml, T<sub>max</sub> and T<sub>1/2</sub> as hours, AUC's as ng/ml\*hr. The mean plasma levels are given in Attachment II.

Table 2.1: Acyclovir mean (n=17) concentrations (ng/ml) with (%CV)

Time(hr)	Test (fast)	Test (fed)	Ref.(fed)	(T/R) fed*100
0.0	0.0	0.0	0.0	-----
0.33	12.31(165.4)	0.0	0.0	-----
0.67	181.52(55.2)	2.92(412.3)	16.41(168.7)	17.8
1.0	284.66(47.0)	25.24(154.8)	63.36(142.8)	39.8
1.33	300.15(43.8)	82.31(79.5)	100.06(117.0)	82.3
1.67	318.39(39.9)	142.03(64.7)	137.86(86.0)	103.0
2.0	313.09(39.4)	206.27(50.8)	188.45(62.8)	109.5
2.5	285.05(33.0)	259.98(38.1)	251.05(39.5)	103.6
3.0	250.13(31.9)	279.06(35.4)	271.51(34.4)	102.8
4.0	196.73(35.8)	263.12(25.9)	252.09(36.0)	104.4
5.0	146.90(31.4)	199.56(23.1)	201.14(31.7)	99.2
6.0	116.36(29.5)	139.57(24.4)	147.54(28.5)	94.6
8.0	68.92(24.4)	93.25(45.2)	81.84(27.0)	113.9
10.0	44.68(23.5)	57.56(55.7)	49.85(26.1)	115.5
12.0	30.61(29.2)	37.30(53.3)	31.65(27.7)	117.8
16.0	17.36(46.3)	17.36(66.4)	15.94(46.1)	108.9
24.0	9.73(68.4)	5.35(127.0)	4.99(126.1)	107.2

Figure 2. Acyclovir mean levels for the non-fasting study, bar graph

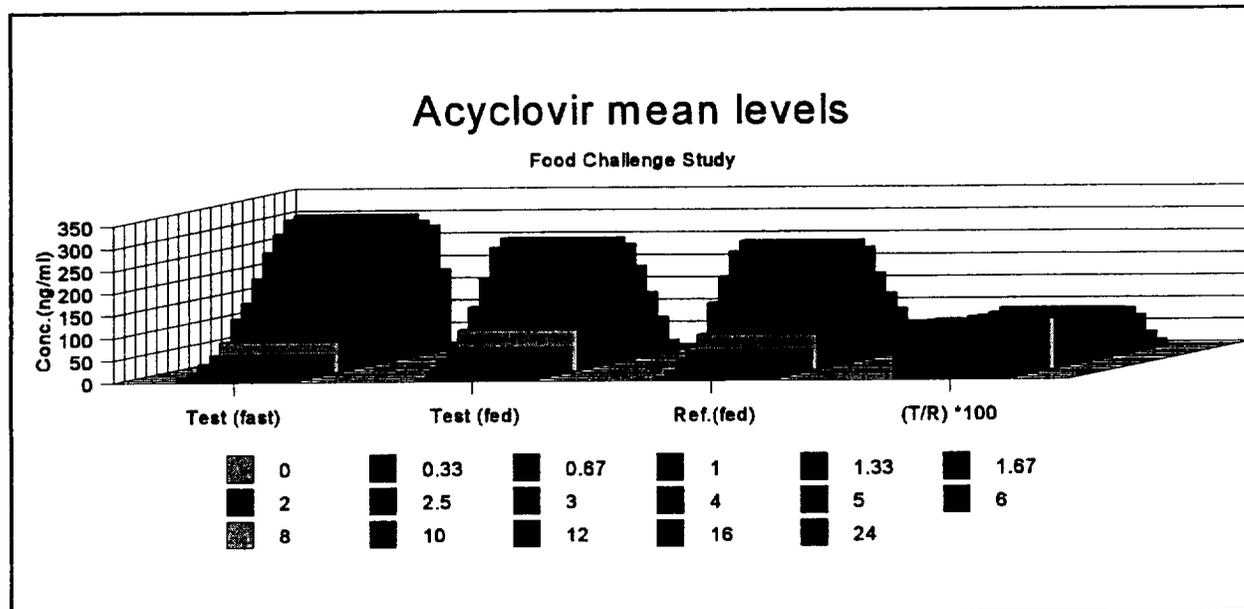


Table 2.2: LSMEAN (n=17) pharmacokinetic parameters, Food Challenge Study

Parameter	Test(fast)	Test(fed)	Ref.(fed)	%Ratio (T/R,fed)
LnAUCt	1723.49	1636.41	1576.14	103.8
LnAUCinf	1859.58	1718.14	1668.28	103
LnCmax	351.265	305.128	306.373	99.6
Tmax*	1.529	3.265	2.961	110.3
T <sub>1/2</sub> *	5.612	4.119	4.108	100.3
AUCt	1809.6	1668.2	1625.8	102.6
AUCinf	1942.2	1753.1	1716.7	102.1
Cmax	370.28	313.52	316.04	99.2

\* = Arithmetic mean

K. ADVERSE EFFECTS: Only one adverse event, headache, was reported with treatment 'A'. The intensity was moderate, was categorized as non-serious and no medication was necessary for the relief.

L. COMMENTS ON THE POST PRANDIAL BIO-STUDY:

1. Food challenge apparently has delayed acyclovir absorption. A lag time is evident in almost all subjects with the food challenge. The pharmacokinetic parameters in Table 2.2 suggest that food did not dramatically alter the extent of absorption (AUC<sub>fed(test)</sub>/AUC<sub>fast(test)</sub> ratios more than 90%).

2. The mean AUC<sub>t</sub> parameter was about 95% of the AUC<sub>inf</sub> parameter indicating the adequacy of sampling scheme. Following the food challenge, both the test and reference mean C<sub>max</sub>, T<sub>max</sub> and T<sub>1/2</sub> were altered similarly compared to the fasting treatment, C<sub>max</sub> being slightly reduced and T<sub>max</sub> slightly delayed. The mean pharmacokinetic parameter test/ref. ratios for the fed treatments were close to 1.0. The mean plasma level test/ref. ratios for the fed treatments also approached unity after 1.67 hours. The mean test(fed) pharmacokinetic point estimate parameters were within 20% of the mean ref.(fed) parameters and thus complied with the regulatory food challenge study requirement.

VI. DISSOLUTION METHODOLOGY: The firm has used the following methodology for the comparative dissolution of the test and reference bio-study lots. The method is not recommended by either the U.S.P. or the FDA handbook.

Apparatus: U.S.P. XXIII Apparatus II (paddle)  
Speed: 50 rpm  
Medium: 0.1N HCl  
Volume: 900 ml  
Firm Proposed 'Q': NLT % in 30 minutes.

A. RESULTS OF THE DISSOLUTION TESTING: The reported dissolution test study results are given in Table D1.

B. COMMENTS ABOUT THE DISSOLUTION TESTING:

1. The firm has provided comparative dissolution data for only six capsule units of the test and the reference lots. It is unclear whether the test lot studied for the dissolution (04826) was the actual bio-study lot (reported as 04799).

## VII. DEFICIENCIES:

1. The firm should conduct the dissolution using the following FDA recommended dissolution methodology and specifications:

Apparatus: U.S.P. XXIII Apparatus I (basket)

Speed: 100 rpm

Medium: Deaerated water

Volume: 900 ml

FDA dissolution handbook recommended 'Q': NLT % in 30 minutes.

Comparative dissolution should be conducted on 12 units of the test and reference bio-study lots. The results should be reported in terms of the mean, range and percent coefficient of variation.

2. The dissolution has been conducted on the test lot CT04826. The relationship between CT04826 and the number used in the study CT04799 should be clarified.

3. The firm has stated that "one of the extracted blanks had an interference at the retention time of the analyte approximately 30% of the LOQ". Since no other statement was made in relation to specificity, please provide the chromatogram of that sample.

## VIII. OVERALL COMMENTS:

1. Based on the provided information and data, the bioequivalence studies appear to be acceptable. Based on the objectives of the study, the firm has rightfully modified the blood sample scheme for the food challenge study compared to the fasting study.

2. The reported dissolution testing data and results are not acceptable.

## IX. RECOMMENDATIONS :

1. The bioequivalence studies conducted by Ranbaxy Labs. on its 200 mg acyclovir capsule lot #CT04799, comparing it to Zovirax<sup>R</sup> 200 mg capsule have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Ranbaxy Labs' acyclovir 200 mg capsule is bioequivalent to the reference product, Zovirax<sup>R</sup> 200 mg acyclovir capsule manufactured by Burroughs Wellcome.

2. The dissolution testing conducted by Ranbaxy Labs on its Acyclovir, 200 mg capsule,

lot #CT04826, is not acceptable. The firm should conduct dissolution testing on 12 individual dosage units of the test and the reference bio-study lots using 900 ml of deaerated water at 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than 70% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. From the bioequivalence point of view, the firm has not met the requirements of in-vitro dissolution testing and the application has been found incomplete by the Division of Bioequivalence.

4. The firm should submit additional data as stated in Deficiencies 1-3.

*JSI*  
3/7/97

Pradeep M. Sathe, Ph.D.  
Division of Bioequivalence,  
Review Branch I.

RD INITIALED BY YCHUANG  
FT INITIALED BY YCHUANG

*JSI*

3/12/97

Concur: *JSI*

Date: 3/12/97

Rabindra Patnaik, Ph.D.

Acting Director, Division of Bioequivalence  
*for*

cc: ANDA #74-975 (Original, Duplicate), Sathe, HFD-652 (Huang), Drug File, Division File.

**Table D1 . In Vitro Dissolution Testing**

Drug (Generic Name): Acyclovir  
 Dose Strength: 200 mg capsule  
 ANDA No.: 74-975  
 Firm: Ranbaxy labs  
 Submission Date: October 9, 1996

**I. Conditions for Dissolution Testing:**

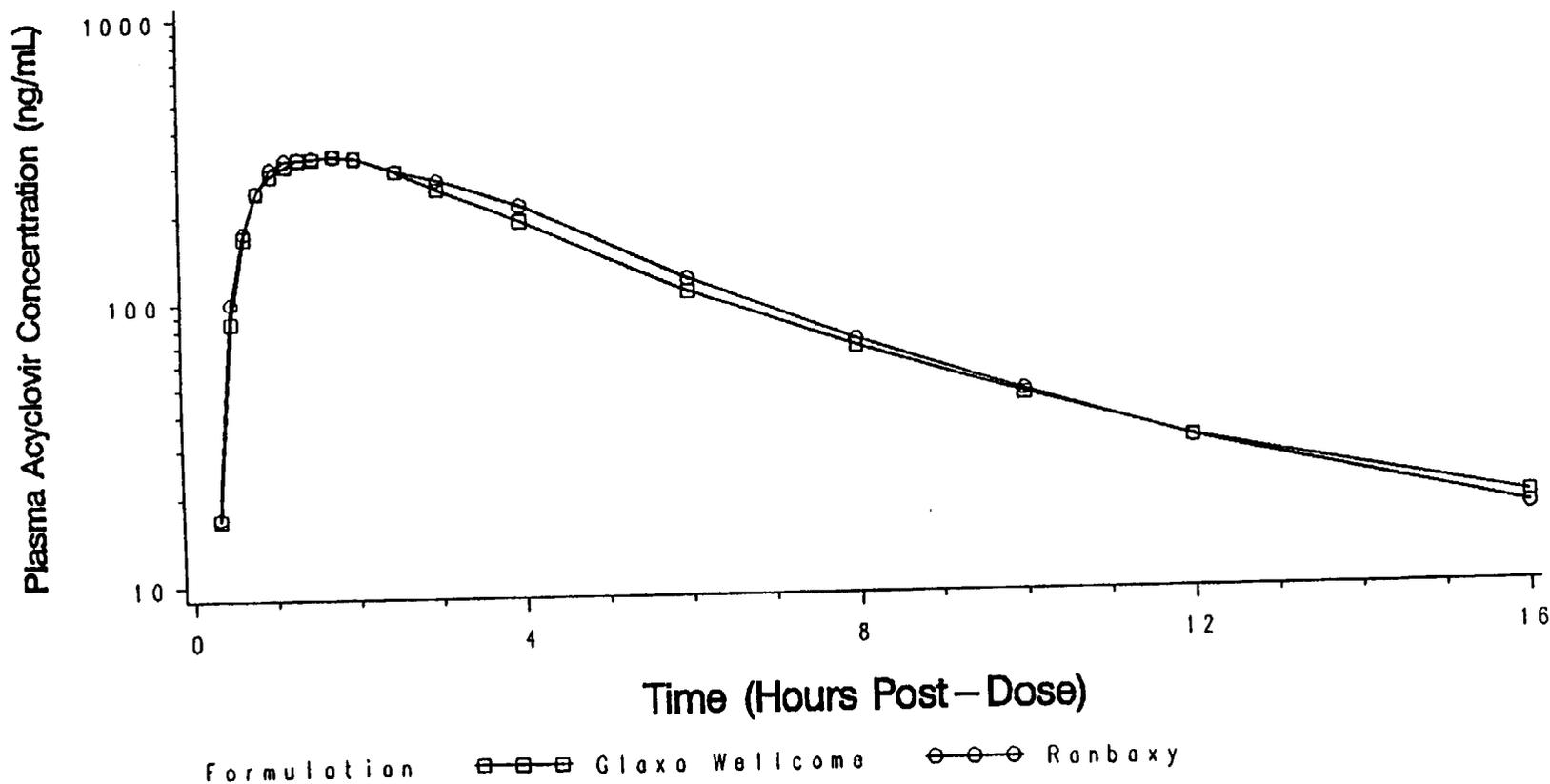
U.S.P. XXIII (Paddle) RPM: 50  
 No. Units Tested: 6  
 Medium: 0.1N HCl Volume: 900 ml  
 Firm's Specification: NLT % dissolved in 30 minutes.  
 Reference Drug: Zovirax<sup>R</sup> by Burroughs Wellcome  
 Assay Methodology:

**II. Results of In Vitro Dissolution Testing:**

Sampling Times (Minutes)	Test Product: Acyclovir capsule Lot #CT04826 Strength (200 mg)			Reference Product: Zovirax Lot # 5O2064 Strength (200 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
5	93		NR	53		NR
10	101		NR	95		NR
15	102		NR	101		NR
30	102		NR	101		NR

NR = Not reported

Figure 1  
Project No. 960902  
Mean Plasma Acyclovir Concentrations  
(Semi-Log Plot)

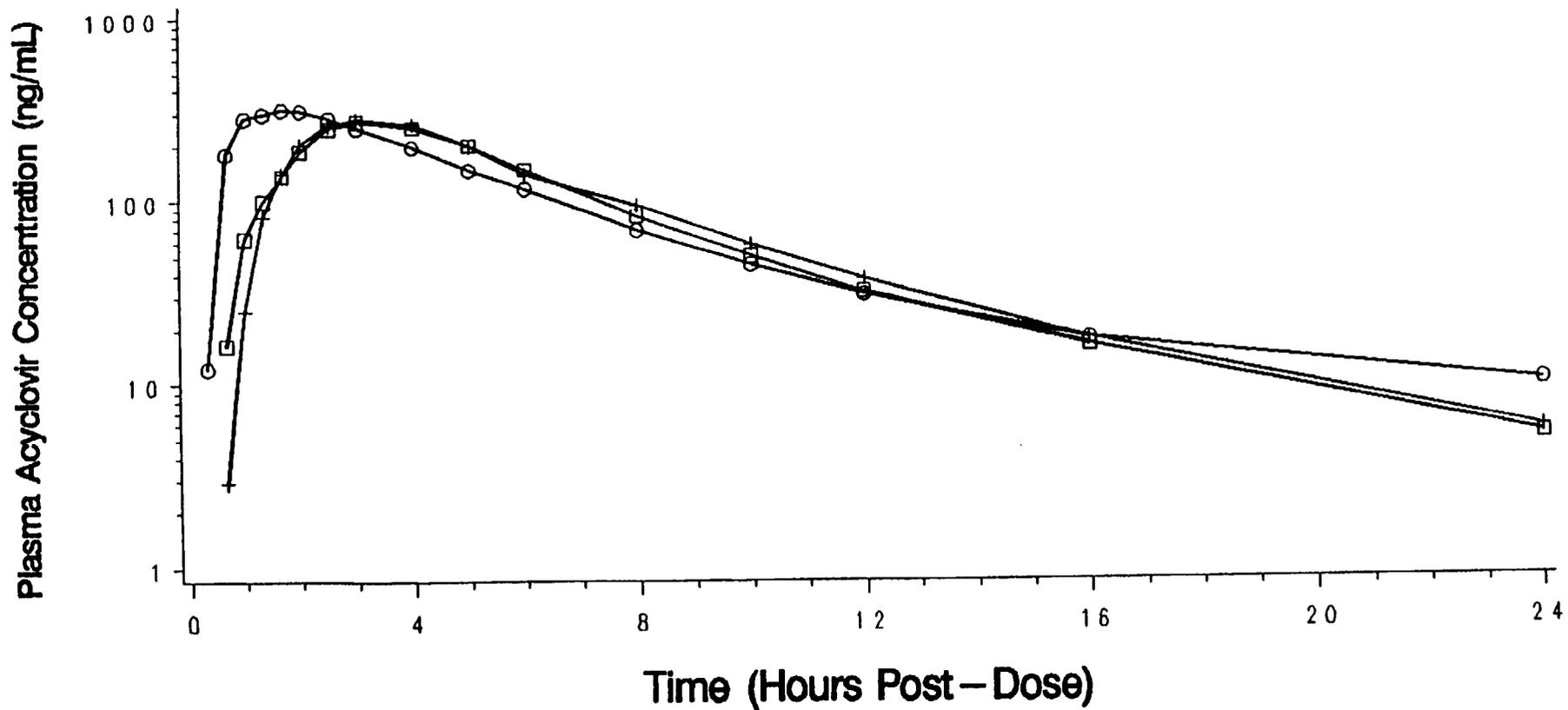


DATA/PROFILES

DEFAULT (07AUG96)

Attachment I

**Figure 1**  
**Project No. 951321**  
**Mean Plasma Acyclovir Concentrations**  
**(Semi-Log Plot)**



Formulation      □-□-□ BW (Fed)                      ○-○-○ Ranboxy (Fasted)  
                          +--+ Ranboxy (Fed)



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**74975**

**ADMINISTRATIVE DOCUMENTS**

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

---

ANDA Number: 74-975

Date of Submission: August 24, 1998

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Acyclovir Capsules, 200 mg

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s & 500s

Satisfactory in FPL as of 7/22/98 submission

Professional Package Insert Labeling:

Satisfactory in FPL as of 8/24/98 submission

*Combined Insert (shared with ANDA 74-980)*

Revisions needed post-approval:

Encourage the relocation of "Rx only" to the TITLE section.

**BASIS OF APPROVAL:**

Was this approval based upon a petition? Yes

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

NDA Number: 18-828

NDA Drug Name: Zovirax® Capsules

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: May 29, 1998/  
S-020

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

Was this approval based upon an OGD labeling guidance? No

Other Comments:

The firm has proposed for a **combined package insert** for separate applications for acyclovir tablets 74-980) and capsules (74-975). Please note that these applications **must be approved at the same time**, or further revisions may be necessary prior to approval.

---

---

**FOR THE RECORD:**

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

2. Dispensing recommendations:

USP: Not USP [However, USP packaging and storage for acyclovir is "Preserve in tight containers].

PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]

NDA: Well-closed container as defined in the USP [Container]

ANDA: Dispense in a tight, light-resistant container. [Container]

Storage recommendations:

PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]

NDA: Store at 15° to 25°C (59° to 77°F) and protect from moisture. [Insert]  
Store at 15° to 25°C (59° to 77°F). [Container]

ANDA: Store at 15° to 25°C (59° to 77°F) and protect from moisture. [Insert]

Store at 15° to 25°C (59° to 77°F) and protect form light and moisture. [Container]

We will **NOT** ask to delete the terms "light" and "light-resistant" from container labels. (See FTR #74946 in the file holder)

3. With respect to the previous comment (b)(ii) on "Pregnancy exposure registry..." in the last review, see FTR #74946 in the file holder and FTR #11 below.

4. DOSAGE AND ADMINISTRATION (Bioequivalence of dosage forms):

Refer to the previous comment (d) (iii) under INSERT. This comment in the last review is based on the FTR #74946 in the file holder.

5. Patents/Exclusivity

No patent and exclusivity. The firm's information is accurate.

6. Components/Composition

The list of inactive ingredients in the DESCRIPTION section is consistent with the firm's components and composition statement, [Vol. B.1.1, Section VII/p.18, 19, 20, 25 & 34].

7. Container/Closure

200 mg: 100s and 500s - Opaque white HDPE/non-CRC  
[Vol. B1.2, Section XIV, p. 3]

8. The firm's capsule imprints described in the HOW SUPPLIED section are consistent with the firm's finished dosage form description. [Vol. B1.2, section XV, p.3 (also see, B1.1 section VII, p.18 &22)]

9. Manufacturing functions:

-Applicant's name: Ranbaxy laboratories Limited.  
-Manufacturer's name: : Eli Lilly and company/Indianapolis, Indiana  
[Vol. B1.1, section IX]

10. This ANDA shares the insert with ANDA 74-980 for acyclovir tablets.

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

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 Submission: July 22, 1998

Date of Review: August 21, 1998

Reviewer:

/S/

9/8/98  
Date:

Team Leader:

an an

Date:

/S/

9/9/98

cc:

ANDA 74-975  
DUP/DIVISION FILE  
HFD-613/CHolquist/JGrace (no cc)  
X:\NEW\FIRMSNZ\ANBAXY\LTRS&REV\74975NA3.L  
Review

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**74975**

**CORRESPONDENCE**

ANDA 74-975

Lilly Ranbaxy Pharmaceuticals, L.L.C.  
Attention: Jeffrey R. Ferguson  
U.S. Agent for: Ranbaxy Laboratories Limited  
One College Park  
8910 Purdue Road, Suite 230  
Indianapolis, IN 46268

DEC 4 1996

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.

We also refer to your correspondence dated October 21, 1996 and November 25, 1996.

NAME OF DRUG: Acyclovir Capsules, 200 mg

DATE OF APPLICATION: October 9, 1996

DATE OF RECEIPT: October 10, 1996

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

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

Should you have questions concerning this application contact:

Tim Ames  
Project Manager  
(301) 594-0305

Sincerely yours,

/S/

12/4/96

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

MAR 18 1997

Lilly Ranbaxy Pharmaceuticals, L.L.C.  
Attention: Jeffrey R. Ferguson  
U.S. Agent for: Ranbaxy Laboratories Limited  
One College Park  
8910 Purdue Road, Suite 230  
Indianapolis, IN 46268

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on October 9, 1996 for Acyclovir 200 mg Capsules.

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

1. The dissolution should be conducted using the following FDA recommended dissolution methodology and specifications:

Apparatus: USP 23 Apparatus I (basket)  
Speed: 100 rpm  
Medium: Deaerated water  
Volume: 900 mL  
Specifications: 'Q': NLT % in 30 minutes.

Comparative dissolution should be conducted on 12 units of the test and reference bio-study lots. The results should be reported in terms of the mean, range and percent coefficient of variation.

2. The dissolution has been conducted on the test lot CT04826. The relationship between CT04826 and the number used in the study CT04799 should be clarified.
3. You have stated that "one of the extracted blanks had an interference at the retention time of the analyte approximately % of the LOQ"; since no other statement was made in relation to specificity, please provide the chromatogram of that sample.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

*NS*

*fr* Nicholas Fleischer, Ph.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research



**Lilly Ranbaxy Pharmaceuticals, L.L.C.**  
 One College Park  
 8910 Purdue Road, Suite 230  
 Indianapolis, IN 46268

*73, 11/19/96  
 10/30/96  
 C. P. ...  
 11/19/96*

**FEDERAL EXPRESS**

**AMENDMENT**

October 21, 1996

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

*3-10-1996*

**RECEIVED**

**OCT 21 1996**

**GENERIC DRUGS**

Re: ANDA# 74-975  
 Acyclovir Capsules, 200 mg  
**Amendment - Drug Substance DMF Number**

Dear Mr. Sporn:

We are submitting an amendment to Ranbaxy Laboratories Limited's pending Abbreviated New Drug Application for Acyclovir Capsules, 200 mg in accordance with Section 505(j) of the Federal Food, Drug, and Cosmetic Act and as described in 21 CFR 314.60.

Per our commitment in the initial ANDA application dated October 9, 1996 for the above referenced product, we are updating the application to provide the Drug Master File number for the Acyclovir drug substance. The FDA assigned DMF number is [redacted]. An updated DMF Authorization Letter from Ranbaxy Pharmaceuticals, Inc. (DMF U.S. Agent for Ranbaxy Laboratories Limited) is attached. Please incorporate this information into the application.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the coverletter and return it in the self-addressed, stamped envelope.

Sincerely,

Mr. Jeffrey R. Ferguson  
 Regulatory Affairs Director  
 Lilly Ranbaxy Pharmaceuticals, L.L.C.  
 (U.S. Agent for Ranbaxy Laboratories Limited)

Attachment

**RANBAXY**  
**PHARMACEUTICALS INC.**

4600 MARRIOTT DRIVE-SUITE 100 RALEIGH, NORTH CAROLINA 27612  
PHONE : (919) 510 0949 FAX : (919) 510 0958.

ANDA ORIG AMENDMENT  
AB

January 9, 1998

Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855

**FEDERAL EXPRESS**

**BIOEQUIVALENCE  
AMENDMENT**

Reference :           **ANDA 74-975**  
                          Acyclovir Capsules, 200 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 74-975 for Acyclovir Capsules, 200 mg.

Reference is also made to the FDA Bioequivalence Deficiency Letter dated March 18, 1997. The questions and responses follow in the same order as in the letter. They are attached.

If you have any questions, regarding the submission, please call me at (919) 510-0949 ext 224 or Shirley Ternyik at ext 237.

Sincerely,

*for Shirley Ternyik*  
Jim Sibert  
US Agent for Ranbaxy Laboratories Limited

**RECEIVED**

**1 JAN 12 1998**

**GENERIC DRUGS**





Lilly Ranbaxy Pharmaceuticals, L.L.C.  
One College Park  
8910 Purdue Road, Suite 230  
Indianapolis, IN 46268

May 23, 1997

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

NEW DRUGS  
NC

Re: ✓ ANDA 74-975                      ANDA 74-980  
      Acyclovir Capsules, 200 mg        Acyclovir Tablets, 400 & 800 mg

Dear Mr. Sporn:

This letter is to advise you and your staff that effective May 23, 1997 I will be leaving my position as Director of Regulatory Affairs for Lilly Ranbaxy Pharmaceuticals. I'm currently the listed US agent for the Ranbaxy Laboratories Limited (India) Acyclovir ANDAs referenced above.

Effective May 23, 1997, Mr. Jim Sibert from Ranbaxy's North American Office will assume my US agent responsibilities. The official designation of Jim Sibert as the US agent will be provided by Ranbaxy under separate cover. All further communications regarding the above referenced ANDAs should be directed to Mr. Sibert at the following address:

James L. Sibert  
Executive Director, Regulatory Affairs  
Ranbaxy Pharmaceuticals Inc.  
4600 Marriott Drive, Suite 100  
Raleigh, NC. 27612  
Phone: (919) 510-0949 ext. 224

If you have any questions regarding this submission, please call either Mr. Sibert or myself.

Sincerely,

Jeffrey R. Ferguson  
Director, Regulatory Affairs

MAY 27 1997

cc: Jim Sibert, Ranbaxy Pharmaceuticals Inc.

**RANBAXY**  
PHARMACEUTICALS INC.

March 26, 1998

Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855

**FEDERAL EXPRESS**

**MAJOR  
AMENDMENT**

**Reference:            ANDA 74-975**  
**Acyclovir Capsules, 200 mg**

*FPL*  
*74-975*  
*AC*

Dear Sir/Madam:

Reference is made to the pending ANDA 74-975 for Acyclovir Capsules, 200 mg.

Reference is also made to the FDA Major Deficiency Letter dated August 20, 1997. The questions and responses follow in the same order as in the letter. They are attached.

Also, please note that the name and address of the US Agent has changed. See attached US Agent letter from Ranbaxy Laboratories Ltd., India.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this submission has been provided to the Food and Drug Administration Detroit District Office in Detroit, Michigan.

If you have any questions, regarding the submission, please call me at (609) 720-5612.

Sincerely,

*Shirley Ternyik*

Shirley Ternyik  
US Agent for Ranbaxy Laboratories Limited

ST/mtr

**RECEIVED**

**MAR 30 1998**

# RANBAXY

LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001  
PHONE: (91-124) 342001-10, FAX: (91-124) 342017, 342030

FPL

ORIG AMENDMENT

N/AF

August 24, 1998

Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855

FEDERAL EXPRESS

LABELING  
AMENDMENT

**Reference: ANDA 74-975**  
**Acyclovir Capsules, 200 mg**

Dear Sir/Madam:

Reference is made to the pending ANDA 74-975 for Acyclovir Capsules, 200 mg.

Reference is also made to the FDA Labeling Deficiency Letter dated July 26, 1998 and the response submitted July 22, 1998.

Reference is also made to a telephone call on August 24, 1998 requesting twelve copies of real Final Printed package inserts. They are attached.

If you have any questions regarding this submission, please call me at (609) 720-5612.

Sincerely,



Shirley Ternyik  
US Agent for Ranbaxy Laboratories Limited

RECEIVED

AUG 25 1998

GENERIC DRUGS

**RANBAXY**  
PHARMACEUTICALS INC

**FPL**  
ORIG AMENDMENT  
N/AF

July 22, 1998

Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855

**FEDERAL EXPRESS**

**LABELING  
AMENDMENT**

**Reference: ANDA 74-975  
Acyclovir Capsules, 200 mg**

Dear Sir/Madam:

Reference is made to the pending ANDA 74-975 for Acyclovir Capsules, 200 mg.

Reference is also made to the FDA Labeling Deficiency Letter dated July 26, 1998 (copy attached). Twelve copies of revised Final Printed Labeling are attached. They have been revised as requested.

To facilitate your review and in accordance with 21 CFR 314.914, we have provided a side-by-side comparison of our Final Printed Labeling, versus the last amendment, with all differences annotated.

If you have any questions regarding this submission, please call me at (609) 720-5612.

Sincerely,



Shirley Ternyik  
US Agent for Ranbaxy Laboratories Limited

Enclosures

**RECEIVED**  
JUL 30 3 1998  
GENERIC DRUGS



**Lilly Ranbaxy Pharmaceuticals, L.L.C.**  
One College Park  
8910 Purdue Road, Suite 230  
Indianapolis, IN 46268

*Handwritten:*  
J. M. ...  
10/30/96

**FEDERAL EXPRESS**

October 9, 1996

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

**RECEIVED**

**OCT 10 1996**

Re: Initial ANDA Submission  
Acyclovir Capsules, 200 mg

Dear Mr. Sporn:

**GENERIC DRUGS**

**Ranbaxy Laboratories Limited, New Delhi, India** is hereby submitting an Abbreviated New Drug Application for Acyclovir Capsules, 200 mg as required by Section 505 of the Federal Food, Drug, and Cosmetic Act, and described in 21 CFR 314.94.

This application is submitted by Lilly Ranbaxy Pharmaceuticals, L.L.C., as the U.S. Agent/Representative to FDA for Ranbaxy Laboratories Limited. A letter appointing Mr. Jeffrey R. Ferguson as U.S. Agent can be found on the next page. Correspondence concerning this submission should be addressed as follows:

Mr. Jeffrey R. Ferguson  
Regulatory Affairs Director  
Lilly Ranbaxy Pharmaceuticals, L.L.C.  
One College Park  
8910 Purdue Road, Suite 230  
Indianapolis, Indiana 46268

Please note that the drug substance manufacturer is also Ranbaxy Laboratories Limited. Their Drug Master File (DMF) was filed on October 8, 1996. The DMF number has not been assigned by the FDA. We commit to file an amendment to the ANDA application providing the DMF number as soon as it is assigned.

This drug product was developed by Ranbaxy Research Laboratories (a division of Ranbaxy Laboratories Limited) and technology transferred to Eli Lilly and Company, Indianapolis, Indiana. Eli Lilly and Company manufactured the exhibit batch and will manufacture the commercial batches for Ranbaxy Laboratories Limited. The drug product will be marketed in the United States by Lilly Ranbaxy Pharmaceuticals, L.L.C., a marketing joint venture between Ranbaxy Laboratories Limited and Eli Lilly and Company.

A comprehensive table of contents is provided which shows the volume and page number of our submission's contents, as required by the regulations part 314.94(a)(2).

This submission consists of the following designated volumes:

<b>Contents</b>	<b>Jacket Color</b>	<b>Number of Volumes</b>
<b>Complete Application (total of 9 volumes):</b>		
FDA Chemistry and Labeling Archival Copy	Blue	2
FDA Pharmacokinetic Archival Copy	Blue	7
<b>Partial Applications:</b>		
FDA Chemistry and Labeling Review Copy	Red	2
FDA Pharmacokinetic Review Copy	Orange	7
Methods Validation Package (in triplicate)	Purple	3

As instructed by the Indianapolis FDA office, a field copy in a burgundy jacket containing the technical section has been forwarded to the District Office at this address:

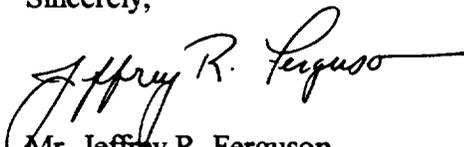
John P. Dempster  
Director Enforcement Branch  
U.S. Food and Drug Administration  
1560 East Jefferson Avenue  
Detroit, MI 48207

Section I of this submission contains a field copy certification of the authenticity of this copy.

Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and return it in the self-addressed envelope provided.

Feel free to contact me by telephone at (317) 655-2006 if any questions arise with which I may help. We thank you for your time in the review of this application and look forward to receipt of your response.

Sincerely,



Mr. Jeffrey R. Ferguson  
Regulatory Affairs Director  
Lilly Ranbaxy Pharmaceuticals, L.L.C.  
(U.S. Agent for Ranbaxy Laboratories Limited)