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 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^{R} 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^{R} 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 % 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/

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[R] 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

2.1

JUN 17 1998

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,

/S/

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^{R}) capsule formulations.

As per the orange book, Burroughs Wellcome's Zovirax^{R} 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	%
Theoretical Total Weight	**mg**	**%**

* = 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^{R}) 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^{R}) 200 mg Acyclovir caspsules 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 Phase I	Phase II	Volunteer Number
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^{R} 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^{0}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 AUCt, area under the plasma concentration time curve from time 0 to infinity, calculated as AUCt+Ct/Kel where Ct is the last measurable concentration and Kel is the terminal elimination rate constant, maximum measurable concentration Cmax, time of the maximum measured concentration Tmax, terminal elimination rate constant Kel, terminal half-life $T_{1/2}$ and ratio of AUCt/AUCinf. Analysis of variance was performed and AUCt, AUCinf and Cmax 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 Cmax were reported as ng/ml, Tmax 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

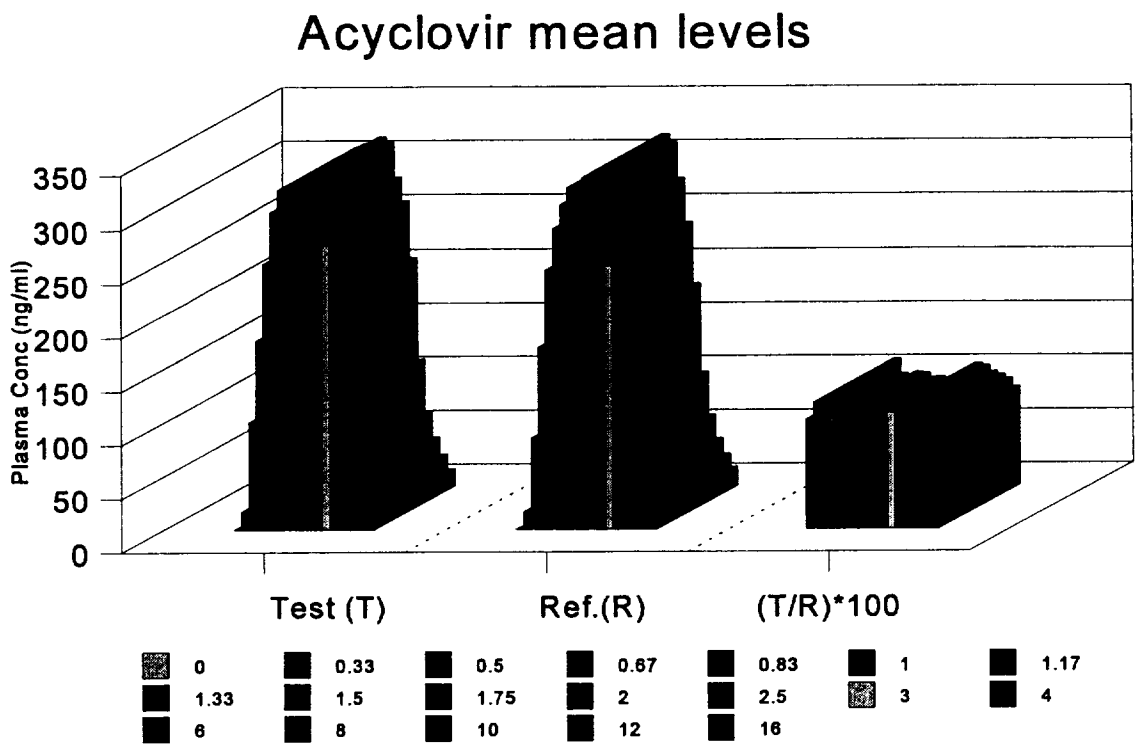


Figure 1. Acyclovir mean levels for test and reference formulation, bar graph

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	----------
$T_{1/2}$	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 Tmax and $T_{1/2}$, are comparable. The area under the curve from zero to last measurable sample point AUCt, is more than 93% of AUCinf, 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			
Phase I	Phase II	Phase III	Volunteer Number
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^{R} 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^{0}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 Cmax were expressed as ng/ml, Tmax and $T_{1/2}$ 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

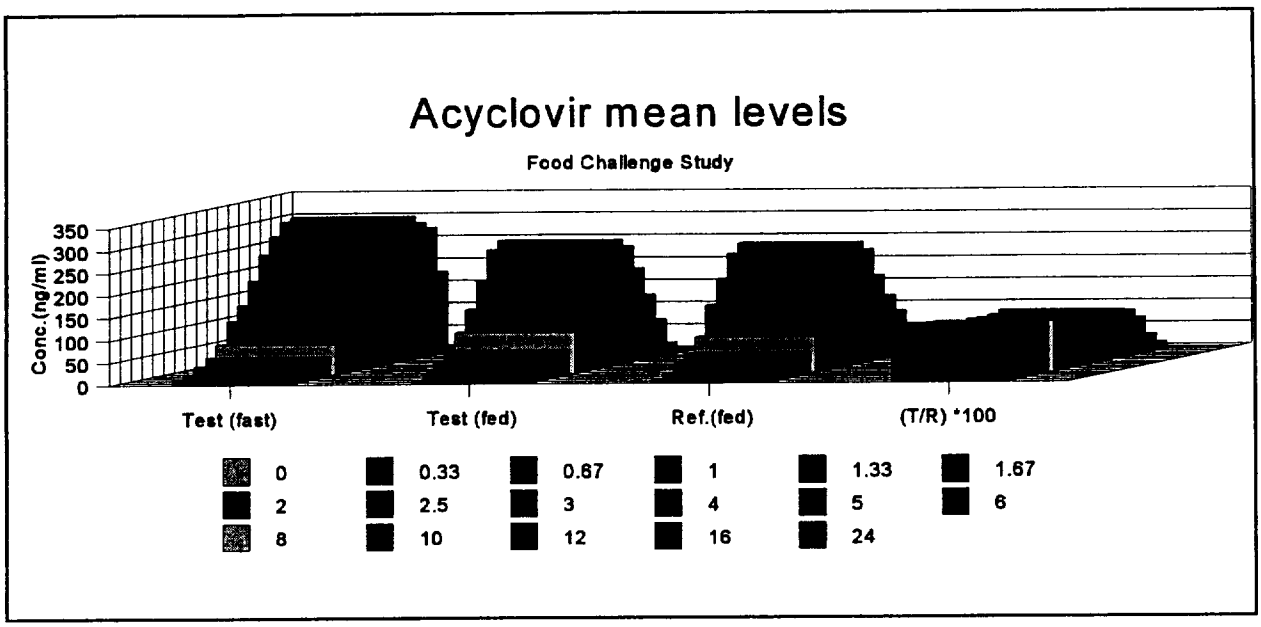


Table 2.2: LSMEAN (n=17) pharmacokinetic parameters, Food Challenge Study

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
$T_{1/2}$*	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 (AUCfed(test)/AUCfast(test) ratios more than 90%).

2. The mean AUCt parameter was about 95% of the AUCinf parameter indicating the adequacy of sampling scheme. Following the food challenge, both the test and reference mean Cmax, Tmax and $T_{1/2}$ were altered similarly compared to the fasting treatment, Cmax being slightly reduced and Tmax 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^{R} 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^{R} 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 % 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.

/S/ 3/7/97

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

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG /S/ 3/12/97

Concur: /S/ Date: 3/12/97

Rabindra Patnaik, Ph.D.
~~Acting~~ for Director, Division of Bioequivalence

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[R] 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

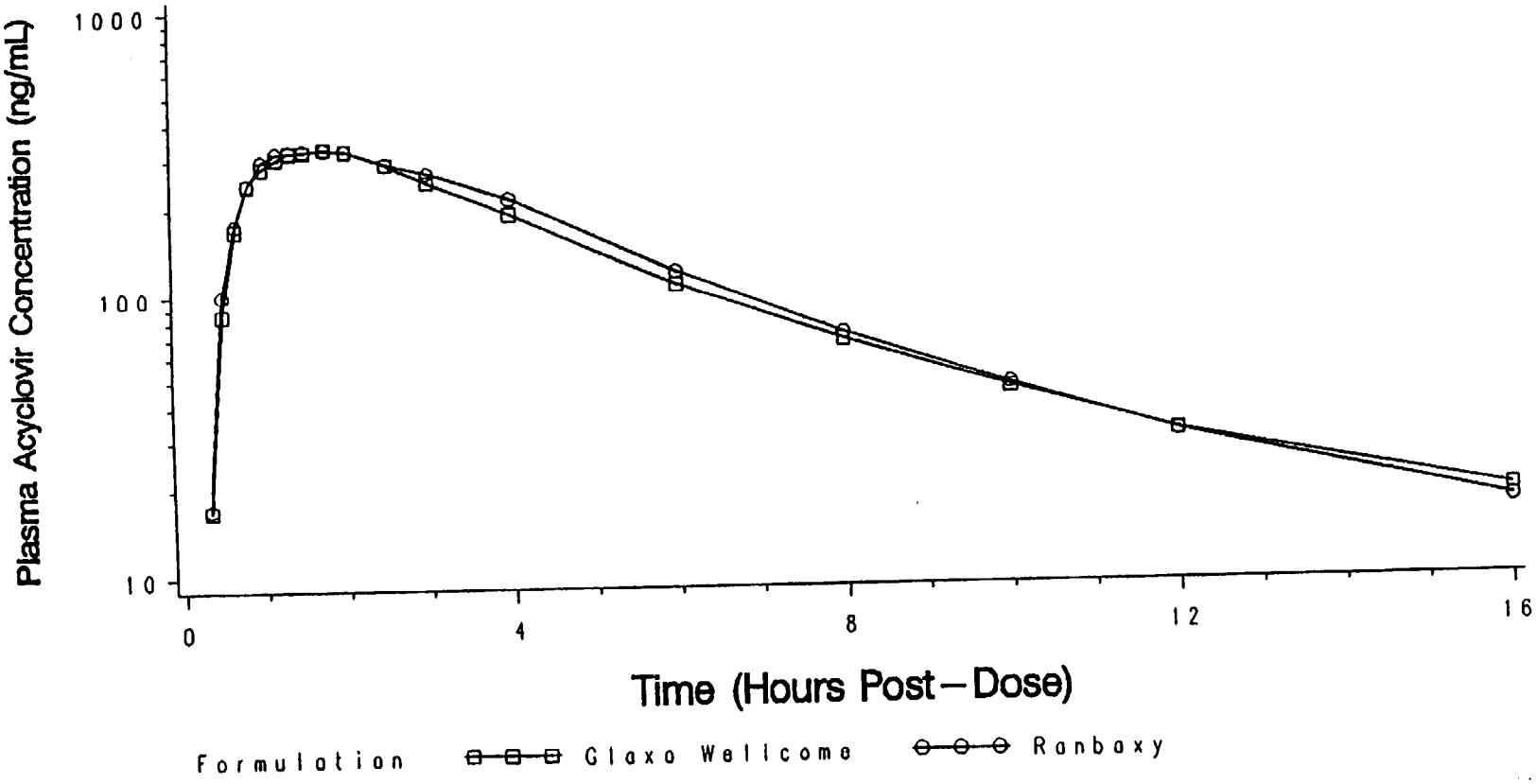
NR = Not reported

Figure 1

Project No. 960902

Mean Plasma Acyclovir Concentrations

(Semi–Log Plot)



DEFAULT (07AUG96)

Attachment I

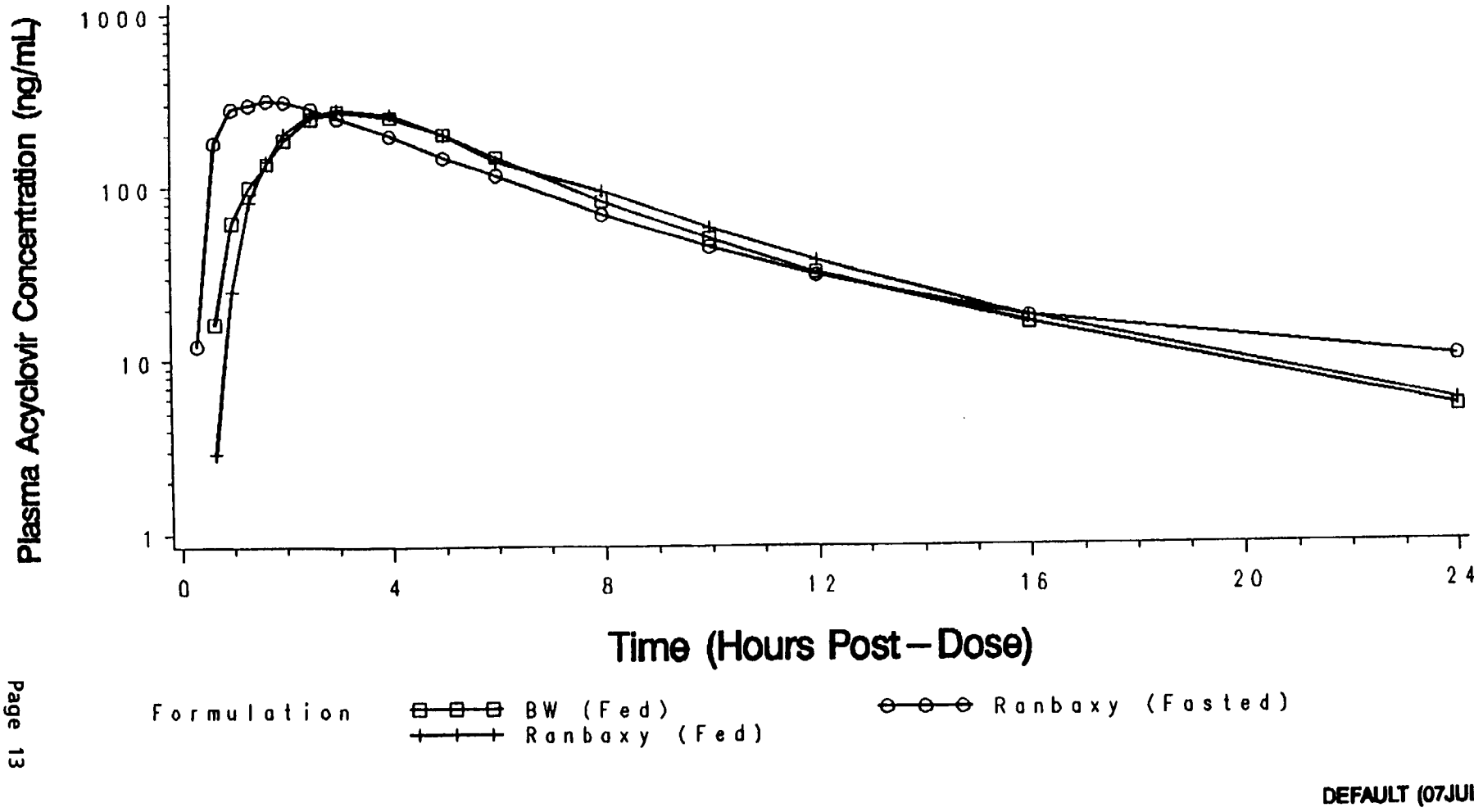
DATA/PROFILES

Figure 1

Project No. 951321

Mean Plasma Acyclovir Concentrations

(Semi – Log Plot)



Attachment II

DEFAULT (07JUL96)