CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74976

BIOEQUIVALENCE REVIEW(S)

ANDA 74-976

OCT 10 1997

Lipha Pharmaceuticals, Inc.
U.S. Agent for Genpharm, Inc.
Attention: Anita M. Goodman
9 West 57th Street, Suite 3825
New York NY 10019-2701

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir tablets, 400 mg and 800 mg.

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

2. 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 0.1 N HCL using USP 23 apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT - 5 1997

Acyclovir
800 mg Tablet
400 mg Tablet
ANDA # 74976
Reviewer: A.J. Jackson

Genpharm Pharmaceuticals
Ontario, Canada
Submission Date:
June 2, 1997
September 8, 1997

WP # 74976A.697

Review of Correspondence on Fasting and Post-Prandial Bioequivalence Studies and Dissolution Data for the 800 mg Tablet and Waiver Request for 400 mg Tablet

INTRODUCTION

The firm submitted a study on September 27, 1996 on their Acyclovir tablet which was found to be incomplete. The current submission contains the firm's response to the deficiencies from the study.

Comment 1.

Lot 102563 of Acyclovir was used for the biostudy. In volume 1.5 page 002374 information relating to the potency of bulk lot # 102394 is given. The sponsor must establish that big-lot 102563 is the same as bulk lot 102394 for the dissolution data to be acceptable. If not, what is the potency for the big-lot? Also, if they are different, a dissolution study must be done in 0. IN HCI using the big-lot since the proposal is to establish 0.1N HCI as the dissolution media.

Response to Comment 1.

The big-study batch was packaged into two packaging formats, bottles of 100 and blister strips of 10. The test batch for the 400 mg tablets was packaged into bottles of 100. Genpharm's SOP on lot numbering requires that a different lot # be assigned for different packaging formats. Summarized below is a breakdown of the lot numbers derived from the bulk lot 102393 and 102394 for the 400 mg and 800 mg tablets respectively.

Strength	Lot Number Batch Size	Bulk Lot	Packaged Product
400 mg		102393	Bottles of 100's Lot No. 102760
800 mg		102394	Bottles of 100's Lot No. 102563
			Blister of 10's Lot No. 102706

Appendix I, appended to this review, contains the first pages of the executed packaging documents supporting the assignment of lot numbers.

FDA Reply:

The firm's explanation is acceptable.

Comment 2.

The following subjects in the fasting study exhibited an increase in the terminal phase of their plasma concentration time curves:

Treatment-Test

Subject	Time	Conc

Treatment-Reference

Subject	Time	Conc

Please explain how it was determined that these subjects were in the log-linear phase since the terminal data was increasing.

Response to Comment 2.

Section 2.2.1, details the criteria upon which the terminal elimination phase is determined by the pharmacokineticist. Specifically, the terminal phase is selected based upon an in-depth analysis of the semi-log plasma profiles for each subject, with integration of the following four (4) factors:

(I) the terminal phase with the greatest r value;
(ii) the terminal phase with the greatest number of points;
(iii) the competing principles of absorption, distribution, and elimination; and, (iv) assay variability as it relates to individual concentrations.

A review of the Kel values was conducted for Study # 1642, and using linear regression analysis of the terminal data, all subjects in question showed positive Kel values, indicating a valid terminal phase with an overall negative slope. The observed increase in the 24-hour plasma acyclovir concentration of the subjects indicated above may be due either to analytical variation, and/or to marginal redistribution of the drug.

FDA Reply:

The firm's explanation is acceptable.

Comment 3.

The data for the subjects in deficiency # 2 should be deleted from the estimation of AUC (0-infinity).

Response to Comment 3.

AUC(0-infinity) was recalculated with the following subjects eliminated, and the results are presented in Appendix 2.0.

Genpharm formulation (A): Subjects #02, #09, #15, #18, #28,

#33, and #35.

Burroughs-Wellcome formulation (B): Subjects #09, #26, and #30.

The appendix also includes the other parameters which were recalculated, namely half-life (t1/2), elimination rate constant (Kel), and the correlation coefficient (r value) of the most linear portion of the terminal elimination phase. For AUC (0 - infinity), the analysis of variance (ANOVA) on log-transformed data was conducted, and the 90% geometric confidence interval and ratio of means were calculated. For t1/2 and Kel, the ANOVA on untransformed data was conducted. In addition, the frequency distribution of the regimen differences and regimen ratios among the subjects are presented in Figures A and B for AUC (0 - infinity).

It is noted that the test and reference formulations of acyclovir 800 mg tablets under fasted conditions are bioquivalent, based on the 90% geometric confidence intervals for AUC (0 -t hrs), AUC (0 - infinity), and Cmax.

FDA Reply:

The firm's response is acceptable and the 90% confidence interval for the recalculated AUC(0-infinity) of 90.7-117.8 is within the acceptable limits.

Comment 4.

The submission of September 27, vol1.5 page 002372, includes dissolution data for a study conducted in acid for the 400 mg tablet with no statistical summary. In the January 22 submission, dissolution data collected in acid was submitted on pages 4-5, which was difficult to interpret and appeared to be done on only 6 tablet data. In the February 5 submission, no data was submitted for dissolution in acid for the 400 mg tablet. Please submit completely documented comparative dissolution data, including conditions for 12 tablets each of both test and reference acyclovir products in 0.1NHCI, which is proposed as the final dissolution medium.

Response 4.

Submitted on the following pages are the dissolution data for the 400 mg tablets study conducted in 0.1 N HC1 (both test and reference acyclovir products, lots (L) 102760 and (L) 4Z2486 respectively). Along with the individual dissolution

data for the 12 tablets, we have provided the comparative dissolution profiles with the statistical summary (Mean of 12 tablets, SD, RSD and the Range).

Also, please find attached a letter dated April 7,1997 from USP stating the change in the dissolution medium for the Acyclovir tablets and capsules monograph in the Pharmacopeia Forum.

FDA Reply:

The firm's reply is acceptable. The dissolution Table 1 also contains the data for the 800 mg tablet in acid.

Comment 5.

Explain why the reported value in the long-term stability study for QC low at
different from the standard.

Response to Comment 5.

It is unclear why the of one of the two Quality Control (QC) samples at showed a large difference from the theoretical value. However, this was clearly an outlier because in the samples, the concentrations were found to be acceptable

FDA Reply:

The firms response is acceptable.

Comment 6.

Also submit additional dissolution data in the following media so that this information can be used in establishing a dissolution specification for their tablet. The media and conditions requested are.

I. Apparatus: II
Medium: 0.05 M Phosphate Buffer pH=6.8
RPM: 50
No. of Units: 12
II. Apparatus: II
Medium: 0.05 MAcetate Buffer pH=4. 5
RPM: 50

No. of Units: 12

Response 6.

Additional dissolution studies were performed as per the methods detailed above. Provided on the following pages are the comparative dissolution profiles, with the individual dissolution data and the statistical summaries (mean of 12 tablets, SD, RSD and the Range) for the following studies:

*Study	Strength Lot # used	Genpharm Product	Innovator Product Lot # used
Study 1	400 mg	bulk lot 102393 packaged lot 102760	lot 4Z2486 exp.: 01/98
	800 mg	bulk lot 102394 packaged lot 102563	lot 5T1785 exp.: 10/97
Study 2	400 mg	bulk lot 102393 packaged lot 102760	lot 4Z2486 exp.: 01/98
	800 mg	bulk lot 102394 packaged lot 102563	lot 5T1785 exp.: 10/97

***Study 1: (Medium:0.05 M Phosphate Buffer pH=6.8)**
***Study 2: (Medium:0.05M Acetate Buffer pH=4.5)**

FDA Reply:

The firm's response is acceptable. The dissolution data is appended to this review.

Comment:

1. Since the firm has supplied a letter from the USP dated April 7, ~~1~~997 recommending that 0.1 N HCL be used as the dissolution medium, the Division of Bioequivalence will accept this as an interim dissolution medium for this product.

2. The dissolution data for the 800 mg and 400 mg tablets are acceptable.

Recommendation

1. The bioequivalence study conducted by Genpharm on its Acyclovir, 800 mg, tablet, Lot # 102563, comparing it to Glaxo Wellcome's, 800mg, Zovirax® tablets, has been found to be acceptable by the Division of Bioequivalence. The study demonstrates that Genpharm's, Acyclovir, 800 mg tablet is bioequivalent to the reference product, Zovirax, 800 mg, tablet manufactured by Glaxo-Wellcome.

2. The dissolution testing conducted by Genpharm on its Acyclovir, 800 mg, tablet, Lot # 102563, is acceptable. The firm has conducted an acceptable in-vivo bioequivalence study submission dated September 27, 1996 comparing its Acyclovir, 800 mg, tablet, Lot # 102563 of the test product with the 800 mg, tablet of the reference product Zovirax manufactured by Glaxo-Wellcome. The formulation for the 400 mg tablet of the test product is proportionally similar to the 800 mg tablet strength of the test product which underwent bioequivalence testing. Therefore, the waiver of in vivo bioequivalence study requirements for the 400 mg strength is granted.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1 N HCL using USP 23 apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

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

Andre J. Jackson
Division of Bioequivalence I
Review Branch I

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Date: 9/16/97

Concur: _____ Date: 10/5/97

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

cc: ANDA 74-976 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File, Division File, HFD-650(Director).

Table 1. In Vitro Dissolution Testing

Drug (Generic Name):Acyclovir
Dose Strength:800 mg
ANDA No.:74-976
Firm:Genpharm
Submission Date:June 2, 1997
File Name:74976DW.697

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: x RPM:50
No. Units Tested: 12
Medium: 0.1 N HCL Volume:900 ml
Specifications: NLT n 30 min

Reference Drug: Zovirax
Assay Methodology:

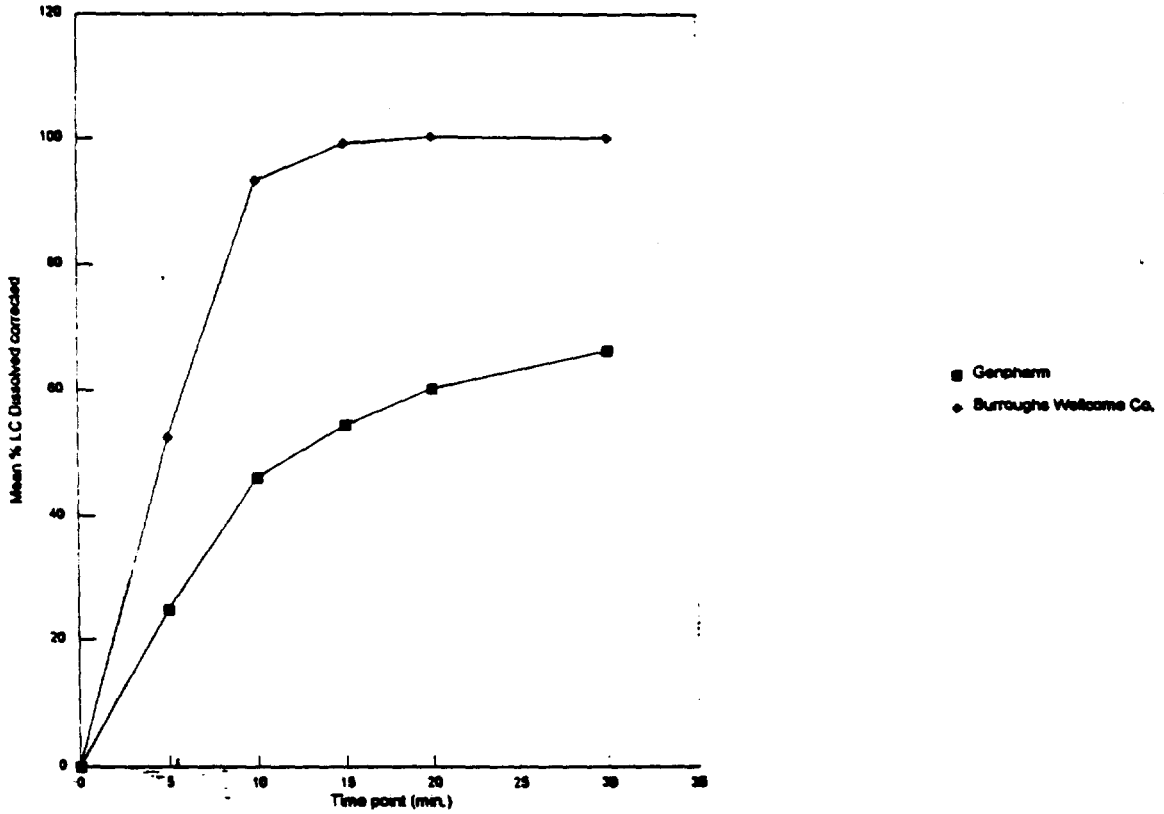
II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 102394 Strength(mg) 800			Reference Product Lot # 5T1785 Strength(mg) 800		
	Mean %	Range	%CV	Mean %	Range	%CV
0	0.00	0	0	0	0	0
5	66.8		8.57	54.6		15.71
10	90.8		8.26	93.3		5.20
15	100.4		1.36	101.5		1.15
20	101.6		0.77	102.3		0.83
30	102.2		1.00	102.0		1.25

Sampling Times (Minutes)	Test Product Lot #102393 Strength(mg)400			Reference Product Lot # 4Z2486 Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
0	0	0	0	0	0	0
5	57.1		16.52	76.8		6.30
10	90.4		3.96	99.1		1.39
15	100.2		1.37	99.4		2.21
20	102.0		0.77	99.5		2.02
30	102.0		0.76	99.9		1.86

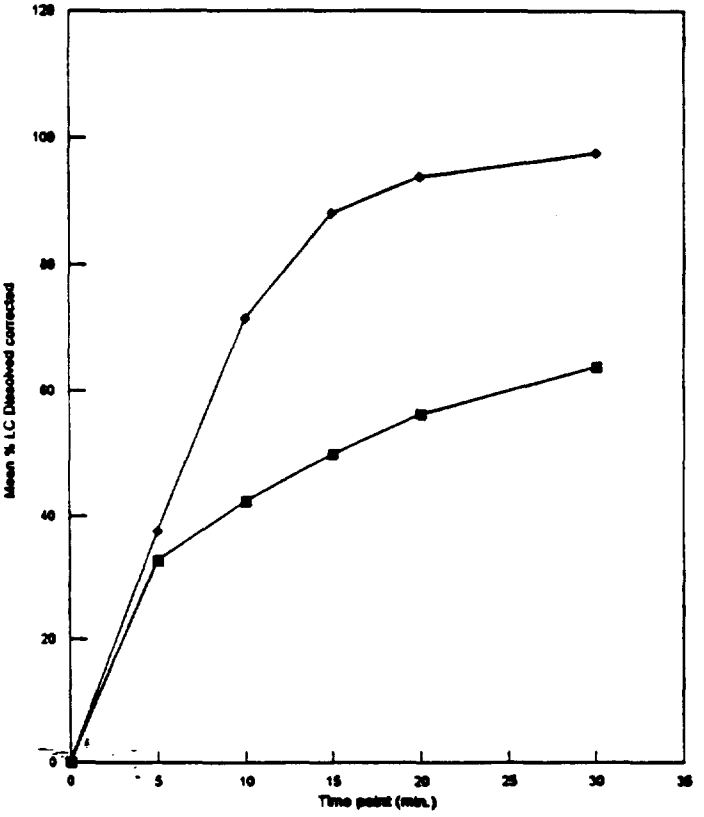
Comparative Dissolution Profiles of Acyclovir Tablet 400mg

	Acyclovir Tablet 400mg Lot # 102760, Bulk (L) 102393 Lab # 7-5-336 Genpharm Medium: 0.05M phosphate buffer pH6.8 Book L1667 & page # 55 n= 12				Zovirax (Acyclovir) Tablet 400mg Lot # 4Z2486, Exp Date: 01/98 Lab # 7-5-336 Burroughs Wellcome Co, U.S.A. Medium: 0.05M phosphate buffer pH6.8 Book L1667 & page # 55 n= 12			
Time (min.)	Mean (%)	SD	RSD	Range (%)	Mean (%)	SD	RSD	Range (%)
0	0				0			
5	24.8	6.31	25.38		52.5	11.19	21.33	
10	48.1	1.72	3.73		93.3	2.50	2.68	
15	54.4	1.27	2.33		99.2	1.33	1.34	
20	60.2	1.39	2.31		100.2	1.29	1.29	
30	66.3	1.86	2.85		100.1	0.73	0.73	



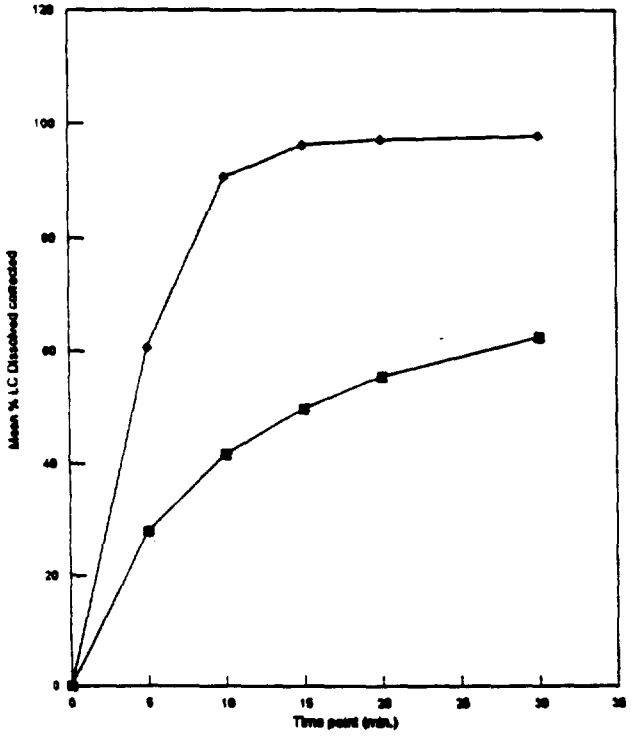
Comparative Dissolution Profiles of Acyclovir tablets 800mg

	Acyclovir tablets 800mg Lot # 102563,Bulk (L)102384 Lab # 7-5-337 Genpharm Medium:0.05M phosphate buffer pH 6.8 Book L16564 page # 73 n=12				Zovirax(Acyclovir) tablets 800mg Lot # ST1786,Exp. 10/97 Lab # 7-5-338 Burroughs Wellcome, USA Medium:0.05M phosphate buffer pH 6.8 Book L16564 page # 73 n=12			
Time (min.)	Mean (%)	SD	RSD	Range (%)	Mean (%)	SD	RSD	Range (%)
0	0				0			
5	32.8	4.96	15.10		37.6	7.96	21.16	
10	42.4	4.23	9.96		71.6	8.46	11.86	
15	49.9	5.14	10.30		88.2	5.41	6.13	
20	58.3	5.83	10.00		93.9	2.41	2.57	
30	63.8	4.00	6.27		97.6	1.60	1.64	



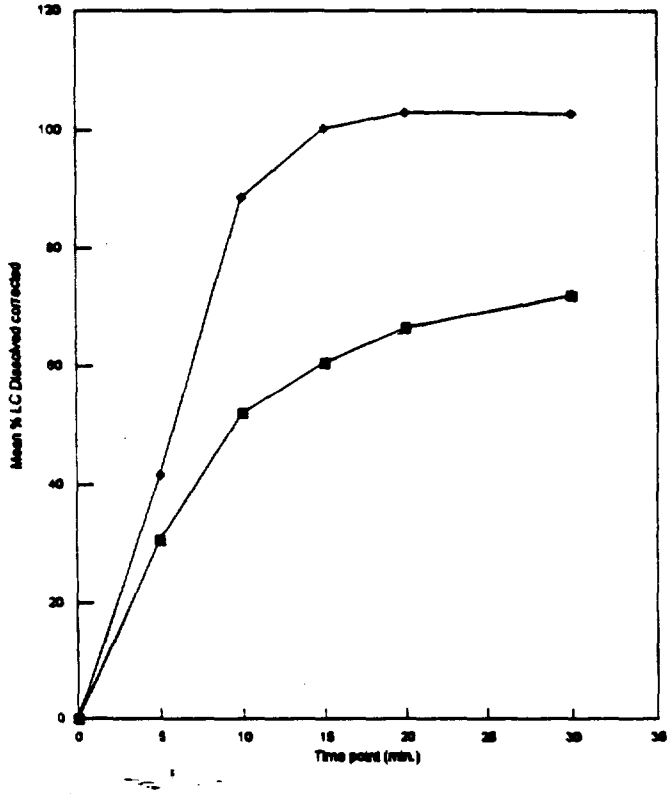
Comparative Dissolution Profiles by UV of Acyclovir Tablets, 400mg

	Acyclovir Tablets, 400mg Lot # 102760, Bulk (L) 102369 Lab # 7-5-336 Genpharm Medium: 0.05M Acetate Buffer, pH 4.5 Book L1611 & page # 62 n=12				Zovirax Tablets, 400mg Lot # 4Z2488, Exp. 01/98 Lab # 7-5-336 Burroughs Wellcome Co., U.S.A. Medium: 0.05M Acetate Buffer, pH 4.5 Book L1611 & page # 62 n=12			
Time (min.)	Mean (%)	SD	RSD	Range (%)	Mean (%)	SD	RSD	Range (%)
0	0				0			
5	27.9	5.82	20.86		80.5	8.05	13.31	
10	41.7	2.21	5.29		90.7	2.02	2.23	
15	49.8	1.69	3.38		96.3	2.38	2.49	
20	56.5	1.68	3.03		97.2	3.18	3.28	
30	62.4	2.56	4.10		97.7	2.01	2.06	



Comparative Dissolution Profiles by UV of Acyclovir Tablets, 800mg

	Acyclovir Tablets, 800mg Lot # 102563, Bulk (L) 102394 Lab # 7-5-337 Genpharm Medium: 0.05M Acetate Buffer, pH 4.5 Book L1611, L1667 & page # 82, 89 n=12				Zovirax Tablets, 800mg Lot # 5T1786, Exp. 10/97 Lab # 7-5-336 Burroughs Wellcome Co., U.S.A. Medium: 0.05M Acetate Buffer, pH 4.5 Book L1611, L1667 & page # 82, 89 n=12			
Time (min.)	Mean (%)	SD	RSD	Range (%)	Mean (%)	SD	RSD	Range (%)
0	0				0			
5	30.7	7.16	23.29		41.6	5.50	13.23	
10	52.2	2.67	5.12		86.7	3.61	4.29	
15	60.6	2.68	4.43		100.4	2.08	2.07	
20	66.4	2.84	4.28		103.0	2.48	2.41	
30	71.7	3.44	4.80		102.8	2.10	2.04	



■ Genpharm

◆ Burroughs Wellcome Co., U.S.A.