CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75211

BIOEQUIVALENCY REVIEW(S)

Acyclovir Tablets
400 MG, 800 MG
ANDA #75-211
Reviewer: S.P. Shrivastava
WP #75211SDW.997

Mylan Pharmaceuticals, Inc.
Morgantown, WV
Submitted:
September 9, 1997

REVIEW OF TWO BIOEQUIVALENCE STUDIES, DISSOLUTION DATA AND A WAIVER REQUEST

I. OBJECTIVES

Review of Mylan's two *in vivo* bioequivalence studies comparing its 800 mg strength Acyclovir Tablets to Burroughs-Wellcome's800 mg strength Zovirax^R Tablets, under fasting and non-fasting conditions. The firm has also submitted *in vitro* dissolution data for 400 and 800 mg strengths for review.

II. BACKGROUND

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

Acyclovir oral absorption is slow, variable, and incomplete, with absolute bioavailability estimated at about 15-30%. Peak blood concentrations occur approximately 1.5-2.5 hours following oral dosing. There are no active metabolites. Studies in which 0.5 to 15 mg/kg were administered I.V. to patients with normal renal function yielded elimination half-lives of 2 to 3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine.

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

III. SUMMARY OF BIOEQUIVALENCE STUDY PROTOCOLS

A. Single-Dose Fasting Study

1. Protocol # ACYC9601A

This randomized, single-dose, two-way crossover study was conducted with 34 healthy male volunteers in accordance with the protocol. In each period, subjects received a single 800

mg dose of either Mylan's acyclovir tablets or BW's Zovirax[R] tablets following an overnight fast. There was a one-week wash-out period between treatments. Blood samples were collected pre-dose and for 24 hours after each dose. Plasma concentrations of acyclovir was measured by a fully validated procedure. Pharmacokinetic and statistical analyses were performed to compare the test and reference products.

2. Objective of the study

The objective of this study was to determine the bioequivalence of two acyclovir formulations after administration of single doses to healthy volunteers under fasting conditions.

3. Study design: Randomized, single-dose, two-way crossover study.

4. Study sites Clinical study: Mylan Pharm., Inc., Morgantown, WV
Analytical study: Mylan Pharm., Inc., Morgantown, WV

5. Study dates:

Clinical study:	3/8/97-3/17/97
Analytical study:	3/25/97-4/24/97
Storage Time:	47 Days

6. Investigators: Principal Investigators - Thomas Clark, M.D.
Dorian Williams. MD

A. Reference: 800 mg Zovirax[R] Tablets (Burroughs Wellcome, Lot #5T1792);
Exp. Date 11/97; Potency - 100.8%.
B. Test: 800 mg Acyclovir Tablets (Mylan, Lot #2C005L);
Rel. Date - 11/07/96; Lot Size - Potency - %.
Randomization Scheme: AB - 2, 5, 7, 8, 9, 12, 13, 16, 18, 19, 20, 21, 25, 26, 27, 31, 34
BA - 1, 3, 4, 6, 10, 11, 14, 15, 17, 22, 23, 24, 28, 29, 30, 32, 33

7. Dosing: All doses were administered with 360 mL of water at room temperature. Subjects will fast for at least 10 hours pre- and 5 hours post-dosing.

8. Subjects: The 34 subjects who entered in this study were normal healthy male volunteers between the ages 18-50 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

All 34 subjects completed the study.

9. Food and fluid intake: Standard lunch was served 5 hours post-dose, and dinner was served as scheduled on each day of drug administration. The drug products were administered with 360 mL of water. Water was allowed *ad lib.* except during one-hour pre- and two-hour, post-dosing periods.

10. Washout period: One week.

11. Blood samples: In each period, 10 mL of blood samples were collected in heparinized tubes at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours. Plasma was separated and all plasma samples were stored frozen at -70°C until ready for analysis.

12. Subject safety monitoring: Subjects were asked to spontaneously report any signs or symptoms that might be related to the drug products.

13. Adverse reactions: On each dosing period subjects were asked to report any signs or symptoms judged to be drug related.

14. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for acyclovir. 90% confidence intervals were calculated for $LAUC_{0-t}$, $LAUC_{0-inf}$ and LC_{max}.

B. Limited-Food Study

1. Protocol # ACYC9602

2. Study design: Randomized, single-dose, three-way crossover, six sequence study under fasting/non-fasting conditions.

3. Study Sites and Investigators: Same as in the fasting study

4. Study dates:
   Clinical study: 11/18/96-12/4/96
   Analytical study: 2/4/97-2/25/97
   Total Storage Period: 98 Days

5. Treatments:

   A. Reference: 1 X 800 mg Zovirax[R] tablet (Burroughs Wellcome, Lot #5T1792, Exp. Date 11/97) under non-fasting conditions; Potency %.
   B. Test: 1 X 800 mg Mylan acyclovir tablets (Mylan, Lot #2C005L, Manuf. Date 10/21/96) under non-fasting conditions; Potency - . %.
   C. Test: 800 mg Acyclovir Tablets (Mylan, Lot # #2C005L, Manuf. Date 10/21/96) under fasting conditions: Potency - %.

Randomization Scheme: ABC- 3, 8, 13; ACB-1, 7, 18; BAC-4, 12, 14;
BCA- 5, 10, 15; CAB-6, 9, 16; CBA-2, 11, 17

6. Dosing: All doses were administered with 240 mL of water at room temperature following an overnight fast or within 30 minutes of starting the breakfast depending on the dosing schedule.

7. Subjects: All eighteen subjects entered and completed the study.

8. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 240 mL of water. Water was allowed *ad lib.* except during two-hour pre-dose and two-hour post-dose periods.

9. Wash-out period: One week.

10. Blood samples: Same as in the fasting study.

IV. PRE-STUDY VALIDATION OF ASSAY METHOD FOR PLASMA SAMPLES

Methods:

Inter-Day: Results are shown in Table 1.

Table 1. Calibration Standards for Acyclovir

Theoretical Conc, ng/mL	10	25	100	750	1000
Sample Number (n)	17	18	18	18	12
Mean Conc.	10.23	25.19	99.69	743.38	1032.64
Precision, % CV	4.39	3.17	1.19	1.85	5.49
Accuracy, % Diff.	2.23	0.78	-0.31	-0.88	3.26

e. Intra-Day Precision: Acyclovir sample data are summarized in Table 2

Table 2. Intra-Day Precision of Acyclovir Samples

Theoretical Conc, ng/mL	10	25	100	750	1000
n	6	6	6	6	6
Mean	9.94	24.65	100.27	753.39	982.71
Precision, %	6	3.65	0.94	0.54	2.36
Accuracy, % Diff.	-0.64	-1.42	0.27	0.45	-1.73

f. Absolute Recovery: Percent extracted vs. unextracted, data are given in Table 3.

Table 3. Acyclovir Recovery Data (n=6)

Nominal Conc., ng/mL	25	100	750	Average
Recovery, %	99.24	90.03	91.8	93.7
%CV	1.82	7.1	1.86	5.2

g. Stability of Acyclovir : Stability was checked under various conditions, including refrigeration at 0-5 ^{0}C, in biological matrix at bench-top for 4 hours, during three freeze-thaw cycles, on auto-sampler for 96 hours, and long-term stability at -70 ^{0}C for 98 days. Plasma samples are stable under the study conditions.

Storage Test Conc.	ng/mL	Storage Period	Temperature	% Diff.
System-Check (Autosampler) (n=3)	750	96 Hrs	Room	0.04
Three Freeze-Thaw Cycles (n=6)	25 750	-------	Room/-20 °C	7.14 1.94
Bench-Top (n=6)	750	4 Hours	Room	0.11
Long-Term Stab. (n=2)	23.2 681.2	98 Days	-70 °C	13.79 10.02

V. RESULTS

A. Single-Dose Fasting Study

Within-Study Validation

	Conc., ng/mL		CV, %	Error, %
Std. Curve;	n=25	10	1.6	0.5
	n=25	25	3.5	-0.4
	n=25	50	2.3	-1.4
	n=25	75	3.0	-0.0
	n=25	100	1.6	-0.8
	n=25	250	2.1	-0.6
	n=25	500	3.1	0.9
	n=25	750	1.6	-0.0
	n=25	1000	2.2	0.3
	n=25	1250	4.6	2.4
	n=25	1500	4.1	-0.8
QC Samples;	n=71	25	9.8	-3.6
	n=71	100	7.9	-1.3
	n=71	1000	6.4	-1.2

1. **Blood/Plasma Drug Concentration:** The mean plasma concentration data are

given in Table 4, and graphic profiles are shown in Attachment 1.

2. **Pharmacokinetic Parameters**: The statistical analyses were carried out by the reviewer and the mean PK parameters are given in Tables 5-6. The PK parameter values obtained by the firm and by the reviewer are comparable. Individual data are shown in Attachments 2-3.

- The 90% CI for LAUCs are within % as required (Tables 6).
- ANOVA analysis showed no significant treatment, sequence or period effects on AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}.
- Individual Test/Reference ratios for AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and T_{half} averaged between 1.01 and 1.04.
- The ratios of AUC_{0-t}/AUC_{0-inf} averaged 90%.
- None of the subjects showed C_{max} at first non-zero time point.
- AUC_{0-inf} values were obtained for all subjects.

3. Adverse Reaction: Mild headaches were experienced by 4 and 2 subjects dosed with test and reference products, respectively. No other serious or unexpected adverse reactions were reported.

Conclusion: The *in vivo* fasting study is acceptable.

TABLE 4. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)
(n=34)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	100.63	85.58	132.24	85.74	0.76
0.67	406.26	187.42	471.89	196.16	0.86
1	569.63	211.76	588.52	206.08	0.97
1.33	645.41	209.76	622.24	189.85	1.04
1.67	637.81	200.77	606.39	177.37	1.05
2	619.15	216.69	568.15	163.57	1.09
2.5	540.27	221.59	509.68	173.60	1.06
3	467.03	203.58	447.31	188.18	1.04
4	356.54	165.10	338.72	161.02	1.05
5	261.77	119.26	264.63	134.95	0.99
6	194.06	81.79	197.20	90.67	0.98
8	120.66	45.53	120.79	50.25	1.00
10	81.35	28.76	81.11	30.35	1.00
12	60.80	18.55	59.97	20.21	1.01
16	35.86	11.71	37.05	13.33	0.97
24	25.58	9.21	24.62	10.51	1.04

1=TEST, 2=REFERENCE

TABLE 5. TEST MEAN/REFERENCE MEAN RATIOS (n=34; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	3867.80	1063.89	3809.19	1100.01	1.02
AUCT	3478.78	1044.85	3432.32	1056.15	1.01
CMAX	756.99	205.12	726.95	174.29	1.04
KE	0.08	0.04	0.08	0.03	1.02
LAUCI	3731.52	0.27	3675.94	0.26	1.02
LAUCT	3336.85	0.29	3298.44	0.28	1.01
LCMAX	730.87	0.27	706.27	0.25	1.03
THALF	10.20	3.76	9.89	3.09	1.03
TMAX	1.40	0.50	1.39	0.61	1.01

1=TEST, 2=REFERENCE

TABLE 6. LSMEANS AND 90% CONFIDENCE INTERVALS (n=34)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	3867.80	3809.19	1.02	93.18	109.90
AUCT	3478.78	3432.32	1.01	91.73	110.97
CMAX	756.99	726.95	1.04	95.58	112.69
LAUCI	3731.52	3675.94	1.02	94.18	109.42
LAUCT	3336.85	3298.44	1.01	92.98	110.07
LCMAX	730.87	706.27	1.03	95.39	112.26

1=TEST 2=REFERENCE

B. Limited Food Study

Within-Study Validation

	Conc., ng/mL	CV, %	Error, %
Std. Curve;			
n=15	10	1.6	0.1
n=15	25	2.7	-0.3
n=15	50	4.2	-0.7
n=15	75	3.2	1.8
n=15	100	2.7	-1.0
n=15	250	2.3	-0.1
n=15	500	4.1	-0.8
n=15	750	3.2	0.5
n=15	1000	3.3	0.0
n= 8	1250	2.0	2.6
n= 8	1500	5.7	-1.7
QC Samples			
n=39	25	4.5	-5.7
n=39	100	4.7	1.7
n=20	750	4.8	2.1
n=20	1000	6.0	1.4

A total of 18 subjects participated and completed the study successfully.

1. Blood/Plasma Drug Concentration

The average plasma concentration data, test/reference ratios, and plasma profiles are given

in Tables 7-8 and Attachment-4. T/R (food) ratios during 1-24 hours are 0.8-1.1, and generally food increases the drug plasma concentration.

2. Pharmacokinetic Parameters: The statistical analyses were carried out by the reviewer. The PK parameter values obtained by the firm and by the reviewer are comparable.

- Average pharmacokinetic parameters and test/reference (food) ratios are given in Tables 9-11.
- The ratios of average test/reference (food) for AUCs and C_{max} are within 0.8-1.2 as required (Table 10).
- ANOVA analysis showed no significant period or sequence effects on AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}.
- None of the subjects showed C_{max} at first non-zero time point.
- AUC_{0-inf} values were obtained for all subjects.
- Individual PK parameters are given in Attachments 5-7.
- Food increases the C_{max}, T_{max} and AUCs, and it decreases T_{half}.

Conclusion: The non-fasting *in vivo* study is acceptable.

TABLE 7. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS (N=18)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	7.96	9.84	14.34	16.44	112.13	96.63
0.67	110.53	99.71	193.95	201.31	501.17	233.88
1	361.11	275.85	464.76	321.31	665.09	256.14
1.33	683.62	349.66	717.30	379.03	717.95	347.82
1.67	930.57	358.38	864.07	416.96	682.58	278.85
2	1082.11	338.75	948.47	371.85	671.31	263.70
2.5	1029.68	234.63	968.38	273.87	581.65	227.87
3	985.71	281.21	952.44	268.73	502.00	181.91
4	826.87	234.19	861.82	197.85	380.79	135.94
5	668.75	243.00	674.57	173.02	284.32	90.16
6	492.04	161.62	472.84	173.85	205.38	64.27
8	267.97	110.34	267.42	93.78	123.96	39.29
10	167.44	55.26	165.87	59.12	87.33	28.76
12	104.89	33.32	104.23	37.42	60.14	17.41
16	54.00	16.72	56.22	20.91	38.67	9.71
24	31.04	12.16	31.09	7.02	25.76	7.34

1=TEST FED 2=REFERENCE FED, 3=TEST FASTING

TABLE 8. RATIO OF TEST/REFERENCE MEAN PLASMA ACYCLOVIR LEVELS (N=18)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.33	0.56	0.07	0.13
0.67	0.57	0.22	0.39
1	0.78	0.54	0.70
1.33	0.95	0.95	1.00
1.67	1.08	1.36	1.27
2	1.14	1.61	1.41
2.5	1.06	1.77	1.66
3	1.03	1.96	1.90
4	0.96	2.17	2.26
5	0.99	2.35	2.37
6	1.04	2.40	2.30
8	1.00	2.16	2.16
10	1.01	1.92	1.90
12	1.01	1.74	1.73
16	0.96	1.40	1.45
24	1.00	1.21	1.21

1=TEST FED 2=REFERENCE FED, 3=TEST FASTING

TABLE 9. TEST MEAN/REFERENCE MEAN (n=18; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	6575.36	1226.19	6559.50	1010.49	4209.10	1089.60
AUCT	6270.12	1260.56	6231.63	1025.36	3751.23	1108.86
CMAX	1203.22	304.19	1167.06	222.59	785.02	337.07
KE	0.11	0.03	0.11	0.04	0.07	0.03
LAUCI	6465.02	0.19	6487.28	0.15	4060.26	0.29
LAUCT	6145.92	0.21	6153.75	0.16	3586.67	0.32
LCMAX	1164.09	0.27	1144.85	0.21	723.72	0.42
THALF	7.05	2.21	7.15	2.09	11.35	5.07
TMAX	2.58	1.10	2.29	0.72	1.44	0.56

1=TEST FED 2=REFERENCE FED 3=TEST FASTING

TABLE 10. TEST MEAN/REFERENCE MEAN RATIOS (n=18; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.00	1.56	1.56
AUCT	1.01	1.67	1.66
CMAX	1.03	1.53	1.49
KE	1.02	1.45	1.43
LAUCI	1.00	1.59	1.60
LAUCT	1.00	1.71	1.72
LCMAX	1.02	1.61	1.58
THALF	0.99	0.62	0.63
TMAX	1.13	1.79	1.58

1=TEST FED 2=REFERENCE FED 3=TEST FASTING

TABLE 11. LSMEANS AND RATIOS (n=18)

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	6575.36	6559.50	4209.10	1.00	1.56	1.56
AUCT	6270.12	6231.63	3751.23	1.01	1.67	1.66
CMAX	1203.22	1167.06	785.02	1.03	1.53	1.49
LAUCI	6465.02	6487.28	4060.26	1.00	1.59	1.60
LAUCT	6145.92	6153.75	3586.67	1.00	1.71	1.72
LCMAX	1164.09	1144.85	723.72	1.02	1.61	1.58

VI. FORMULATION

Table 12. shows the composition of the test products, 400 mg and 800 mg acyclovir tablets manufactured by Mylan. The 400 mg and 800 mg strengths are exactly proportional in active and inactive ingredients.

[NOT FOR RELEASE UNDER F.O.I.]

Table 13. Composition of Mylan's Acyclovir Tablets

Ingredient	400 mg Test	400 mg Reference	800 mg Test	800 mg Reference
Acyclovir, USP				
Povidone, USP				
Microcrystalline Cellulose				
Sodium Starch Glycolate				
Magnesium Stearate/ Sodium Lauryl Sulfate				
Magnesium Stearate				
Croscarmellose Sodium				
Dye FDC Blue #2				
Ferric Oxide, Red				
Total Tablet Weight				

VII. *IN VITRO* RESULTS (DISSOLUTION): Currently there is no official USP dissolution test. The innovator's dissolution method specifies water as the medium, which has been accepted by the OGD in the past for approval of applications. In September-October issue of *Pharmacopeial Forum*, **23** (5): 4692 (1997), USP has proposed to adopt the FDA dissolution method except for 0.1 N hydrochloric acid as the medium (see Attachment 8). However, that is not final as yet. Therefore, FDA method, used by the firm should be acceptable (Also see Attachment 9).

Both, 400 and 800 mg tablets meet the dissolution requirement of Q=NLT % in 45 minutes (Table 14).

TABLE 14. *In Vitro* Dissolution Testing

A. Conditions

Method, Apparatus II (Paddle) **RPM: 50** **No. of Units: 12**
Medium: Distilled water **Volume:** 900 mL
Reference Drug: Zovirax[R] **Manufacturer:** Burroughs-Wellcome
Assay Methodology:

B. Results

Sampling Time (Minutes)	Test Product Mean % Dissol.	Range	CV	Reference Product Mean % Dissol.	Range	CV
	Lot #2C005L	**Strength 800 mg**		**Lot # 5T1792**		
15	71		8.0	88		3.8
30	92		2.4	94		2.8
45	96		2.6	94		2.6
	Lot #2C004L	**Strength 400 mg**		**Lot #5U2007**		
15	84		5.2	83		3.5
30	92		3.5	89		2.3
45	96		2.4	93		1.6

VIII. DEFICIENCIES

None

IX. RECOMMENDATION

1. The *in vivo* bioequivalence study conducted under fasting conditions by Mylan on its Acyclovir Tablets, 800 mg strength, Lot #2C005L, comparing it to Burroughs-Wellcome's 800 mg strength Zovirax[R] Tablets, 800 mg strength, Lot #5T1792, has been found acceptable by the Division of Bioequivalence.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Mylan on its Acyclovir Tablets, 800 mg strength, Lot #2C005L, comparing it to Burroughs-Wellcome's Zovirax[R] Tablets, 800 mg strength, Lot #5T1792, has been found acceptable by the Division of Bioequivalence.

3. The dissolution testing conducted by Mylan, on its acyclovir 800 and 400 mg tablets, Lot #2C005L and Lot #2C004L, is acceptable.

   The dissolution testing should be incorporated into the firm's manufacturing controls and stability program, and it should be conducted in 900 mL of water at 37 °C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following specifications:

   Not less than % of the labeled amount of acyclovir in the dosage form is dissolved in 45 minutes.

4. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability and *in vitro* dissolution testing requirements for its acyclovir 800 mg tablets, and the application is acceptable.

5. The formulation for 400 mg strength is proportionally similar to the 800 mg strength, which underwent bioequivalence testing. The request for waiver of its acyclovir 400 mg tablets is granted.

The firm should be informed of the recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar

/S/

Date 2/19/1998

Concur: /S/ Date: 2/23/98

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

Attachments-9

SPS/sps/2-13-98/75211SDW.997
cc: ANDA #75211 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

BIOEQUIVALENCY COMMENTS

ANDA: 75-211 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Acyclovir Tablets, 800 and 400 mg strengths

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

Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water, at 37 °C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than %(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 Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

File ANDA 75-211

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-211 SPONSOR: Mylan Pharmaceuticals, Inc.
DRUG & DOSAGE FORM: Acyclovir Tablets
STRENGTHS/(s): 400, 800 mg
TYPE OF STUDY: Single dose fasting and non-fasting studies
STUDY SITE: Mylan Pharm, Inc., Morgantown, WV

STUDY SUMMARY: Bioequivalence between the test and reference products was determined on the basis of pharmacokinetic and dissolution data of acyclovir tablets. The firm has conducted single-dose fasting and nonfasting studies, and dissolution testing on test and reference products. The results of the studies indicate that Mylan's 800 mg tablets are bioequivalent to the reference product, Burroughs-Wellcome's Zovirax® 800 mg tablets. The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{inf}$, and LC_{max} are in the acceptable range of 80-125 for single-dose study. As required, under fed conditions, the test/reference ratios for PK parameters were within 0.8-1.2.

DISSOLUTION:
The test products 400 and 800 mg tablets meet the agency's dissolution specifications (non-USP Method). The amount of drug dissolved from the test product was NLT % in 45 minutes.

PRIMARY REVIEWER: S.P.Shrivastava, Ph.D. BRANCH: II

INITIAL: S.P.S. DATE 2/19/98

BRANCH CHIEF: S. G. Nerurkar, Ph.D. BRANCH: II
INITIAL: SGN DATE 2/19/1998

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INITIAL: DPC DATE 2/23/98

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