CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40-298

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40-298 SPONSOR: Mylan Pharmaceuticals
DRUG: phenytoin
DOSAGE FORM: extended ~~release~~ capsule
STRENGTHS/(s): 100 mg
TYPE OF STUDY: Single ✓ Multiple _ Fasting ✓ Fed _
STUDY SITE: Mylan Pharmaceuticals, Morgantown, WVa.

STUDY SUMMARY: 22 evaluable subjects in a replicate design

In transformed scale CI [92; 101] AUC
[93; 101] AUC inf
[85; 98] Cmax

DISSOLUTION: ok per USP

PRIMARY REVIEWER: Jenny Lee BRANCH: II

INITIAL: R.S. DATE 8/10/98

TEAM LEADER: S. Nerurkar, Ph.D BRANCH: II

INITIAL: [signature] DATE 8/14/1998

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale Conner, Pharm.D

INITIAL: [signature] DATE 8/17/98

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

CC: ANDA 40-298
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Nerurkar for BioSign Off List
HFD-655/ J. Lee R.S. 8/10/98
BIO DRUG FILE NR 8/17/98 8/14/98

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF) Strengths: 100 mg
Clinical: Mylan **Outcome:** **AC**
Analytical: Mylan

5. **STUDY AMENDMENT** (STA)6/25/98 Strengths: 100 mg
Outcome: **AC**

OUTCOME DECISIONS:
AC - Acceptable **NC** - No Action

WINBIO COMMENTS:
Fasting study now complete and acceptable.

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-298 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Extended phenytoin sodium, 100 mg capsule

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23, eighth supplement.

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

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BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF)
Clinical: Mylan
Analytical: Mylan

Strengths: 100 mg
Outcome: **AC**

5. **STUDY AMENDMENT** (STA)6/25/98

Strengths: 100 mg
Outcome: ~~**AC**~~

OUTCOME DECISIONS:
AC - Acceptable

NC - No Action

WINBIO COMMENTS:
Fasting study now complete and acceptable.

Extended Phenytoin Sodium
100 mg capsule
NDA #40-298
Reviewer: J. Lee
40298SD.698

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission date:
February 27, 1998
June 25, 1998

Review of an in-vivo Bioavailability Study and Dissolution Testing Data

Objective:

To assess the rate and extent of absorption of two extended phenytoin sodium capsule formulations (Mylan product vs Dilantin® Kapseals) after administration of single doses to subjects under fasted conditions.

Study Design:

The clinical study (PHEN-9760) was conducted at . in . under the supervision of .

Twenty-three healthy, non-smoking, male volunteers between the ages of 18-50 years and within 10% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination, clinical laboratory tests and 12-lead ECG. They had no history of significant chronic diseases, hepatitis or drug/alcohol abuse.

Rx and OTC medications were not allowed within 14 days of the first drug administration. There was to be no alcohol or consumption of caffeine- or xanthine-containing foods or beverages 48 hours prior to drug administration and throughout the study period.

The study was designed as a randomized, open-label, two-treatment, two-sequence, four period crossover study [replicate design] with a three week washout period between dosings. Treatments consisted of a single 100 mg dose of the following:

A. Extended Phenytoin Sodium
   100 mg capsule, batch #2D004K
   Mylan Pharmaceuticals Inc.
   mnfg. date: May 22, 1997

B. Dilantin® Kapseals®
   100 mg capsule, batch #02416F

Parke-Davis
expiry date: December, 1997

Twenty-three subjects were dosed according to the following scheme:

	Period I 10/11/97	Period II 11/01/97	Period III 11/22/97	Period IV 12/13/97
sequence I	A	B	B	A
sequence II	B	A	A	B

sequence I - subj. 3, 4, 5, 6, 9, 12, 13, 16, 17, 21, 23
sequence II - subj. 1, 2, 7, 8, 10, 11, 14, 15, 19, 20*, 22

*Subject #20 did not return for period II dosing for personal reasons. Twenty-two subjects completed the study.

After an overnight fast, subjects were given a 100 mg dose of extended phenytoin sodium with water. Fasting continued for 5 hours post-dose. Blood samples (10 ml) were drawn in heparinized tubes at 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours. Subjects were released after the 24 hour blood draw and returned to the study facility for subsequent blood draws. All blood draws were taken within the allowable variance per protocol except for subject #12 (per III, ref.) whose 72 hour sample was taken 24 minutes late (insignificant). Plasma samples were extracted and stored in labeled tubes : pending assay.

Eighteen medical experiences were reported, most of which centered around headache and nausea. All were mild in severity. The adverse experiences summary is attached.

Deviations from protocol were minimal and unremarkable.

Analytical: [Not for release under FOI]

Data Analysis:

Plasma data was analyzed by an analysis of variance procedure (SAS-GLM) to determine statistically significant differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters. Of the original twenty three subjects enrolled in the study, one did not complete the crossover; twenty-two datasets were analyzed.

The data was also reviewed by the Division of Biometrics, QMR.

Results:

There was <3% difference between the test and reference formulations for plasma levels of phenytoin in AUC_{0-t} and AUC_{inf} and ~8% difference in C_{max}. The 90% shortest confidence intervals for phenytoin are presented below:

		90% CI
ln-transformed scale	AUC_{0-t} (n=44)	[92; 101]
	AUC_{inf} (n=44)	[93; 101]
	C_{max} (n=44)	[85; 98]

Mean plasma level data and pharmacokinetic summary are attached.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the current USP method. The resultant summaries are attached.

Potency:

The assay for potency for the Mylan product was 100.9%. For Dilantin®Kapseals® the potency was 100.4%.

Batch Size:

The batch size for the bio-batch of Mylan's 100 mg extended phenytoin sodium capsule is units.

Recommendation:

1. The bioequivalence study conducted by Mylan Pharmaceuticals Inc. on its extended phenytoin sodium 100 mg capsule, batch #2D004K, comparing it to Dilantin® Kapseals®, 100 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's extended phenytoin sodium 100 mg capsule is bioequivalent to the reference product, Dilantin® Kapseals®, 100 mg, manufactured by Parke-Davis.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XXIII apparatus I (basket) at 50 rpm. The test product should meet the following specification:

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

R. Lee 8/10/98

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR /S/ 8/14/1998
FT INITIALED SNERURKAR

Concur: /S/ Date: 8/17/98

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

JLee/jl/08-06-98

cc:

USP XXIII Apparatus _I_ Basket _x_ Paddle _____ rpm

Medium: water @ 37°C Volume:_ _ml

Number of Tabs/Caps Tested: 12

Reference Drug: Dilantin® Kapseals® 100 mg capsule

Assay Methodology:

Results

Time (min)	Test Product Lot # 2D004K Mean % Dissolved	Range	(CV)	Reference Product Lot # 02416F Mean % Dissolved	Range	(CV)
15	11		(18)	14		(6.5)
30	30		(6.5)	35		(6.3)
60	58		(4.5)	56		(5.9)
90	81		(4.1)	67		(5.4)
120	92		(2.5)	75		(5.7)
			( )			( )
	Lot #_____			Lot #_____		
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

Mean Plasma Levels
(mcg/ml)

Trt A (Mylan)

Time (hour)	N	Mean	Std Dev	CV
0	44	0	0	.
0.5	44	0.111	0.117	105.44
1	44	0.448	0.339	75.78
2	44	0.918	0.463	50.40
3	44	1.056	0.337	31.93
4	44	1.082	0.270	24.95
5	44	1.102	0.245	22.25
6	44	0.999	0.211	21.09
8	44	0.936	0.199	21.25
12	44	0.835	0.182	21.78
16	44	0.705	0.185	26.30
24	44	0.550	0.162	29.42
36	44	0.342	0.149	43.55
48	44	0.184	0.118	64.17
72	44	0.061	0.071	116.15
96	44	0.013	0.035	268.87

Trt B (Dilantin Kapseals)

Time (hour)	N	Mean	Std Dev	CV
0	44	0	0	.
0.5	44	0.254	0.220	86.91
1	44	0.670	0.415	61.93
2	44	1.006	0.397	39.46
3	44	1.132	0.345	30.49
4	44	1.146	0.300	26.19
5	44	1.177	0.256	21.73
6	44	1.080	0.231	21.35
8	44	0.990	0.194	19.63
12	44	0.864	0.162	18.82
16	44	0.730	0.146	20.07
24	44	0.547	0.149	27.21
36	44	0.338	0.144	42.63
48	44	0.184	0.113	61.60
72	44	0.053	0.077	144.58
96	44	0.014	0.033	244.89

Pharmacokinetic Parameters

Trt A (Mylan)

Parameter	N	Mean	Std Dev	CV	T/R
AUC	44	30.010	9.505	31.67	0.976
AUCINF	44	32.172	9.887	30.73	0.979
CPEAK	44	1.176	0.272	23.10	0.923
TPEAK	44	4.409	3.552	80.57	1.084
HALF	44	15.490	3.985	25.73	1.046
KEL	44	0.048	0.013	27.45	0.958
LAUC	44	3.357	0.301	8.96	0.991
LAUCINF	44	3.430	0.284	8.28	0.992
LCPEAK	44	0.133	0.253	190.63	0.609

Trt B (Dilantin Kapseals)

Parameter	N	Mean	Std Dev	CV
AUC	44	30.756	9.120	29.65
AUCINF	44	32.876	9.336	28.40
CPEAK	44	1.274	0.268	21.02
TPEAK	44	4.068	2.396	58.89
HALF	44	14.809	4.090	27.62
KEL	44	0.050	0.013	25.12
LAUC	44	3.387	0.278	8.21
LAUCINF	44	3.457	0.264	7.64
LCPEAK	44	0.218	0.229	105.00

ADVERSE EXPERIENCE REPORT

Phase/ Date	Vol#	Start Time	End Time	Symptom	How Severe	Treatment	Probably Drug Related	Possibly Drug Related	Remotely Drug Related	Not Drug Related
I-10/11/97	4	1:50 pm	7:00 pm	headache	mild	none	✓			
I-10/11/97	7	4:00 pm	5:40 pm	itchy, flat, lt. red, lesions on chest	mild	none		✓		
I-10/11/97	21	11:00 am	7:15 pm	headache	mild	none	✓			
I-10/11/97	21	6:20 pm	6:45 pm	indigestion and nausea	mild	none		✓		
I-10/11/97	10	3:00 pm	11:00 pm	headache	mild	intermittent ice pack	✓			

Study: Phenytoin Sodium ER/Dilantin 100 mg "fasting" Bioequivalence Study
Mylan #PHEN-9760; CPR-PH3

Signature: D Williams **Date:** 1/15/98

Thomas S. Clark, M.D., M.S. or
Dorian Williams, M.D.

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ADVERSE EXPERIENCE REPORT

Phase/ Date	Vol#	Start Time	End Time	Symptom	How Severe	Treatment	Probably Drug Related	Possibly Drug Related	Remotely Drug Related	Not Drug Related
II-11/1/97	21	6:30 am	12:00 am (11/2/97)	sore throat	mild	none				✓
II-11/1/97	21	10:00 am	11:00 pm	headache	mild	none	✓			
II-11/1/97	10	4:00 pm	1:30 am (11/2/97)	headache	mild	none	✓			
II-11/1/97	6	5:10 pm	12:30 am (11/2/97)	headache	mild	none	✓			
II-11/1/97	2	4:30 pm	2:00am (11/2/97)	headache	mild	none	✓			

Study: Phenytoin Sodium ER/Dilantin 100 mg "fasting" Bioequivalence Study
Mylan #PHEN-9760; CPR-PH3

Signature: _____ Date: 1/15/98

Thomas S. Clark, M.D., M.S. or
Dorian Williams, M.D.

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ADVERSE EXPERIENCE REPORT

Phase/ Date	Vol#	Start Time	End Time	Symptom	How Severe	Treatment	Probably Drug Related	Possibly Drug Related	Remotely Drug Related	Not Drug Related
III-11/22/97	4	12:00 pm	7:30 pm	nausea	mild	none	/			
III-11/22/97	4	12:00 pm	7:30 pm	headache	mild	none	/			
III-11/22/97	2	2:30 pm	7:30 pm	headache	mild	none	/			
III-11/22/97	10	7:30 pm	8:00 am (11/23/97)	headache	mild	none		/		
IV-12/13/97	10	12:00 pm	6:30 pm	headache	mild	none	/			

Study: Phenytoin Sodium ER/Dilantin 100 mg "fasting" Bioequivalence Study
Mylan #PHEN-9760; CPR-PH3

Signature: D. Williams Date: 1/21/98

Thomas S. Clark, M.D., M.S. or
Dorian Williams, M.D.

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ADVERSE EXPERIENCE REPORT

Phase/ Date	Vol#	Start Time	End Time	Symptom	How Severe	Treatment	Probably Drug Related	Possibly Drug Related	Remotely Drug Related	Not Drug Related
IV-12/13/97	7	4:00 pm	7:15 pm	headache	mild	ice pack from 4:45 pm until 5:10 pm	✓			
IV-12/13/97	5	5:00 pm	7:00 pm	headache	mild	none	✓			
IV-12/13/97	5	12/17/97	continues	hypertension	mild	advised to see local physician				✓

Study: Phenytoin Sodium ER/Dilantin 100 mg "fasting" Bioequivalence Study
Mylan #PHEN-9760; CPR-PH3

Signature: D Williams Date: 1/21/98

Thomas S. Clark, M.D., M.S. or
Dorian Williams, M.D.

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